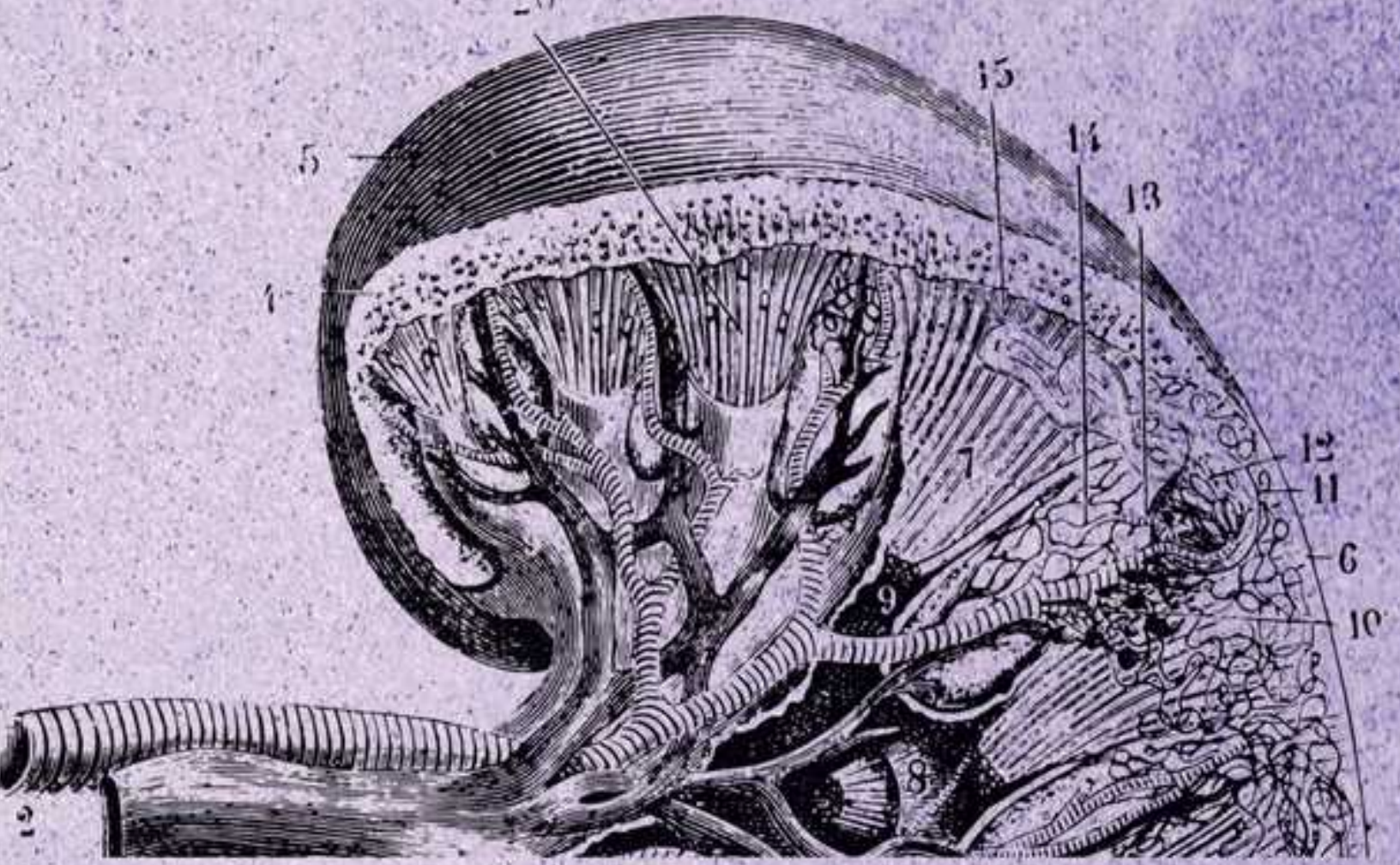
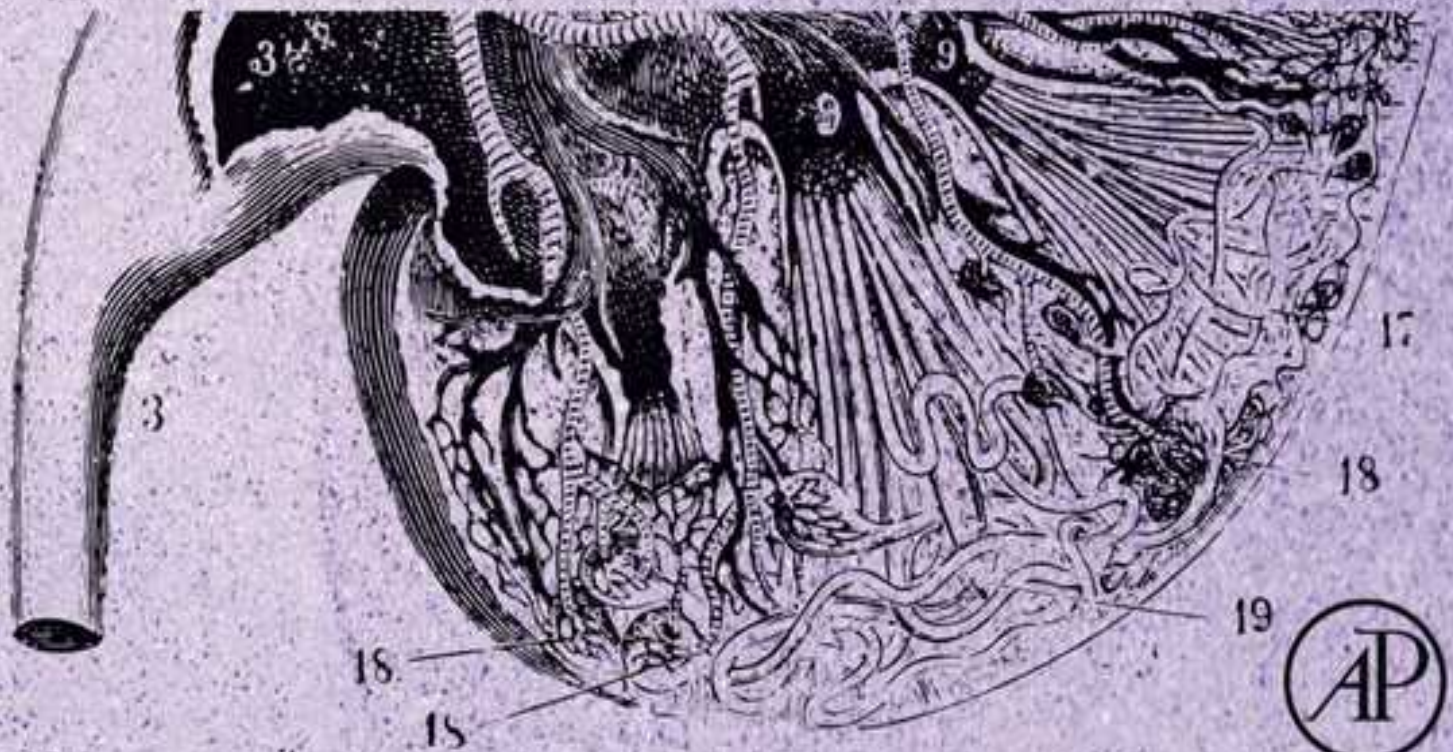


Second Edition

CHRONIC RENAL DISEASE

Edited by **Paul L. Kimmel and Mark E. Rosenberg**



CHRONIC RENAL DISEASE

SECOND EDITION

Edited by

PAUL L. KIMMEL

MARK E. ROSENBERG

ACADEMIC PRESS
An imprint of Elsevier

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

Notices
Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-0-12-815876-0

Publisher: Stacy Masucci
Acquisition Editor: Tari K. Broderick
Editorial Project Manager: Tracy Tufaga
Production Project Manager: Punithavathy Govindaradjane
Cover Designer: Miles Hitchen

Typeset by TNQ Technologies

Dedication

I face the dual challenges of looking forward and back as the Second Edition of *Chronic Renal Disease* emerges into print. I am delighted with the reception the First Edition received and took it as a summons to create an even better second effort. We have sought to put new information into perspective, vital for the care of patients, and to recruit the best authors to update the text and present complex new concepts in a meaningful way.

This Second Edition is dedicated to my teachers, who showed me the beauty of physiology, pathophysiology, and treatment, as well as the interconnections between ourselves as teachers and physicians, and our patients and their families. The greatest teachers fostered critical thinking and inspired me to ask and try to answer many different questions about renal disease. Each one had a distinctive persona. I am both impressed by and amused by the multiplicity of viewpoints in our discipline. Countless colleagues worked with me on projects, helping me to see findings in different ways, enhancing my approaches to understanding data. In addition, I recognize the role of my parents and sister in this effort. They would have truly loved to have seen this book.

This Second Edition has new authors and new chapters, making it more comprehensive, useful, and focused on our patients worldwide. The chapter authors—all recognized experts in their fields—have done a remarkable job of conceptualizing their subjects in clear language and pictures, as well as responding to many and diverse editorial quibbles and cavils. The interaction between authors and editors has been both scholarly and very productive. I thank the returning authors as well as the new ones heartily. My coeditor has been a joy to work with, complementing my deficiencies with thoughtfulness, equanimity, good sense, and good humor. I thank the staff at Elsevier for their guidance and perseverance. They all understood and immediately shared the goal of creating a scientific, well-written, useful, and beautiful book. I hope we have achieved those goals.

This book is also meant to improve the care and lives of our patients. The last five years have witnessed a sea change in clinical research in nephrology, including patients as partners and collaborators in all aspects of the research enterprise. This book is for them as well. Finally and perhaps foremost, this book is for our students, who continue to teach as well as challenge us, in addition to hopefully learning from us. I hope they will find this book helpful in thinking about the kidney and renal disease, and in caring for their patients. And how could I not thank my wife? This book could certainly have been written without her, but it would not have been as much fun. I deeply appreciate her wisdom and consideration.

Paul L. Kimmel

This book is dedicated to the many students, residents, and fellows who continue to inspire me to teach and learn, to my mentors who have shown me the pathways to follow in medicine and life, and to the patients I have cared for who have taught me about the perseverance and courage needed to live with a chronic illness. Heartfelt thanks to the many authors who have contributed to this book and to the editorial team at Elsevier for their outstanding work. Most of all, I dedicate this book to my wife Monica and my children Joel, Madeline, and Jack—thanks for your unending love, support, and motivation, and for teaching me how to have fun!

Mark E. Rosenberg

List of Contributors

Blaise Abramovitz Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States

Dwomoa Adu Honorary Senior Research Fellow and Consultant Nephrologist, School of Medicine and Dentistry, University of Ghana, Accra, Ghana

Farsad Afshinnia Division of Nephrology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, United States

Anupam Agarwal Division of Nephrology, University of Alabama at Birmingham, Birmingham Veterans Administration Medical Center, Birmingham, AL, United States

Sarah C. Andrews Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States

Gerald Appel Division of Nephrology, Columbia University Medical Center, New York, NY, United States

James L. Bailey Renal Division, Emory University, Atlanta, GA, United States

George L. Bakris Comprehensive Hypertension Center, Department of Medicine, The University of Chicago Medicine, Chicago, IL, United States

Carolyn A. Bauer Division of Nephrology, Bronx, NY, United States

Pravir V. Baxi Division of Nephrology, Rush University Medical Center, Chicago, IL, United States

Jeffrey S. Berns Renal-Electrolyte and Hypertension Division, Department of Medicine, Perelman School of Medicine of the University of Pennsylvania School of Medicine, Philadelphia, PA, United States

Peter Birks British Columbia Renal Agency, Vancouver, BC, Canada

Andrew Bomback Division of Nephrology, Department of Medicine, Columbia University Irving Medical Center, New York, NY, United States

Anirban Bose Division of Nephrology, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY, United States

Frank C. Brosius, 3rd Division of Nephrology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, United States; Division of Nephrology, University of Arizona College of Medicine, Tucson, AZ, United States

Lee K. Brown Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, NM, United States; University of New Mexico Health Sciences Center, Albuquerque, NM, United States; University of New Mexico School of Engineering, Albuquerque, NM, United States; University of New Mexico Health System Sleep Disorders Centers, Albuquerque, NM, United States

David A. Bushinsky Division of Nephrology, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY, United States

Laurence W. Busse Emory University, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Department of Medicine, Emory Johns Creek Hospital, Johns Creek, GA, United States

Ruth C. Campbell Medical University of South Carolina, Division of Nephrology, Charleston, SC, United States

Mark Canney UBC Division of Nephrology and British Columbia Renal Agency, Vancouver, BC, Canada

Helen Cathro Department of Pathology and Laboratory Medicine, University of Virginia Medical Center, Charlottesville, VA, United States

Jonathan Chávez-Iñiguez Division of Nephrology, Hospital Civil de Guadalajara, University of Guadalajara Health Science Center, Guadalajara, Jalisco, México

Lakhmir S. Chawla Department of Anesthesiology and Critical Care Medicine, George Washington University Medical Center, Washington, DC, United States; Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States; University California of San Diego, San Diego, CA, United States

Sheldon Chen MD Anderson Cancer Center, Houston, TX, United States

Glenn M. Chertow Stanford University School of Medicine, Division of Nephrology, Palo Alto, CA, United States

Emily Y. Chew Division of Epidemiology and Clinical Applications, National Eye Institute, National Institutes of Health, Bethesda, MD, United States

Michel Chonchol Division of Renal Diseases and Hypertension, University of Colorado Denver Anschutz Medical Campus, Aurora, CO, United States

Deborah J. Clegg University of California at Los Angeles, Medical Center, Los Angeles, CA, United States

David M. Clive University of Massachusetts Medical School, Department of Medicine, Division of Renal Medicine, Worcester, MA, United States

Pia H. Clive UMass Memorial Medical Center, Worcester, MA, United States

Scott D. Cohen Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States

Ashte' K. Collins Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States

James E. Cooper Division of Nephrology, University of Colorado Anschutz Medical Campus, Aurora, CO, United States

Ricardo Correa-Rotter Department of Nephrology and Mineral Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, México

Daniel Cukor Behavioral Health, The Rogosin Institute, New York, NY, United States

Monica Dalal Medical Faculty Associates, George Washington University, Washington, DC, United States

Andrew Davenport UCL Centre for Nephrology, University College London, Royal Free Hospital, London, United Kingdom

Scott Davis Division of Nephrology, University of Colorado Anschutz Medical Campus, Aurora, CO, United States

Sara N. Davison Department of Medicine, University of Alberta, Edmonton, AB, Canada

Pierre Delanaye Department of Nephrology-Dialysis-Transplantation, University of Liège, Liège, Belgium

Dick de Zeeuw Department of Clinical Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Mirela A. Dobre Case Western Reserve University, School of Medicine, University Hospital Case Medical Center, Cleveland, OH, United States

Paul Drawz Division of Renal Diseases and Hypertension, University of Minnesota Medical School, Minneapolis, MN, United States

Natalie Ebert Charité University Hospital, Institute of Public Health, Berlin, Germany

Paul Eggers National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, United States

Silvia Ferrè Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, Dallas, TX, United States; Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, United States

Barry I. Freedman Department of Internal Medicine; Section on Nephrology, Wake Forest School of Medicine, Medical Center Boulevard, Winston–Salem, NC, United States

Susan L. Furth The Children's Hospital of Philadelphia, Philadelphia, PA, United States

Bixia Gao Renal Division, Department of Medicine, Peking University First Hospital; Peking University Institute of Nephrology, Beijing, China

Guillermo García-García Division of Nephrology, Hospital Civil de Guadalajara, University of Guadalajara Health Science Center, Guadalajara, Jalisco, México

Casey N. Gashti Division of Nephrology, Rush University Medical Center, Chicago, IL, United States

Gregory G. Germino National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health, Bethesda, MD, United States

David Goldsmith Guy's and St Thomas' Hospital, London, United Kingdom

Ladan Golestaneh Albert Einstein College of Medicine, Renal Division, Montefiore Medical Center, Bronx, NY, United States

Michael S. Goligorsky Departments of Medicine, Pharmacology and Physiology, Renal Research Institute, New York Medical College, Valhalla, NY, United States

Arthur Greenberg Division of Nephrology, Department of Medicine, Duke University Medical Center, Durham, NC, United States

L. Parker Gregg University of Texas Southwestern and Veterans Affairs North Texas Health Care System, Dallas, TX, United States

Lisa M. Guay-Woodford The George Washington University, Center for Translational Science, Clinical and Translational Institute at Children's National, Children's National Health System, Washington, DC, United States

Lee Hamm Tulane University, New Orleans, LA, United States

Allyson Hart Division of Nephrology, Hennepin Healthcare, University of Minnesota Medical School, Minneapolis, MN, United States

Danielle Haselby Division of Nephrology, Hennepin Healthcare, University of Minnesota Medical School, Minneapolis, MN, United States

S. Susan Hedayati University of Texas Southwestern, Dallas, TX, United States

Hiddo J.L. Heerspink Department of Clinical Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Charles A. Herzog Division of Cardiology, Department of Medicine, Hennepin County Medical Center and University of Minnesota, Minneapolis, MN, United States

Thomas H. Hostetter Department of Medicine, University of North Carolina, Chapel Hill, NC, United States

Andrew A. House Division of Nephrology, Department of Medicine, Western University and London Health Sciences Centre, London, ON, Canada

Keith A. Hruska Division of Pediatric Nephrology, Department of Pediatrics, Washington University, St. Louis, MO, United States; Departments of Medicine and Cell Biology, Washington University, St. Louis, MO, United States

Areef Ishani Minneapolis VA Health Care System, University of Minnesota, Minneapolis, MN, United States

Robert T. Isom Stanford University School of Medicine, Division of Nephrology, Palo Alto, CA, United States

Matthew T. James Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

Kenar D. Jhaveri Division of Kidney Diseases and Hypertension, North Shore University Hospital and Long Island Jewish Medical Center, Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY, United States

Kirsten Johansen Division of Nephrology, Hennepin County Medical Center, Minneapolis, MN, United States

Richard J. Johnson Division of Renal Diseases and Hypertension, University of Colorado Anschutz Medical Campus, Aurora, CO, United States

Duk-Hee Kang Division of Nephrology, Department of Internal Medicine, Ewha Women's University School of Medicine, Seoul, South Korea

Hiroko Kanno Tokyo Women's Medical University, Tokyo, Japan

Yoshihiko Kanno Tokyo Medical University, Tokyo, Japan

Amrita D. Karambelkar Department of Internal Medicine, Emory University School of Medicine, GME Office of Graduate Medical Education, Atlanta, GA, United States

Fiona E. Karet Frankl Department of Medical Genetics and Division of Renal Medicine, University of Cambridge, Cambridge, United Kingdom

Charbel C. Khoury Washington University in St. Louis, St. Louis, MO, United States

Paul L. Kimmel Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States

Jeffrey B. Kopp National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, United States

Stephen M. Korbet Division of Nephrology, Rush University Medical Center, Chicago, IL, United States

Etty Kruzel-Davila Department of Nephrology, Rambam Health Care Campus, Rappaport Faculty of Medicine and Research Institute, Technion—Israel Institute of Technology, Haifa, Israel

Andrew Kummer HealthPartners Nephrology, St. Paul, MN, United States

Laura LaFave Division of Endocrinology, Hennepin Healthcare, University of Minnesota Medical School, Minneapolis, MN, United States

Jay I. Lakkis University of Hawaii John A. Burns School of Medicine, Wailuku, HI, United States

Lilach O. Lerman Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, United States

Adeera Levin UBC Division of Nephrology and British Columbia Renal Agency, Vancouver, BC, Canada

Susie Q. Lew Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States

Valerie A. Luyckx Institute of Biomedical Ethics and the History of Medicine, University of Zurich, Zurich, Switzerland; Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

Tej K. Mattoo Children's Hospital of Michigan, Wayne State University School of Medicine, Detroit, MI, United States

Sharon E. Maynard University of South Florida Morsani College of Medicine, Lehigh Valley Health Network, Allentown, PA, United States

Peter A. McCullough Baylor University Medical Center, Dallas, TX, United States; Baylor Heart and Vascular Institute, Dallas, TX, United States; Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, TX, United States

Rajnish Mehrotra University of Washington, Seattle, WA, United States

Timothy W. Meyer Stanford University, School of Medicine, Veterans Affairs Health Care System, Palo Alto, CA, United States

William E. Mitch Nephrology Division, Baylor College of Medicine, Houston, TX, United States

Orson W. Moe Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, Department of Internal Medicine, Department of Physiology, University of Texas Southwestern Medical Center, Dallas, TX, United States

Samer Mohandes Division of Nephrology, Department of Internal Medicine, Ohio State University Wexner Medical Center, Columbus, OH, United States

Alvin H. Moss Center for Health Ethics and Law, Robert C. Byrd Health Sciences Center, West Virginia University, Morgantown, WV, United States

Marva Moxey-Mims Children's National Health System, The George Washington University School of Medicine, Washington, DC, United States

Sangeetha Murugapandian Division of Nephrology, University of Arizona College of Medicine, Tucson, AZ, United States; Banner University Medical Center Tucson and South, Tucson, AZ, United States

Karl A. Nath Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, United States

Joel Neugarten Albert Einstein College of Medicine, Renal Division, Montefiore Medical Center, Bronx, NY, United States

Javier A. Neyra Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, Dallas, TX, United States; Department of Internal Medicine, Division of Nephrology, Bone and Mineral Metabolism, University of Kentucky, Lexington, KY, United States

Allen R. Nissenson Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA, United States; DaVita, Inc., Denver, CO, United States

Ehsan Nobakht Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States

Thomas D. Nolin Center for Clinical Pharmaceutical Sciences, Department of Pharmacy and Therapeutics and Department of Medicine Renal Electrolyte Division, University of Pittsburgh Schools of Pharmacy and Medicine, Pittsburgh, PA, United States

Keith C. Norris Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA, United States

Jenna M. Norton National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, United States

Kristen L. Nowak Division of Renal Diseases and Hypertension, University of Colorado Denver Anschutz Medical Campus, Aurora, CO, United States

Akinlolu O. Ojo Associate Vice President for Clinical Research and Global Health Initiatives, University of Arizona Health Sciences, Tucson, AZ, United States

Madeleine V. Pahl Division of Nephrology and Hypertension, UCI Medical Center, Orange, CA, United States

Mark S. Paller University of Minnesota, Minneapolis, MN, United States

Biff F. Palmer Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, United States

Nicholette D. Palmer Department of Biochemistry, Wake Forest School of Medicine, Medical Center Boulevard, Winston−Salem, NC, United States

Samir S. Patel Renal Section, Veterans Affairs Medical Center, Washington, DC and George Washington University Medical Center, Washington, DC, United States

Roberto Pecoits-Filho School of Medicine, Pontificia Universidade Catolica do Parana, Curitiba, Brazil

Steven J. Peitzman Drexel University College of Medicine, Philadelphia, PA, United States

Aldo J. Peixoto Section of Nephrology, Yale School of Medicine, and Hypertension Program at the Yale New Haven Hospital Heart and Vascular Center, New Haven, CT, United States

Phuong-Thu T. Pham Department of Medicine, Nephrology Division, David Geffen School of Medicine at UCLA, Kidney Transplant Program, Los Angeles, CA, United States

Phuong-Chi T. Pham Department of Medicine, Nephrology and Hypertension Division, David Geffen School of Medicine at UCLA, UCLA-Olive View Medical Center, Sylmar, CA, United States

Beth Piraino University of Pittsburgh, Pittsburgh, PA, United States

Roberto Pisoni Medical University of South Carolina, Division of Nephrology, Charleston, SC, United States

Ton Rabelink Department of Nephrology, Leiden University Medical Center, Leiden, Netherlands

Jai Radhakrishnan Division of Nephrology, Department of Medicine, Columbia University Irving Medical Center, New York, NY, United States

Mahboob Rahman University Hospitals Cleveland Medical Center, Case Western Reserve University, Louis Stokes Cleveland VA Medical Center, Cleveland, OH, United States

Dominic S. Raj Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States

Juan C. Ramírez-Sandoval Department of Nephrology and Mineral Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, México

Janani Rangaswami Einstein Medical Center, Philadelphia, PA, United States; Sidney Kimmel College of Thomas Jefferson University, Philadelphia, PA, United States

Jane F. Reckelhoff Women's Health Research Center, University of Mississippi Medical Center, Jackson, MS, United States

Renu Regunathan-Shenk Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States

Scott Reule Minneapolis VA Health Care System, University of Minnesota, Minneapolis, MN, United States

Claudio Ronco Università degli Studi di Padova, Padova, Italy; Department of Nephrology, Dialysis and Transplantation, San Bortolo Hospital, Vicenza, Italy

Mark E. Rosenberg Division of Renal Diseases and Hypertension, University of Minnesota Medical School, Minneapolis, MN, United States

Mitchell H. Rosner Divison of Nephrology, University of Virginia, Charlottesville, VA, United States

Brad Rovin Division of Nephrology, Department of Internal Medicine, Ohio State University Wexner Medical Center, Columbus, OH, United States

Prabir Roy-Chaudhury The University of North Carolina Kidney Center, Chapel Hill, NC, United States

Rebecca Ruebner Johns Hopkins University School of Medicine, Baltimore, MD, United States

Andrew D. Rule Division of Nephrology and Hypertension and Division of Epidemiology, Mayo Clinic, Rochester, MN, United States

Jeff M. Sands Renal Division, Emory University, Atlanta, GA, United States

Lynn E. Schlanger Renal Division, Emory University, Atlanta, GA, United States

Sarah J. Schrauben Renal-Electrolyte and Hypertension Division, Department of Medicine, Perelman School of Medicine of the University of Pennsylvania School of Medicine, Philadelphia, PA, United States

Stephen Seliger Department of Medicine, Division of Nephrology, University of Maryland School of Medicine, Baltimore, MD, United States

Maulin Shah Nephrology Division, Baylor College of Medicine, Houston, TX, United States; Nephrology Section, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, United States

Richard H. Sterns University of Rochester School of Medicine and Dentistry and Rochester General Hospital, Rochester, NY, United States

Erik Stites Division of Nephrology, University of Colorado Anschutz Medical Campus, Aurora, CO, United States

Toshifumi Sugatani Division of Pediatric Nephrology, Department of Pediatrics, Washington University, St. Louis, MO, United States

Stephen C. Textor Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, United States

Ravi Thadhani Cedars-Sinai Medical Center, Los Angeles, CA, United States; Harvard Medical School, Boston, MA, United States

Bijin Thajudeen Division of Nephrology, University of Arizona College of Medicine, Tucson, AZ, United States; Banner University Medical Center Tucson and South, Tucson, AZ, United States

Surabhi Thakar University of Minnesota, Minneapolis, MN, United States

George Thomas Cleveland Clinic Foundation, Cleveland, OH, United States

Raymond R. Townsend Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

Jeffrey Turner Yale University, New Haven, CT, United States

Mark L. Unruh Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, NM, United States; Nephrology Section, New Mexico Veterans Hospital, Albuquerque, NM, United States

Bradley L. Urquhart Department of Physiology and Pharmacology and Division of Nephrology, Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada

Joseph A. Vassalotti Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, and National Kidney Foundation, Inc., New York, NY, United States

Nosratola D. Vaziri Division of Nephrology and Hypertension, UCI Medical Center, Orange, CA, United States

Manuel T. Velasquez Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States

Nisha Ver Halen Center for Integrative Health and Wellbeing, Weil Cornell Medicine, New York, NY, United States

Salina P. Waddy Atlanta Veterans Administration, Department of Neurology, Decatur, GA, United States

Jinwei Wang Renal Division, Department of Medicine, Peking University First Hospital; Peking University Institute of Nephrology, Beijing, China

Marc Weber Kidney Specialists of Minnesota, Minneapolis, MN, United States

Matthew R. Weir Division of Nephrology, University of Maryland School of Medicine, Baltimore, MD, United States

Christine A. White Division of Nephrology, Queen's University, Kingston, ON, Canada

William L. Whittier Division of Nephrology, Rush University Medical Center, Chicago, IL, United States

Matthew J. Williams Division of Pediatric Nephrology, Department of Pediatrics, Washington University, St. Louis, MO, United States

Alexander C. Wiseman Division of Nephrology, University of Colorado Anschutz Medical Campus, Aurora, CO, United States

David C. Wymer University of Florida, Malcom Randall VAMC, Gainesville, FL, United States

David T.G. Wymer Mount Sinai Medical Center, Miami Beach, FL, United States

Jerry Yee Henry Ford Hospital, Division of Nephrology and Hypertension, Detroit, MI, United States

Luxia Zhang Renal Division, Department of Medicine, Peking University First Hospital; Peking University Institute of Nephrology, Beijing, China

Shougang Zhuang Department of Nephrology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China

Fuad N. Ziyadeh Faculty of Medicine, American University of Beirut, Beirut, Lebanon

About the Editors

Paul L. Kimmel, MD, MACP, FRCP, FASN, was educated at Yale College and the New York University School of Medicine. He completed his internal medicine residency at Bellevue Hospital in New York City and Nephrology fellowship at the Hospital of the University of Pennsylvania. He was a member of the faculty at the University of Pennsylvania and the George Washington University, where he attained the rank of professor. From 2001 to 2006, Dr. Kimmel served as Director of the Division of Renal Diseases and Hypertension at George Washington University. From 2006 to 2008, he was the Director of Education of the American Society of Nephrology. Dr. Kimmel currently is Clinical Professor of Medicine at George Washington University in Washington, DC. His interests include psychosocial adaptation to chronic renal disease, sleep disorders in patients with kidney disease, zinc metabolism in renal diseases, HIV-associated kidney diseases, the clinical genetics of common kidney disease, and the interrelationships between acute kidney injury and chronic kidney disease.

Mark E. Rosenberg, MD, FASN, attended medical school at the University of Manitoba in Winnipeg, Canada, and did his internal medicine residency and nephrology fellowship at the University of Minnesota. He served as Director of the Division of Renal Diseases and Hypertension at the university from 2000 to 2009. From 2009 to 2012, he was the Chief of Medicine and Director of the Primary and Specialty Medicine Service Line at the Minneapolis VA Health Care System. Dr. Rosenberg currently serves as Vice Dean for Education and Academic Affairs, and Professor of Medicine at the University of Minnesota Medical School in Minneapolis, Minnesota. In this position, he is responsible for the continuum of medical education. He served as Chair of the Postgraduate Education Committee and Education Director for Kidney Week for 6 years before being elected in 2013 to the Council of the American Society of Nephrology. Dr. Rosenberg served as President of the American Society of Nephrology in 2019. His interests include pathophysiology and progression of chronic kidney disease, kidney regeneration following acute injury, models of care delivery including telehealth, and workforce issues in nephrology.

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
ACR	Albumin:creatinine ratio
ADPKD	Autosomal dominant polycystic kidney disease
AIDS	Acquired immunodeficiency syndrome
AKI	Acute kidney injury
ARB	Angiotensin receptor blocker
BMI	Body mass index
bpm	Beats per minute
CCB	Calcium channel blocker
CHF	Congestive heart failure
CKD	Chronic kidney disease
CPAP	Continuous positive airway pressure
CRS	Cardiorenal syndrome
CrCl	Creatinine clearance
CRP	C-reactive protein
CT	Computed tomography
CVD	Cardiovascular disease
DM	Diabetes mellitus
DN	Diabetic nephropathy
DR	Diabetic retinopathy
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agent
ESRD	End-stage renal disease
FDA	Food and Drug Administration
FGF-23	Fibroblast growth factor 23
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
mGFR	Measured glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HD	Hemodialysis
HIV	Human immunodeficiency virus
HIVAN	Human immunodeficiency virus−associated nephropathy
HTN	Hypertension
HUS	Hemolytic uremic syndrome
IL	Interleukin
LN	Lupus nephritis
MN	Membranous nephropathy
MCD	Minimal change disease
MGUS	Monoclonal gammopathy of unknown significance
MRI	Magnetic resonance imaging
NAD	Nicotinamide adenine dinucleotide
NIH	National Institutes of Health
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NSAID	Nonsteroidal antiinflammatory drug
OSA	Obstructive sleep apnea
PCR	Protein:creatinine ratio
PD	Peritoneal dialysis
RAAS	Renin−angiotensin−aldosterone system
RBC	Red blood cells
RVD	Renal vascular disease
RCT	Randomized controlled trials
RRT	Renal replacement therapy
RT	Renal transplantation
SC	Subcutaneous
SCD	Sickle cell disease
SCN	Sickle cell nephropathy
SLE	Systemic lupus erythematosus
S[Alb]	Serum albumin concentration
S[Ca]	Serum calcium concentration
S[Cr]	Serum creatinine concentration
S[K]	Serum potassium concentration
S[Mg]	Serum magnesium concentration
S[P]	Serum phosphate concentration
S[UA]	Serum uric acid concentration
S[X]	Serum X concentration
T1DM	Diabetes mellitus, type 1
T2DM	Diabetes mellitus, type 2
TGF	Transforming growth factor
TNF	Tumor necrosis factor
TTP	Thrombotic thrombocytopenic purpura
UNA	Urinary nitrogen appearance
UAlbV	Urinary albumin excretion
UACR	Urine albumin:creatinine ratio
UProV	Urinary protein excretion
UPCR	Urine protein:creatinine ratio
USRDS	United States Renal Data System
VEGF	Vascular endothelial growth factor
$25(OH)D_3$	25 hydroxyvitamin D
$1,25(OH)_2D_3$	1,25 dihydroxycholecalciferol, calcitriol

CHAPTER

1

Introduction
Chronic Renal Disease

Paul L. Kimmel[a], *Mark E. Rosenberg*[b]

[a]Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States; [b]Division of Renal Diseases and Hypertension, University of Minnesota Medical School, Minneapolis, MN, United States

INTRODUCTION TO THE FIRST EDITION

In our discussions as we planned this work, we were struck that no major textbook had considered the relatively new field of chronic kidney disease—CKD—as a coherent whole. It must be acknowledged that the CKD revolution has transformed the clinical and scientific landscapes of nephrology, by systematizing the classification of the protean aspects of the discipline, and setting boundaries that have allowed clinical epidemiology and clinical research to advance, perhaps exponentially. CKD classifications have led to new nomenclature for acute renal disease as well, which has proved useful. In addition, the approach has led to advances in considering acute kidney injury (AKI) and CKD as interrelated syndromes. Nevertheless, the classification approach must not narrow the richness of clinical observation and diagnostic etiologic clarity that has characterized our field over the last century or so. This book covers broadly, but comprehensively, the history, pathophysiology, and practical approaches to diagnosis, patient care, and treatment issues in CKD. The scope of this book is limited to CKD—up to the initiation of end-stage renal disease (ESRD) care. This delineated population, however, entails the vast majority of CKD patients.

We have specifically solicited preeminent authors who are experts in the scientific underpinnings and the clinical implications of their chosen topics to contribute to the book. Basic biologic knowledge of course is the foundation of pathophysiologic approaches and clinical therapeutics. Over the past decade, enormous advances have been made in our understanding of the genetics of kidney disease. Our appreciation of an important cause of CKD as a common disorder that has Mendelian aspects as well has made us reassess approaches to screening and treatment and may revolutionize patient care, bringing personalized medicine to the CKD clinic. We understand CKD as a disease that varies across the globe, as a result of complex interactions of genetics and the environment, including poverty. Great strides have been made in our understanding of the breadth and natural history of pediatric CKD, in part because of the establishment of well-designed observational studies more than a decade ago. The role of common comorbidities such as diabetes mellitus and hypertension has been studied, but as with nutrition and its improvement in this population, much work remains to be done. Over the past two decades, the role of inflammation in CKD has been increasingly determined, but treatments using this knowledge have been elusive. Treatments of organ system complications of diminution in glomerular filtration rate (GFR) and uremia are at widely varying stages of development and maturity, and our evidence base in a few of these domains and in specific patient subpopulations is woefully inadequate. Although several pathways culminating in kidney disease have been identified, with diverse treatment opportunities and implications, we have learned to our chagrin that more treatment is not necessarily better treatment. We must develop and test novel therapies and interventions to prevent the initiation and ameliorate the progression of CKD. If and when the time comes, we must help our patients prepare for ESRD care. Advances in the clinical trials and basic sciences

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00001-2

associated with CKD may help us achieve our goals—improving the quantity and quality of life of our patients with CKD.

This book, we hope, will be a reference for all who want to know about or increase their knowledge regarding any or all aspects of CKD. As befits a 21st century publication, it is available in paper and electronic versions. There are specific chapters regarding considerations of certain patient scenarios or syndromes. Each chapter is grounded in the experience of a specific patient—whom we have seen, and that you have seen or will encounter over your career. Perusing the Table of Contents, a few chapters may at first blush seem duplicative, but they in fact approach problems from very different angles, with different expertise. The problems in CKD are necessarily interdigitated and overlapping. We did not want the authors to be artificially limited by chapter titles. It is hoped that each chapter is comprehensive and can stand on its own as a reference. We owe a great debt to the individual authors and thank them sincerely for their exemplary work. This book is after all just paper and bytes without them.

We set a high bar for this text. We intended the book to be patient-oriented, to deal with common clinical problems, but at the same time to be synoptic in scope, broadly inclusive, scientific, and useful as a reference for therapy. We believe that the authors have achieved this goal!

This book is knowingly and specifically titled *Chronic Renal Disease* to highlight its embedding in the scientific literature. "Kidney" is the Middle English term for the organ we love. "Renal" and "nephrology" (from the French and Greek, respectively) are scientific terms for use by professionals. As we grappled with "hypertension" compared with "high blood pressure" in our educational youth, we had to learn a nomenclature as we developed medical expertise. As "hypertension" and "high blood pressure" mean the same thing, "kidney" and "renal" are the same, while at the same time having different, important connotations. The intellectual mansion built by our predecessors, Bright, Addis, Peters, Richards, and Smith, to name a few, has many rooms. In keeping with the scientific focus of *Chronic Renal Disease*, all the book chapters are grounded in basic and clinical scientific principles, so the clinical characteristics and therapy of the individual topic under consideration in each chapter can be appreciated as a logical development from previous knowledge. Controversial issues are highlighted and dealt with clearly, directly, and emphatically. When there are gaps or deficiencies in the literature, or in our therapeutic knowledge—and there are—these are clearly acknowledged. This is a book for clinicians and scientists, not necessarily the lay public.

We hope this book will serve people interested in clinical CKD—ranging from medical students, to residents, internists, and pediatricians, to renal fellows, nephrology faculty, and practitioners. Educational principles have advanced as well over the last decades. We know that different readers, including those who tackle a subject from varying levels and perspectives, learn in different ways. Each chapter is accompanied by multiple choice questions. We conceived the questions as an integral part of the book—complementing the chapters, and functioning as both self-study tools and the point of departure for discussion in clinical conferences. The electronic version of the text and questions will help mobile users keep current on the go. In keeping with current notions of CKD, a set of abbreviations has been used consistently throughout the text.

We are interested in your feedback and constructive and other criticisms. Please let us know what you think of the book—including overall perceptions and comments regarding individual chapters. You are encouraged to contact us—with your kudos and concerns—by contacting our publisher. We hope you enjoy the book and find it useful simultaneously.

Paul L. Kimmel
Mark E. Rosenberg

INTRODUCTION TO THE SECOND EDITION

The reception of the first edition of *Chronic Renal Disease* has been very gratifying. The publication of the second edition allows one to consider the changes that have occurred in understanding and treating kidney disease over the last half decade, as well as factors that have not changed appreciably over time. In many ways, progress has been incremental, rather than radical.

The clinical utility of apolipoprotein L1 (APOL1) variants still remains to be determined, as do the underlying mechanisms of injury. We still do not know how to use knowledge regarding APOL1 variants to assist patients in making choices or how to craft preventive or therapeutic approaches, although prospective studies to evaluate the course of kidney transplant patients may hold promise.

We await the identification and validation of biomarkers that will enhance the value of measuring GFR and proteinuria, and their longitudinal assessments, in patients with CKD and at risk for developing CKD, to provide better prognostication of course and response to therapies, with hope but healthy skepticism. The clinical utility of these simple metrics developed in the early 20th century must be acknowledged as simply remarkable, while admitting that their robust value highlights the lack of progress we have been able to achieve in this field. In nephrology, we truly stand on the shoulders of giants.

The interrelationship between AKI and CKD appears to have been strengthened by evidence garnered over the last several years, but how to treat patients after the development of AKI, in the clinic after hospital discharge, to prevent the development of CKD, or to ameliorate its progression is unknown, and stands as a major gap in clinical practice.

The mediators of progression of CKD appear to be unchanged from those outlined in the first edition: pathogenic fibrosis as a result of attempts to repair injury, vicious cycles set up by components of the renin−angiotensin−aldosterone system, and the deleterious effects of inflammation and hypertension. Single nephron GFR (SNGFR), an important parameter for our understanding of common mechanisms of progressive kidney disease in animal models, can now be estimated in humans. Such studies have provided confirmatory evidence that hyperfiltration may truly be an important pathogenic factor in disease in our patients. Perhaps advances in imaging techniques will allow the measurement of SNGFR in humans in the near future.

Advances in addressing fibrosis remain stubbornly resistant to translation into clinical practice. Efforts to use kidney tissue to elucidate pathways of repair, injury, and progressive dysfunction are needed and in fact, beginning, but therapeutics in this field are in their infancy.

The SPRINT trial has led to advances in understanding approaches to treating hypertension in patients with CKD, but the precise sweet spot for the goal blood pressure, and optimizing the balance between therapeutic responses and adverse effects remain to be determined.

We do not yet know how to better address the ravages of inflammation in our patients, with either relatively prevalent causes of CKD or with the rarer but devastating multisystem autoimmune disorders, to achieve better outcomes. Advances in understanding the genetics of pediatric renal disease have not culminated in the development of therapeutic agents for children.

This edition of *Chronic Renal Disease* highlights the importance of consideration of pain in our patients, as well as the potentially devastating effects of opioid prescriptions in this population. More research remains to be done to improve the quality of life of patients with CKD.

Meanwhile, poverty and racism remain key social determinants of outcomes for CKD patients across the globe. The role of maternal deprivation in causing incipient CKD in offspring is increasingly appreciated. Improvements in these arenas, however, will take more than the combined work of physicians and patients to achieve salutary change and will require the efforts of policy makers across the globe, as well as the assent of the populations and politicians.

We have endeavored to highlight patient-centered issues in CKD, although we acknowledge that this is in large part an asymptomatic illness, until very late stages are encountered. Nonetheless, patients, physicians, and health systems must cooperate in the identification of CKD patients, and in the provision of the best treatments to all, in the US as well as across the globe.

Progress has been made in our understanding of the role of complement biology in the pathogenesis of C3 glomerulopathies and complement-mediated thrombotic microangiopathies, as well as possibly in other kidney diseases. Monitoring levels of circulating phospholipase A_2 receptor during therapy for membranous nephropathy has been a great advance in the treatment of glomerular diseases—truly a landmark biomarker, depending on a rigorous set of preceding basic and clinical studies. As precision medical techniques evolve, we have improved our therapeutic

approaches to patients with lupus nephritis, through well-designed clinical trials. Evidence points to the importance of tubulointerstitial disease as a key prognostic factor in this disorder.

Development of other novel therapeutics has however lagged. CKD is indeed a tough nut to crack.

Advances in research, in addition to the work done in basic and preclinical laboratories, include enhancement of the role of participants in research. As patients assist in designing the research, sit on Steering Committees and Data Safety Monitoring Boards, and help disseminate the triumphs and failures of our work, our joint ability to translate research into cures will be necessarily enhanced, by better research strategies and communication of results.

All these challenges remain as opportunities for future research, as well as for up-and-coming researchers, hopefully with patients as participants and partners in the enterprise.

We have invited authors who wrote well-received chapters to contribute to the second edition. We also have invited new authors to tackle problems and have tried to include new experts to weigh in on issues.

We have added chapters on CKD as a global challenge and enhanced consideration of the social determinants of CKD to a text which already covered the field comprehensively. In addition, this book has been expanded by chapters considering CKD in a global context, focusing on particular regions around the world. The scope of the second edition remains unchanged from the first: the history, pathophysiology, and practical approaches to diagnosis, patient care, and treatment issues in CKD—up to the initiation of ESRD care.

We have been pleased by the feedback regarding the beauty of this book, its scholarly excellence, timeliness, usefulness, and scope, from a spectrum of readers, ranging from medical students to Professors of Medicine. We thank our publishers, and Mara Conner, for guiding us through our first efforts, and Tari Broderick and Tracy Tufaga for making the second edition a reality.

This edition has the clinical multiple choice questions included in the text, which we hope will advance its use as a teaching tool, on many levels. This book is again available in paper and electronic versions to enhance its accessibility and accommodate different learning styles and needs.

Most importantly, we thank the exceptional authors of the first and second editions for producing an important, scholarly, and useful text. Once again, we note that this book is just paper and bytes without the input of the authors. As in the first edition, we sought to combine basic scientific underpinnings with best approaches to practice, to ensure a text that would be satisfying to a broad range of readers. We hope this second edition of *Chronic Renal Disease* will be useful for students, teachers, practitioners, and, perhaps most importantly, for our patients.

We have elected to continue with an old-fashioned title. New therapies build on the collected experience of many years of patient care, when chronic renal disease as terminology was *au courant*. We hope the conjoint perspective on the past and the future is one of the distinctive, unique aspects of this book. Once again, please let us hear from you about what you liked, and what you did not, about this second edition. We hope, again, you enjoy the book and find it useful as well.

Paul L. Kimmel
Mark E. Rosenberg

CHAPTER

2

From Bright's Disease to Chronic Kidney Disease

Steven J. Peitzman

Drexel University College of Medicine, Philadelphia, PA, United States

Abstract

In the 1820s and 1830s, Richard Bright of Guy's Hospital in London showed that dropsy (edema) when associated with heat-coagulable urine (albuminuria) predicted one or another form of pathologically altered kidneys at autopsy. His first cases were of hospitalized patients, but he later recognized and described indolent cases, what we would call chronic disease. Subsequent pathologists created classification schemes for chronic renal disease. In the late 19th century, a movement called "functional diagnosis" turned attention to the kidney's "power" in health and disease, using tests of excretion and concentration. Here arose terms such as "chronic renal failure," which persisted into the 1990s. The notion of renal "work" led to attempts to "rest" the presumably overworking nephrons of impaired kidneys with the low-protein diet. Key figures were Thomas Addis in the 1920–1940s and Barry Brenner in the later decades of the 20th century. Meanwhile, clinicians identified various causes of chronic kidney disease, only in recent decades including diabetes. Treatment from Bright's time onward aimed at reducing symptoms, such as edema, until concepts of hyperfiltration and the injurious effects of proteinuria prompted therapies (beyond diet) aimed at slowing progression. With a sense that the course of chronic renal disease if identified early might be favorably influenced (particularly by inhibition of the renal–angiotensin–aldosterone axis), nephrologists in the US and elsewhere through their organizations effected changes in nomenclature (e.g., "kidney" not "renal") and other measures to demystify and raise awareness of kidney disease. The hope was that earlier detection might allow interventions to slow progression and thus avoid or delay the need for renal replacement therapy.

BRIGHT'S DISEASE

In 1840, Richard Bright (1789–1858) (Figure 2.1), the first authority on proteinuric kidney disease, who unintentionally provided the disorder's earliest name, described what we would call a chronic case. The patient, presumably from Bright's private practice, was a "man, aged about 25, pale and scrofulous in appearance, and deeply pitted with the smallpox," who, in early March of 1835, "came to me, laboring under anasarca, and having albuminous urine." His illness began with a bout of diarrhea. As he recovered, the young man was able to spend a month in the country, but there "his legs began to swell, and anasarca proceeded up his thighs and abdomen." Bright found the urine "exceedingly coagulable" and "frothy on agitation." The patient tended to pass large, not small, quantities of urine. "I ordered him to adopt most strictly a milk diet, and to put on warm clothing, with flannel next to the skin." Because the stomach "sympathized" with the skin and kidneys, its irritability had to be quieted with an easy diet and gentle medicines such as bicarbonate of soda.

The patient improved briefly, with less coagulability of the urine, but in April he developed some cough, and his "skin inclined to be dry." Bright prescribed again some ipecac, as a diaphoretic and "expectorant." By June, the patient had improved greatly, his swelling was almost gone, though the urine still "froths much." Then, a painful "periosteal enlargement" appeared on his left shin, which the patient feared was the reappearance of "some venereal symptoms," presumably syphilis. Bright prescribed a concoction for this. By July 9, the patient was again "greatly improved," and the reader now learns that he was able to return to his work as a bookbinder. Bright desired him "to persist in all his cares and precautions [the restricted diet and flannel on the skin], to abstain from all spirits, and carefully avoid atmospheric exposures."

In February of 1836, Bright "saw him casually" and found that he still worked and had "no complaint to make." But the bookbinder admitted to a slight headache now and then. In addition, the patient himself (a craftsman who worked with his hands) tested his ankles from time to time and found that sometimes pressure of the finger made a pit. He slept well early in the night but became "restless" later and had to get up once to pass urine. The urine was "natural in quantity," but both

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00002-4

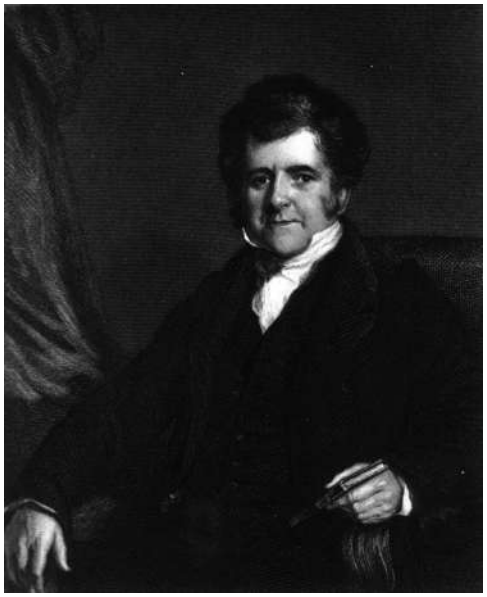


FIGURE 2.1 Richard Bright (1789–1858) as a physician to Guy's Hospital in London showed in the late 1820s that dropsy (generalized edema), when associated with albumen in the urine, predicted diseased kidneys if a patient with these findings came to autopsy. Later, Bright recognized and treated persons with more indolent, or chronic, forms of nephropathy. *Courtesy of the National Library of Medicine.*

heat and nitric acid detected that it was still "very decidedly coagulable." Thus, the disease persisted, though the patient felt generally well. Importantly (in Bright's assessment), the skin was "freely perspirable" and had been for so long now "that he forgets it ever was otherwise." But the young man had ceased taking his medications regularly. The pox-marked bookbinder chose to define himself as among the working, nonsick. However, if he felt some flank pain, or noted some other hint of his complaints returning, for a few weeks he took the powders Bright had prescribed, with "he fancies…the best effect." And he was always very careful to "guard his body with flannel next to the skin."

Then, in October 1839, the gentleman consulted Bright after a 4-year absence ("lost to follow-up" as we would say). He had continued in seeming good health with normal urine output until 3 or 4 months ago. Lately, he suffered "frequent calls to pass it after going to bed," and he complained of headache, nausea, and vomiting. A few days later, Bright was able to test the urine: it coagulated slightly to heat, but readily with nitric acid. He passed now "a large quantity of urine at night, but little in the day; his ankles had swollen slightly of late." Bright commented that "it is difficult to say" to what extent the medicines, or the precautionary measures of diet and clothing, had earlier contributed "to the relief of his disease." There is even a hint in Bright's language (the patient "fancies" the powders did him good) that the prescriber himself felt some skepticism about the actual power of the powders. Here, Bright concludes his patient's story, one that is, in many of its essentials, representative of chronic and slowly progressive proteinuric renal disease at any time. Of course, the story of Richard Bright's bookbinder offers arcane medications and strange therapeutic ideas, and a peculiar sort of pathophysiology involving "sympathy" between the skin, stomach, and kidney, by which a disturbance in one could effect injury and dysfunction in another. In the surprising manner by which old concepts sometimes return with new refinements, when I first wrote this chapter numerous articles in the medical literature refer to the "cross talk" between organs. We shall see some other furloughed ideas enjoy a revival within nephrology later in this chapter.

From a 21st century perspective, the patient described above had "CKD"—chronic kidney disease—and likely nephrotic syndrome. In Bright's day, most physicians came to call that malady comprising edema, albuminous urine, and a variety of symptoms Bright's disease (*morbus Brightii*, *maladie de Bright*), likely the first widely used medical eponym in the English language, and a term that endured roughly through the 1940s (with one revival, as will be seen). Richard Bright, working at Guy's Hospital in London during the era of clinical–pathological correlation, had shown that the urine of some patients with dropsy (edema or anasarca) was coagulable by heat (albuminuric) and that when such patients became available for autopsy, the kidneys showed one of several forms of alteration, particularly a "granular degeneration."

Bright published his discovery of proteinuric renal disease (and much else) in 1827 in the first volume of his magisterial *Reports of Medical Cases Selected with a View of Illustrating the Symptoms and Cure of Disease by a Reference to Morbid Anatomy*. This work included magnificent colored engravings and is a landmark in nephrology, pathology, and medical publishing. Richard Bright and Bright's disease represent the beginning of a modern understanding of diffuse, chronic renal disease. His fundamental findings linking edema, albuminuria, a set of symptoms, and structurally abnormal kidneys were soon confirmed by other workers such as Robert Christison (1797–1882) in Britain and Pierre Rayer (1793–1867) in France. Bright also came to recognize and describe virtually all elements of uremia including pallor, "lassitude," "hard pulse," vomiting, seizures, pericarditis, and cardiac hypertrophy.

Since, by purpose, the *Reports of Medical Cases* sought to correlate clinical findings in hospitalized patients with findings at necropsy, the renal cases are mostly of short duration, the outcomes necessarily fatal. The term Bright's disease long tagged the process of becoming ill through the kidneys. Perhaps owing to its

early association with the hospital and the dissection table, the disease maintained an ominous reputation in the popular mind as something close to a death sentence, a diagnosis that would extinguish all hope. ("CKD" is likely more obscure to patients than was "Bright's disease," though at least not as uniformly frightening.) Bright, however, came to recognize the more indolent, or chronic, picture, as seen in the dropsical bookbinder. In an article published in 1840, after much experience with renal disease, he offered the sound advice that "whatever remedy is given to overcome a disease so chronic and confirmed, must be administered with exemplary patience and perseverance."[1] That a diagnosis of Bright's disease could be compatible with decades of living was well understood by some later 19th century nephrological authors. British physician Lionel S. Beale in his popular treatise on renal disease assured his readers in 1870 that "with judicious management, a patient may live twenty or twenty-five years although afflicted with incurable renal disease."[2]

My aim is not a detailed exposition of scientific accomplishment, but rather an investigation of several themes. At times, nonetheless, the narrative will seem like a linear, almost inevitable, march toward the present—a type of story most distasteful to modern historians of science, who call its production *presentism*. A short account such as this recalls those individuals whose ideas survived, as it ignores the countless errors, fancies, and failed hypotheses—as well as possibly valid and useful practices which nonetheless sunk into the medical shadowland. The history of treatment of irreversible renal failure by dialysis or transplantation is not covered in this chapter in keeping with the overall intent of the volume. Once the patient has reached "end-stage renal disease," the failed kidneys themselves are no longer much under consideration, and are not being treated. A variety of historical accounts of dialysis and transplant, however, exist.[3–7]

For convenience, I will sometimes use the terms "nephrology" and "nephrologist" anachronistically—that is, before there was a defined specialty and before these words were even known.

PATHOLOGIES

In 1761, the Italian physician Giovanni Battista Morgagni (1682–1771) published his massive *De Sedibus, et causis morborum per anatomen indagatis libri quinque*, or, *On the Seat and Cause of Diseases Shown by Anatomy.* Into the later 18th and early 19th centuries, particularly in post-revolution Paris, but also in other cities of Europe, physicians fervently embraced clinical–pathological correlation as an objective method to study diseases. The object was to correlate patterns of findings in the ill person with localized structural abnormalities deep within the autopsied body. Classifications derived from morbid anatomy would replace nosographies based only on patients' symptoms.

Richard Bright, a major figure in this movement, added an early laboratory manifestation, albuminuria, to the complex. His initial 1827 publication, the *Reports of Medical Cases,* based on 24 cases, suggested three forms of deranged kidney structure, accompanying albuminuric dropsy. The first was a kind of softening with yellow mottling. The second form was one in which "the whole cortical part is converted into a granulated texture…" The third "is where the kidney is quite rough and scabrous to the touch externally, and is seen to rise in numerous projections not much exceeding a large pin's head … [and there is a] contraction of every part of the organ.…"[8] These three descriptions hold little meaning for the nephrologist of the 21st century, who rarely sees or touches a fresh diseased kidney. Bright allowed that the three forms might be only stages of one process, though he seemed to favor three categories. So from the first publication on the disorder, Bright's disease was not held to be one specific entity, not even by Bright.

Although not all subsequent physicians and pathologists would agree that Bright's disease was inflammatory in nature (as did Bright), the term "nephritis" entered use by 1840 for pathological classification, though the broad category of illness remained Bright's disease. The story of the superseding and competing classifications is far too complex to explore except in the broadest of strokes. The microscope came to supplant gross observation and the touching of the renal surface. The great pathologist and theorist Rudoph Virchow (1821–1902) in 1858 suggested "parenchymatous nephritis," "interstitial nephritis," and "amyloid degeneration." Briton George Johnson in 1873 proposed the separation of an acute form ("acute nephritis"), and three chronic varieties: "red granular kidney," "large white kidney" and "lardaceous kidney" (which is the same as amyloid kidney). William Osler (1849–1919) in his popular text *The Principles and Practice of Medicine* favored "acute Bright's disease," "chronic parenchymatous nephritis," and "chronic interstitial nephritis." Amyloid was dispatched to its own pathological category. Into the 20th century, the extremely influential monograph by Franz Volhard (1872–1950) and Theodor Fahr (1877–1945) published in 1914, *Die Brightsche Nierenkrankheit*, provided a fresh—but still trinitarian—organization: degenerative diseases, the "nephroses"; inflammatory diseases, the "nephritides"; and arteriosclerotic diseases, the "nephroscleroses."[9–12] Thomas Addis of Stanford University in the 1920s offered a modification of this last framework which gained some popularity: "hemorrhagic Bright's disease,"

"degenerative Bright's disease," and "arteriosclerotic Bright's disease."[13] It is likely significant that an arteriosclerotic category appeared in the early 20th century, probably an early reflection of our modern manner of becoming chronically ill (see below, "Causes"). Today, we find utility in thinking in terms of glomerular disease, tubulointerstitial disease, or vascular disease, but when appropriate seek a specific, causal diagnosis using biopsy or detection of marker molecules in blood or urine. Of interest here, *chronic* as applied to renal disease for a long time referred to the pathological appearance more than to a defined clinical course. Chronic in good part meant sclerosis or fibrosis. Now, a diagnosis of CKD emphasizes a uniform clinical picture and implies a disinterest in underlying structure. "CKD" repudiates pathology.

PHYSIOLOGIES

Into the 1830 and 1840s, Richard Bright assembled a team of colleagues and pupils at Guy's Hospital and its medical school to study albuminous kidney disease. For part of 1842, they were given two wards to use for their investigations, connected by what we would call a conference room and a small laboratory "fitted up and decorated entirely to our purpose." This arrangement, somewhat prefiguring the metabolic ward, was likely a first in Western medicine. Several of Bright's chemically adept colleagues were able to crudely measure urea retained in the blood of patients with diseased kidneys.[14,15] Physicians of this period of course understood the kidneys as excretory organs, the body's "filters" or "great depurators." One important waste discharged was urea, a nitrogenous product of ingestion of meats and other "proteid" foods. How the kidneys did this was unknown. In the same year that found Richard Bright and his colleagues collecting renal patients in two assigned wards of Guy's Hospital, a young William Bowman (1816–1892) published his paper "On the Structure and Use of the Malpighian Bodies of the Kidney" in which he deduced from the nephron's structure that the glomerulus creates filtrate (he did not use that word) which is then modified by the tubules.[16] Much debate for the next 80 years centered on the validity of filtration–reabsorption versus dominant secretion as the kidney's primary way of making urine.

Into the later 19th century, the center of gravity of medicine shifted from the deadhouses of France and England to the laboratories of Germany, where the experimental approach exemplified by Claude Bernard (1813–1878) and Virchow best took hold. In Germany, beginning in the 1870s, several physiologically minded physicians, most notably Ottomar Rosenbach (1851–1907), apparently fatigued with a half century of pathological classification, advanced a program known as "functional diagnosis." They pursued two objectives. One was to replace static classifications based on structure with a new exploration of what a diseased organ could, or could not, *do*—this information held to be more helpful in the clinic. The second, related notion, was to identify illness in a posited early functional phase, before the development of changes in an organ's fabric. Particularly, thought Rosenbach, "in chronic diseases it must above all be the object to recognize the disease in its very early stage, i.e., the incipient functional disorder."[17] The 21st-century physician likely finds this idea fanciful, even mystical—that some alteration in an organ's function precedes an identifiable change in its structure, especially if we reduce structure to the molecular level. But the belief persisted throughout the 19th century. Richard Bright thought it true of renal disease that a "functional derangement of the organ may sometimes precede the structural change for a period of many weeks and many months."[1]

The clinician-researchers who created functional diagnosis used the language of *work*. One German author wrote in 1903 that "one seeks to become acquainted with the organ when it is at work, and where one's chief desire is to learn whether this work is sufficient for the system or not."[18,19] An American physician's 1907 manual on kidney disease suggested "Nephritis clinically is a question of going beyond the limit of efficiency of the kidneys."[20] Very likely, this language and approach reflected the cultural environment of late 19th and early 20th century Europe and North America. Industrialization enlarged and spread as never before, and the machine (especially the steam engine) ruled. Not unexpectedly, the old idea of the body as machine gained new plausibility: one should analyze the physiological apparatus of an organ as one would measure the maximal work output of a machine. "Efficiency," applied to engines, and all else, became the byword of the Progressive Era, at least in the US.

Rosenbach and other German workers in functional diagnosis relied on the concept and phrase "insufficiency" (*insufficienz*), though it would acquire varying meanings. The method required challenging an organ to measure its "reserve"—a certain kind of test meal to the stomach, a period of brief intense exercise to stress the cardiac muscle, a urea load to assess the renal excretory work. "Relative insufficiency" existed if the organ could not fully call on its reserve (or "compensation") to deal with a challenge, whereas "absolute" or "complete insufficiency" denoted findings of inadequate function at baseline, such as nonprovoked retention of urea in the blood in the case of the kidney.[21] By 1934, the distinguished British authority on kidney disease Robert Platt (1900–1978) used the terms "renal

insufficiency" and "renal failure" to describe the two phases of impaired function.[22] Eventually, "chronic renal failure" ("CRF") came to somewhat loosely label any irreversible rise in blood creatinine concentration (or decrease in glomerular filtration rate (GFR)), even though patients with only small deviations from normal usually felt fine and did not consider themselves, nor their kidneys, to be failures, nor did their doctors, for the most part, though the seniors among us recall readily using the phrase. CRF endured until forcefully struck down by the nephrology discipline in 2000. Few nephrologists by then realized that the newly scorned nomenclature went back 100 years, to the forgotten movement called functional diagnosis.

During the era of functional diagnosis, reliance on creatinine measurement and even the confirmed reality of glomerular filtration were in the future. The kidney was probed as an excretory black box. The European workers saw its "work" as the excretion of concentrated solutes. The Hungarian physician Sandor (Alexander) von Koranyi (1866–1944) applied cryoscopy (measurement of osmolality by freezing point determination) and deemed a kidney "hyposthenuric"—literally "of low urine power"—if it did not adequately concentrate. Others assessed the kidney's ability to discharge urea, salt, or water after a defined load. A variety of investigators devised dye markers, whose excretory rate might aid in the functional diagnosis of renal disease. The most successful of these was the phenolsulfonphthalein excretion test of Leonard Rowntree and John T. Geraghty described in 1912, and mercifully shortened to "PSP" or "phthalein" once in regular use. The dye would be injected, then its appearance determined in timed urine collections. Delayed excretion indicated renal insufficiency. The PSP test was simple and remained in use into the 1950s, later in some areas.[23]

Into the first decade of the 20th century, renal function was tested, as described above, through some measurement of the urine. Urine was, after all, what the kidney made, and usually adequate amounts stood ready for use. Feasible techniques for measuring urea, or other solutes, in small samples of patients' blood did not exist before about 1910. In fact, drawing blood from a vein into a syringe rarely occurred. This changed quickly over the subsequent two decades with the invention of colorimetric techniques suitable for small samples by the Scandinavian Ivar Bang (1869–1918) and (more enduring) by Swedish-American Otto Folin (1867–1934), and the creation of gasometric assays by the American chemist Donald D. Van Slyke (1883–1971). These ingenious systems allowed fairly rapid measurement of urea, uric acid, creatinine concentrations, and acid–base parameters, and clearly aided the early growth of nephrology.

Once urea could be readily measured in urine and blood, early students of renal insufficiency such as the Frenchman Leon Ambard (1876–1962) and the Scots-born American Thomas Addis (1881–1949) learned that neither the simple measurement of retained urea in the blood, the urea concentration in the urine, nor even a day's total urea excretion seemed to reliably correlate with other indicators of the kidney's loss of excretory function or mass. They then tried to establish that some expression of urea excretion in relation to blood urea concentration might predict actual function. After much experimental trial, Ambard in 1910–1912 proposed a complex relationship among the concentrations of urea in blood (B) and urine (U) and the urinary flow rate or volume in a unit of time (V):

$$\text{Ambard's coefficient} = B^2/(UV\sqrt{V})$$

Thomas Addis (1881–1949) of Stanford University, one of the most comprehensive observers of renal disease at the bedside and in the laboratory, also in the 1910s set himself the same task—to find an expression of urea excretion that would answer the question "how can the extent of a renal lesion be measured in a living man?"[24,25] Through extensive and meticulous investigation, Addis and coworkers showed that under conditions of high urine flow, the ratio of the rate of urea excretion to the blood urea concentration (D/B as Addis called it in his 1928 Harvey Lecture, but more familiarly UV/B) correlates with functioning renal mass. Donald D. Van Slyke and coworkers at the Rockefeller Institute for Medical Research and its Hospital eventually arrived at a ratio essentially identical to Addis'. Supposedly, the term "clearance" arose in 1926, when Van Slyke, on a train to Baltimore where he was to lecture, hit on the "word definition": the ratio of urea in 1 h urine over the urea in 100 mL of blood really equals the volume of blood "cleared" of urea by the kidney in that unit of time.[26]

The 1920s saw an international outpouring of new findings and ideas in renal physiology and disease. In 1921, A. Newton Richards and colleagues in Philadelphia succeeded in micropuncturing the frog glomerulus and obtained results strongly supporting the filtration–reabsorption (Ludwig-Cushny) model of urine formation.[27] In 1926, the Danish physiologist Poul Brandt Rehberg (1895–1985) published his investigations nominating creatinine as a suitable "marker" for glomerular filtration, suggesting a value of between 100 and 200 mL/min for man.[28] Thomas Addis in the 1940s used creatinine clearance in his research and proposed a simple method for using serum creatinine concentration (S[Cr]) as an indicator of renal function in clinical work.[29] Probably not too many clinicians used Addis' fond method, which depended on picric acid and

naked-eye color matching, but by the 1950s creatinine (or its clearance) was beginning to replace urea in renal medicine. And so it has been ever since, with regression equations supplanting urine bottles. Chronic renal disease is defined as sustained elevated S[Cr].

The desire to understand the actual disorders of homeostasis caused by chronic renal disease invited more complex analysis than that seen with "functional diagnosis." Robert Platt and others recognized and worked to understand the remarkable adaptations which occur in the chronically diseased kidney (Figure 2.2). Such adaptations, he explained, until the most advanced phase of the disease, maintain normal blood concentrations of potassium, sodium, and phosphate and allow the daily excretion of these substances in amounts to match intake. Accounting for these "compensations" required, for the electrolytes, the concept of glomerular–tubular balance—the now familiar idea that in the face of diminished GFR, tubules adapt to reabsorb less sodium and phosphate and secrete more potassium. Platt described the essentials of these concepts in his Lumleian Lectures to the Royal College of Physicians of London in 1952.[30] Early in his lecture, he clearly stated that the "common structural basis" of "chronic renal failure" is "a diminution in the number of functioning nephrons," heralding a central and enduring principle.[30] (Of interest, many of the authors Platt cited were American. The post-World War II era saw the epicenter of medical research shift to the US, owing in good part to funding from the National Institutes of Health and major foundations, and postwar disruption in Germany.)

In 1960, Neal Bricker published his "exposition of the 'intact nephron hypothesis'," further advancing the notion that in chronic renal disease some nephrons are gone altogether (this is evident histologically), whereas remaining intact nephrons function normally, or adaptively.[31,32] Bricker in this paper tried to revive the term "chronic Bright's disease," because it "tends to group together a number of diseases of diverse etiology, differing pathogenesis and widely varying pathologic characteristics. A singular term implies the existence of a common denominator in these disease entities which supersedes their differences."[31,32] It is no anachronism to assert that Bricker's "chronic Bright's disease" is our "CKD." He added that "the more advanced the pathological process becomes, the less evident are the differentiating features."[31,32] This review from 1960 of course cited Platt, John Merrill,[33] and other experimental workers, as well as studies from his laboratory at Washington University in St. Louis.

In 1972, Bricker offered another "exposition," this time of the "trade-off hypothesis," based on studies of phosphate handling and parathyroid gland activity in "chronic progressive renal disease" or "the uremic state"[34] ("Bright's disease" was reconsigned to the past). The key notion, of course, was that an instrument of compensation for nephron loss—here the elevation of parathyroid hormone level to effect less reabsorption of phosphate—may come at a cost, in this case bone disease. Subsequent decades would see the various adaptations chased down to their oppressively complex molecular level—channels, signaling molecules, growth factors, and the genes for all of these. But the essential

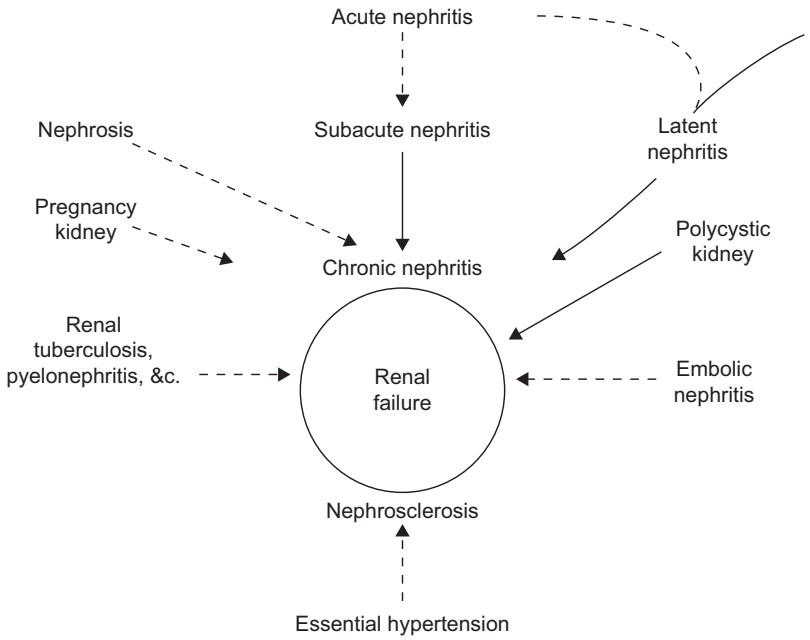


FIGURE 2.2 Robert Platt (1900–1978) was a leading 20th-century British authority on the kidney. Shown here is his concept of the etiology of chronic renal disease. Platt advanced the use of the terms "renal insufficiency" and "renal failure." Platt also was among the first to define the tubular adaptations to nephron loss. *From: Nephritis and allied diseases: their pathogeny and treatment (1934), diagram from p. 37. By permission of Oxford University Press.*

concept of a common set of adaptive physiological processes as the hallmark of the slowly failing kidney, regardless of cause, seemed well established by the early 1970s.

Alterations in tubular function allowed intact nephrons to adapt to overall loss of functioning renal mass. Both in this regard and in the study of normal physiology, academic nephrologists of the 1960 and 1970s mostly attended to the tubule. If you were not micropuncturing somewhere in a tubule to study transport, you weren't anybody. The tubule was the cognitive part of the nephron. Carl Ludwig, Arthur Cushny, and A.N. Richards handed down the concept of the glomerulus as a passive ultrafilter. But in 1982, nephrologist Barry Brenner, of Harvard Medical School and the Peter Bent Brigham Hospital in Boston, with his colleagues, published a review summarizing their micropuncture work in the rat glomerulus. Their proposal was that in chronic renal disease "remnant" glomeruli adapted by hyperfiltering to sustain GFR, but at the cost of further loss of nephrons from a sort of wear and tear injury.[35] The implications of this hypothesis will be discussed under "Treatments."

TABLE 2.1 From Bright's Disease to Chronic Kidney Disease

Repeated attacks of acute nephritis
Overindulgence in meat and canned foods
Intestinal indigestion
Overindulgence in alcohol, especially beer
Prolonged hypertension
Pregnancy
Loose kidney
Syphilis
Gout
Arteriosclerosis
Chronic lead poisoning
Long continued use of mercurial and certain drugs
Repeated exposure to severe cold

Selected causes of "chronic nephritis" from a representative manual of kidney disease from 1917, Oliver T. *Osborne's Disturbances of the Kidney* (Chicago: American Medical Association, 1917), p. 114.

CAUSES

Even if the pathophysiology of chronic renal disease varies little with underlying causation, etiology can matter. The correct diagnosis may critically guide treatment in early phases of some renal disorders—the approach to lupus nephropathy differs greatly from that for adult polycystic kidney disease, though both can go on to the chronic stage. General awareness of causes of kidney disease can suggest prevention: avoiding diabetes would mean fewer destroyed kidneys. Finally, both patients and doctors want to know "why did this happen?".

It has always been legitimate to ask if the cause of cholera is the *vibrio* microbe or a bad water supply, and similar questions. The meaning of causation has never been free of ambiguity and has grown more murky with increased reference to risk factors, genetic predisposition, and even, perhaps, probabilistic or Bayesian thinking. But from an earlier (and simpler?) time, a manual of kidney disease from 1917 included the causes of "chronic nephritis" shown in Table 2.1 (not all from that source are listed).[36]

Readers will tend to mentally rate these from the familiar, through the odd, to the bizarre. Obviously, ideas about causation change over time with shifts (or advances, if you like) in medical theory and practice. *Causes* necessarily come and go: radiocontrast nephropathy could not occur before the invention of radiocontrast. But factors beyond medicine can determine pathogenic causes, or at least the perception of causes. Richard Bright saw the causation of granular kidney this way: "An intemperate course of life, or some such cause, has predisposed the kidney to suffer. The patient has, in this state, been exposed to vicissitudes of temperature; the irritable kidney has immediately sympathized with the skin, and morbid action has been induced in that organ…"[37] Bright meant that excess alcohol ingestion sets the circumstances for renal injury, by way of the skin, when the miscreant endures exposure to *cold*, especially cold and wet. Such a chill would suppress the "insensible perspiration," whose flow early physicians deemed essential for health. Such suppression led, *via* "sympathy," to inflammation or congestion, or some sort of perturbation, in another organ such as the kidney. Hospitals in Bright's time looked after mainly the indigent and working poor—so Bright or his pupils readily obtained histories of drinking, and exposure to cold and damp (England, after all) on the way home from the gin house, or at outdoor labor. Arthur M. Fishberg (1898–1992) still took seriously the notion of cold as a cause of renal disease in his book *Hypertension and Nephritis* of 1930, even reviewing experimental findings that chilling the skin may indeed cause renal vasoconstriction. But soon this purported connection disappeared from books, though it persisted in the popular mind.[38]

The Philadelphia internist and author James Tyson (Figure 2.3) in 1881 held "habitual exposure to cold"

FIGURE 2.3 James Tyson (1841–1919), a professor of medicine at the University of Pennsylvania in Philadelphia, was author of *A Treatise on Bright's Disease and Diabetes*, published in 1881, with a second edition in 1904. This wood engraving from the first edition shows testing for proteinuria using acid precipitation. Tyson also published a widely used manual of urinalysis, a pamphlet on decapsulation as treatment of chronic Bright's disease, and an article on "cardiovascular-renal disease." *Author's collection.*

as a cause of chronic renal disease, but also *scarlatina.* That dropsy and Bright's disease could follow this ailment was clear in the early 19th century. This was, of course, poststreptococcal glomerulonephritis.[9] This cause could only enter the textbooks with the maturation of the germ theory (microbial understanding of disease) in the 1890s and beyond with the work of Louis Pasteur (1822–1895) and Robert Koch (1843–1910). Tyson also cited contemporary reports that malaria might cause renal disease and also listed gout and lead toxicity.

The very late 19th and early 20th centuries brought a novel etiologic possibility to chronic renal disease, which by 1900 in the US was the sixth leading cause of death.[39] William Osler in his *Principles and Practice of Medicine* of 1892 stated that a factor accounting for the prevalence of chronic Bright's disease among men in the US was "the intense worry and strain of business, combined as they often are, with habits of harried and over eating and a lack of proper exercise."[40] In a later edition (1909), he referred to these middle-aged men as the "victims of the strenuous life." A physician in Rochester, New York, Seelye W. Little (1867–1937) in his 1907 book on nephritis confidently identified the likely victim this way: "The ruddy, healthy looking man with a little too much abdominal fat, who is a good liver, who uses alcohol moderately but regularly, and who uses tobacco, is the type of man who in middle life or soon after suffers from certain forms of kidney disease." The cause of most chronic Bright's disease, Little continued, "is generally speaking and most often, simply civilization, especially with reference to food and drink."[20] Richard Bright in the early 1800s had associated renal dropsy with the lower-class working man or woman, the English charity patient too much given to the drinking of spirits, and subject in their daily labors to cold and wet. By the Gilded Age 1890s, chronic renal disease had risen to become a characteristic disorder of the affluent banker or industrialist, a mishap of capitalism at its other pole. As with many diseases, nephropathy, or at least ideas about it, arises within a social and economic framework.

Such a notion continues with diabetic nephropathy and the "epidemic" of diabetes and obesity of the late 20th and 21st centuries, clearly spreading around the developing world. Paul Kimmelstiel and Clifford Wilson described nodular glomerulosclerosis in eight persons with what would now be type 2 diabetes in a pathology, not clinical, journal, in 1936.[41] But even as late as the 1960 and 1970s, textbooks gave very little attention to diabetic renal disease—fewer pages than "hypokalemic nephropathy" in *Diseases of the Kidney* edited by Maurice Strauss and Louis G. Welt, one of the first multiauthor nephrology texts, published in 1963![42] Even the third edition from 1972 of the popular British title *Renal Disease* edited by Douglas Black contained only a few paragraphs on the subject.[43] With the increased availability of maintenance dialysis, at least in the US, by the 1970 and 1980s, it became clear that diabetes was a common substrate for renal failure, particularly when coexistent with hypertension in persons of African background. As with type 2 diabetes itself, diabetic renal disease seemed to be everywhere. Similarly, the number of journal articles dealing with diabetic nephropathy showed a sharp slope upward beginning in the 1980s, from 137 in 1979 to 722 by 2000.[44]

The grievously high prevalence of renal disease among some populations of African background found explanation in the revelatory discovery of variants for the apolipoprotein L1 gene that sharply raise susceptibility to nondiabetic nephropathies, especially focal segmental glomerulosclerosis.[45] An example of the interaction of genetic vulnerability and the social environment, but with the requirement of a microbe, is of course HIV-associated nephropathy. In large regions of Africa where poverty and endemic warfare hinder efforts at public health, partly preventable parasitic

diseases such as malaria and schistosomiasis account for much of the burden of renal disease.

The causes, understood broadly, of chronic renal disease, then, have come and gone with changing social and environmental conditions, the decline of old microbes but appearance of new ones, and, of course, refinement in medical thought and evolving ways of determining what is "evidence."

TREATMENTS AND PROGRESSION

By definition, chronic disease cannot be cured, so treatment of chronic renal disease has aimed at alleviating symptoms and avoiding further injury to the kidneys. Richard Bright saw exposure of the skin to cold as the inciting event for albuminuric renal disease, and in the 1830s recommended warm clothing and travel. Thereafter, seemingly so did every physician who wrote about Bright's disease for the next 80 or so years.

"On the subject of clothing," wrote Bright in 1836, "I have already said all that is necessary: let flannel be worn constantly, and every precaution be habitually adopted which may obviate the effects of whatever is calculated to chill the surface or check the perspiration."[1] Lionel Beale's text of 1870 insisted on "Shetland wool garments, socks, &c," and even specified a shop where such could be obtained year-round.[2] James Tyson in 1881 demanded "*woolen garments next to the skin*" (his italics).[9] Oliver Osborne in his manual of 1917 urged that "warm clothing be worn during the cold season."[36] And although recognizing that "the disease being, unfortunately, most apt to occur in those least able to submit to the absence from business," Bright had advised in his 1836 article that removal to "some decidedly southern abode…One of the more healthy of the West-India islands, as St. Vincent's, would probably be beneficial."[1] Bright admitted, however, that he so far had not encountered any patient who could actually *manage* this recommendation. Tyson, like Bright 50 years earlier, recommended "residence in a warm equable climate."[9] This seemed a favorite phrase, as presumably one author dutifully read (and copied from) his predecessors. Osler also liked "a warm equable climate" in the chapter on chronic Bright's disease in his 1909 edition, specifying Southern California.[11] Elwyn, as late as 1926, mentioned "a warm, dry, equable climate," though with minimal conviction.[21] Removal to a more salubrious place long had been advised for chronic diseases, particularly tuberculosis, but how many nephritic travelers ever found their "equable climate" remains unknown. For that matter, historians can know little about how well general doctors followed the experts' printed advice, or how diligently patients followed their doctors' prescriptions.

No doubt adhering to the plan proves most difficult for diet, which has been varyingly deemed an essential component of therapeutics since the time of Hippocrates. Virtually, all the authors referred to in this chapter, and many others who gave special attention to renal disease, recommended some restriction of meat. Broadly, they saw the main work of the kidney to be excreting nitrogenous waste, and thought it wise to rest the impaired organ. Many renal patients of the 19th and early 20th centuries endured periods of time on a milk regimen. French physiologist Fernand Widal (1862–1919) made clear the association of sodium with edema, so dropsical patients were told to limit salt and intake of water.

In the early decades of the 20th century, diet had become part of the technology of hospital medicine—hospital diet manuals of the 1930s could list as many as 50 diets for all manner of disorders and needs. In this context, Thomas Addis of Stanford (Figure 2.4), more than any other physician focusing on kidney disease, supported the low-protein diet with experimental work. As one example, he and his laboratory "group" (as he called his coworkers) showed that protein feeding induced hypertrophy in the rat remnant-kidney model, which he interpreted as a response to excess work. Addis came to believe that the need to excrete urea against an osmotic gradient constituted a major part of renal work, and that overworking remaining functioning nephrons would eventually destroy them. He

FIGURE 2.4 Thomas Addis (1881–1949) at Stanford University School of Medicine in the 1920–1940s studied chronic renal disease in the clinic and laboratory. He was among the first to recognize the progressive nature of chronic renal disease regardless of cause. Believing that remaining nephrons must suffer injury from an obligatory increased "work" in excreting urea, he designed and prescribed a low-protein diet. *Courtesy of the Stanford Medical History Center.*

prescribed amounts of protein precisely, to the gram, and with his wife, a dietician, did all that was possible to ensure compliance. Among those who succeeded was Linus Pauling, who became Addis' patient and friend when he developed nephrotic syndrome. Pauling's very capable wife, Ava Helen, learned quantitative dietetics as she assumed the responsibility for preparing meals. Pauling recovered completely, whether owing to his 14 years of protein restriction or to a spontaneous remission.[46–49]

The low-protein diet to slow the course of chronic renal disease did not fare well after Addis' death in 1949. But it was not discredited by any clinical trial; these did not exist at the time. Rather, a variety of incidental factors played a role.[47,48] With the 1950s came penicillin and other "wonder" drugs, the intensive care unit, and other new forms of medical technology. Dietary therapy came to seem archaic, and not very interesting. Thomas Addis published his findings and philosophy in an idiosyncratic (but in some ways delightful) book called *Glomerular Nephritis*,[25] at a time when the new and relevant appeared in journals. Addis, working in relative isolation at Stanford University College of Medicine (then in San Francisco), preferred his stable "group" of lab associates and volunteers, including his Chinese-American dieners. He did not raise up disciples. Ironically, the one major figure in nephrology who attributed his interest in the kidney to working with Tom Addis (as a senior student) was Belding Scribner, whose achievement was, of course, the creation of chronic dialysis. With the spread of maintenance dialysis, interest among practitioners centered on, and reward derived from treating patients when they reached the point of uremia, not so much on delaying this outcome. Meanwhile, nephrologists in American academia chose mainly to explore normal renal physiology, a preference readily catalyzed by funding from the National Institutes of Medicine.

Barry Brenner's experimental work showing hyperfiltration in remnant nephrons provided support for dietary interventions for patients with chronic renal disease. Supposing such hyperfiltration to cause further loss of nephrons, Brenner (who cited Thomas Addis) and colleagues coupled this concept with the established knowledge that GFR in mammals varies, to some extent, with protein ingestion. Brenner's group published their synthesis in the prestigious and widely read *New England Journal of Medicine* in 1982, and other researchers advanced compatible findings.[35] The low-protein diet reawakened. But confirming its effectiveness in slowing the progression of chronic renal disease proved elusive. The largest trial, the Modification of Diet in Renal Disease Study, produced equivocal results of sufficient complexity to sustain years of debate following the initial 1994 publication.[50] The availability of angiotensin-converting enzyme inhibitors in the 1990s stimulated a new model, and the benefit of "RAAS inhibition" to slow progression more easily gained acceptance following favorable trials. Along the way, hyperfiltration as culprit gave way to proteinuria (or albuminuria), as studies determined that protein passing through the glomerular sieve itself induces further damage. Protein restriction never vanished altogether, however, at least as a means for reducing symptoms in the patient with uremia.

The concept of "progression" merits further discussion. Physicians going back to Richard Bright understood that persons with renal disease could live and feel well for years or even decades, though eventually uremia (not a term used in Bright's era) would ensue. This was what is sometimes termed "tacit" knowledge: thinking that was not explicitly thought about, almost a given. Of course, there were exceptions, such as Thomas Addis. This changed in the late 1970 and 1980s, when "progression" became reified as something to be discussed, studied, written about, indexed, and taught. Brenner's 1982 paper, the full title of which was "Dietary Protein Intake and the Progressive Nature of Kidney Disease," no doubt played a role. In 1976, William Mitch and colleagues published data which supported the idea that a plot of 1/[creatinine], the reciprocal of S[Cr] and in effect a surrogate for GFR, declined linearly in any given patient with chronic renal disease.[51] Although their findings were challenged and the plot of 1/[creatinine] failed to win lasting use, "progression" had gained a credible scientific image in the form of a *slope*. Journal articles dealing with chronic renal disease containing the word "progression" in their title went from 1 in 1976 to 15 in 1983, then 30 or more by 1988. William Mitch edited a volume titled *The Progressive Nature of Renal Disease* which appeared in 1986.[52] Slowing progression became not only a fruitful subject for research but also a dominant objective of outpatient nephrology. By the mid-1980s, many nephrologists viewed the ceaseless march of patients into dialysis units with frustration, if not despair, and warmly embraced the optimistic notion that end stage might be deferred or even avoided.

Treatment to slow progression, more fully described in a later chapter, fits well into a practice known only to medicine of the last 50 years or so—the prescribing of many medicines for persons who feel well. This is, of course, exemplified by the treatment of hypertension, itself usually a component of management in chronic renal disease. Other medications such as phosphate binders, vitamin D analogues, and sodium bicarbonate have been added over the years to right abnormal laboratory values and (it is hoped) avoid complications, and to protect GFR.

Physicians caring for persons with renal disease have had to seek ways to deal with edema (dropsy), whether from nephrotic syndrome or eventual loss of GFR. The mainstays of traditional Western medicine, purgatives and emetics, probably *did* work for this need, if for little else, as their effect would be to eject salt and water from the body. The same would have been true for drugs considered sudorifics. Some of the plant agents used, or mercurial salts such as the popular preparation calomel (mercurous chloride), might have acted as saluretics. In the 19th century, some practitioners used a contrivance called the hot-air bath, a simple device to flow warm air onto the edematous patient. Clearly effective mercurial diuretics (mainly mercurhydrin) came into use, mainly for heart failure, in the 1920s, following an accidental discovery in 1919 by Alfred Vogl (1895–1973), while a medical student in Germany. He found that the injectable antisyphilitic Novasurol, a mercurial drug, induced a brisk diuresis. From work on sulfonamide carbonic anhydrase inhibitors came the first reliable oral diuretics, chlorothiazide, in 1958, and hydrochlorothiazide in 1959. These proved feeble, however, in the face of severe loss of GFR or intense renal sodium avidity. The first loop diuretic, furosemide, appeared in 1964, and soon won the market. Edema was never the same.[53,54]

CHRONIC KIDNEY DISEASE

Although certain interventions seemed able to delay the onset of terminal renal failure, nephrologists of the 21st century still regularly confronted persons presenting in emergency departments with end-stage disease, already in need of dialysis. Some never knew that they had kidney disease. More awareness and earlier detection seemed imperative. But the lay and professional leaders concerned with kidney disease realized that they first had to overcome a problem with "branding"—that is, among organs, the kidney suffered from poor name recognition and inattention. People contemplated their hearts and attended to their colons, but not their kidneys. A president of the American Society of Nephrology in his annual address at the 2002 meeting said:

> First, we have to market kidney disease better. The people who are interested in stroke, cardiovascular disease, and cancer have done a far more effective job than we have in delivering a message to the lay population and to practicing physicians than we have accomplished.[55]

Some thought that one obstacle to raising awareness of kidney disease was faulty language, particularly "chronic renal failure." Presumably, few persons knew what "renal" meant, and (this is my own speculation) "failure" seemed an unattractive term to the leadership of nephrology in the US. Americans do not like "failure." At the beginning of the "Executive Summary" of the important new set of guidelines for the detection and care of kidney disease from 2002, called the "K/DOQI" or Kidney/Dialysis Outcomes Quality Initiative, sponsored by the National Kidney Foundation, the reader sees this explanation:

> Why "kidney"? – The word "kidney" is of Middle English origin and is immediately understood by patients, their families, providers, health care professionals, and the lay public of native English speakers. On the other hand, "renal" and "nephrology," derived from Latin and Greek roots, respectively, commonly require interpretation and explanation. The Work Group [for these guidelines] and the NKF are committed to communicating in language that can be widely understood…"[56]

Thus, national leaders urged that the simple phrase "chronic kidney disease" shortened to "CKD" replaces "chronic renal failure" to label long-standing and usually progressive loss of kidney filtering capacity, regardless of underlying cause. To bring more order to nomenclature and to aid the development and use of practice guidelines, CKD was stratified into five stages based on GFR estimations from blood creatinine concentration values. "Staging" long had been used for cancer and heart disease. The demystification of language and the staging scheme rapidly won approval following the 2002 publications and presentations. "See-kay-dee" was instantly and everywhere on the lips of American nephrologists and particularly their fellows. Only careless old-timers would occasionally refer to "chronic renal failure." Understanding the merits of the new system and language, I (an old-timer) was still amazed at how quickly the new names and framework "took." Perhaps, hierarchy and authority play a greater role in the conduct of modern medicine and science than we like to think.

Levels of creatinine once deemed of no concern could now denote early-stage chronic renal disease. By extrapolation, eight million or more persons in the US in the early 2000s would have had a "disease" only recently looked on as relatively rare. In 2004, the Council of American Kidney Societies launched a "Chronic Kidney Disease Initiative" in part to further the detection of persons who would fit into an early stage based on blood creatinine concentration (albuminuria came to play a larger role in later revision of the stages).[57] Eventually, the concept spread internationally, including the genesis of a "World Kidney Day" in 2007.[58,59]

Despite the widespread acceptance of the new framework, at least in the US, the United Kingdom,

and Australia—or because of it—controversy and dissent arose. To what extent, it was fair to ask, were the new name and the CKD Initiative part of the identity politics of diseases, and indicative of a propensity for overmedicalization of society? As I worked on this chapter for the first edition, an "Analysis" article appeared in *BMJ* (formerly the *British Medical Journal*) within a "Too Much Medicine" series questioning the validity of diagnosing so many persons as renally diseased.[60] The authors hinted at the possibility of bias, given the pervasive ties between nephrology and its organizations, and the pharmaceutical industry. Those attending the planning workshop for the CKD Initiative had included nephrologists and nurses from private practice and medical schools, one patient, and (among others) representatives from the National Institutes of Health, a large health maintenance organization, Medicare, the dialysis industry, a national laboratory company, foundations, health policy institutes, and four pharmaceutical companies that helped fund the meeting. At least it cannot be denied that Bright's disease, under whatever new name, has come to dwell in an interlocking array of components making up the medical–industrial–governmental complex.

I have reintroduced the term Bright's disease at this point with a purpose. Earlier I suggested an analogy between "Bright's disease" and CKD. Both names referred, or refer, to generalized disease of the kidney, usually producing proteinuria and loss of excretory function, but without implying any cause or very specific pathological alteration. But they differ as well. Bright's disease existed in nature: persons had it and would swell up and eventually feel sick. A *specimen* could be identified, shown, and illustrated—the granulated kidney. Many physicians of Bright's era were skilled naturalists who gathered and classified specimens. Richard Bright particularly knew rocks; like his father, he was a thorough student of geology. Atlases of birds, plants, and minerals of the 18th and 19th centuries were probably the models for colored atlases of pathology, such as the *Reports of Medical Cases*. CKD, on the other hand, is a social construction within the enterprise of medicine and nephrology. It is not an illness born of nature, but rather a concept designed by a committee. Its purpose, as a name, is not to enable a sick person to know "what is my affliction?" but to categorize in a scientific and bureaucratic manner, and to enable the physician to more confidently prescribe a management which is not therapy. However valid might be the CKD concept and "Initiative," it is striking to consider that never before in the history of medicine has the measurement of one innocuous chemical in the blood effected the sudden creation of "disease" in millions of people.

And so it is not surprising, and historically fitting perhaps, that the revised KDIGO guidelines of 2012 gave more attention to proteinuria and some to the specimen—the changed kidney.[61,62] The work group, now notably international, saw albuminuria, investigated in the 1820s with spoon and candle, as having gained greater importance since 2002 not just as a marker of renal disease but also as a process whose inhibition could slow progression. As other "markers of kidney damage," the urine sediment, histologic findings, and "structural abnormalities detected by imaging" were highlighted within the "Criteria for Chronic Kidney Disease," though a GFR consistently less than 60 mL/min per 1.73 m^2 (GFR categories G3a-G5) still could alone qualify for CKD, and the fundamental framework for defining CKD and estimating prognosis remained largely a grid integrating eGFR and albuminuria. The 2012 revisions brought a stronger acknowledgment that cause can matter, though attention to etiology was perfunctory, acknowledging that once a person had an advanced degree of Bright's disease (or CKD!), cause mattered little, and virtually not at all once renal replacement therapy was needed. A qualification that a definition of CKD still based on abnormalities largely of function required "implications for health" likely arose from an acknowledgment that many persons, especially of older age, might have some degree of CKD, but no "D" in the traditional sense. A great deal of attention in the 2012 reworking—an immense deal of work of great value—still centered on GFR, estimating equations, and where cystatin fits in.

The historian of nephrology might hope that some of the regrounding in cause, sediment, morphology, and increased reliance on measurement of albuminuria, grew out of knowledge of the cumulative understanding of generalized kidney disease, but in fact Richard Bright turns up but once in the full report of the 2012 guideline published as a supplement to *Kidney International*, and that to a passing suggestion he made regarding the use of alkali in patients with albuminuric kidney disease. Thomas Addis shows up not at all. Still, though likely unintentionally, the modest concessions in the 2012 KDIGO guidelines did, however gently, draw the elusive disease/nondisease "CKD" back into the broadly understood and historically derived foundations of Western medical thought and practice which preceded the easy ability to measure markers in blood or urine. That is, disease is seated somewhere in a deranged organ (the "Paris Clinical School"); classification and knowing cause are important (nosology); and that always in front of us is not merely a GFR × albuminuria grid, but individuals worried about their health, or loss of it (Addis' book *Glomerulonephritis*). And so the author of this historical chapter hopes that the (probably few) users of this volume who stopped here first have found it a stimulating foundation for the timely coverage of science and practice which follows.

Note: Some of the ideas and content in this chapter appeared in my earlier publications on the history of renal disease, particularly my book *Dropsy, Dialysis, Transplant: A Short History of Failing Kidneys* (Baltimore: Johns Hopkins University Press, 2007).

References

1. Bright R. Cases and observations illustrative of renal disease accompanied with the secretion of albuminous urine. Memoir the Second. *Guy's Hosp Rep* 1840;**5**:101–61.
2. Beale LS. *Kidney diseases, urinary deposits, and calculous disorders: their nature and treatment*. ed. 3. Philadelphia: Lindsay & Blakiston; 1870. p. 84.
3. Cameron JS. *A history of the treatment of renal failure by dialysis*. Oxford and New York: Oxford University Press; 2002.
4. Peitzman SJ. Chronic dialysis and dialysis doctors in the United States: a nephrologist-historian's perspective. *Semin Dial* 2001;**14**: 200–8.
5. Hamilton D. *A history of organ transplantation: ancient legends to modern practice*. Pittsburgh: University of Pittsburgh Press; 2012.
6. Fox RC, Swazey JP. *Spare parts: organ transplantation in American society*. Oxford and New York: Oxford University Press; 1992.
7. Lederer SE. *Flesh and blood: organ transplantation and blood transfusion in twentieth-century America*. Oxford and New York: Oxford University Press; 2008.
8. Bright R. *Reports of medical cases selected with a View of illustrating the symptoms and cure of disease by a reference to morbid anatomy*, 2 vols. London: Longman, Rees, Orme, Brown & Green; 1827–31.
9. Tyson J. *A treatise on Bright's disease and diabetes*. Philadelpha: Lindsay & Blakiston; 1881. p. 79–84 (A summary of early classifications as of 1881).
10. Johnson G. *Lectures on Bright's disease*. London: Smith Elder; 1873.
11. Osler W. *The principles and practice of medicine*. 7th ed. New York: D. Appleton; 1909. p. 686–703.
12. Volhard F, Fahr T. *Die Brightsche Nierenkrankheit*. Berlin: Springer; 1914.
13. Addis T. A clinical classification of Bright's diseases. *J Am Med Assoc* 1925;**85**:163–7.
14. Peitzman SJ. Bright's disease and Bright's generation: toward exact medicine at Guy's Hospital. *Bull Hist Med* 1981;**55**:307–21. 318.
15. Coley NG. Medical chemists and the origins of clinical chemistry in Britain (circa 1750—1850). *Clin Chem* 2004;**50**:961–72.
16. Bowman W. On the structure and use of the Malpighian bodies of the kidney. *Phil Trans* 1842;**132**:57–80.
17. Faber K. *Nosography in modern internal medicine*. New York: Hoeber; 1923. p. 123.
18. Caspar L. *Functional diagnosis of kidney disease, with especial reference to renal surgery*. Philadelphia: Blakiston: tr. Robert C. Bryan and Henry L. Sanford; 1903.
19. Christian HA, Janeway TC, Rowntree LG. On the study of renal function. *Trans Cong Am Physicians Surg* 1913;**9**:1–53.
20. Little SW. *Nephritis: a manual of the disease commonly called nephritis or Bright's disease and of allied disorders of the kidneys*. New York: Grafton Press; 1907.
21. Elwyn H. *Nephritis*. New York: Macmillan; 1926. p. 27–33.
22. Platt R. *Nephritis and allied diseases*. London: Oxford University Press; 1934. p. 33.
23. Rowntree L, Geraghty JT. The phenolsulphonphthalain test in relation to renal function in health and disease. *Arch Intern Med* 1912;**9**: 284–338.
24. Addis T. The renal lesion in Bright's disease. *Harvey Lect* 1927-28; **23**:222–50. 229.
25. Addis T. *Glomerular nephritis: diagnosis and treatment*. New York: MacMillan; 1948.
26. Bradley SE. Clearance concept in renal physiology,. In: Gottschalk CW, Berliner RW, Giebisch GH, editors. *Renal physiology: people and ideas*. Bethesda, MD: American Physiological Society; 1987. p. 63–100.
27. Peitzman SJ. Micropuncture and the mechanistic kidney. *Bull Hist Med* 1991;**65**:366–75.
28. K. Thurau, J.M. Davis, and D.A Häberle, "Renal blood flow and dynamics of glomerular filtration: evolution of a concept from Carl Ludwig to the present day," In Gottschalk et al, Renal Physiology.
29. Addis T, Barrett E, Menzies JT. A clinical method for the approximate determination of serum creatinine concentration. *J Clin Invest* 1947;**26**:879–82.
30. Platt R. Structural and functional adaptation in renal failure. *Br Med J* 1952;**1**:1313–7. 1372-1377.
31. Bricker NS, Morrin PAF, Kime Jr SW. The pathologic physiology of chronic Bright's disease: an exposition of the 'intact nephron hypothesis'. *Am J Med* 1960;**28**:77–97.
32. Bricker NS, Morrin PAF, Kime Jr SW. Milestones in nephrology. *J Am Soc Nephrol* 1997;**8**:1470–6.
33. Merrill JP. *The treatment of renal failure*. New York: Grune & Stratton; 1955.
34. Bricker NS. On the pathogenesis of the uremic state: an exposition of the trade-off hypothesis. *N Engl J Med* 1972;**286**:1093–9.
35. Brenner BM, Meyer T, Hotstetter T. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N Engl J Med* 1982;**307**:652–9.
36. Osborne OT. *Disturbances of the kidney*. Chicago: American Medical Association; 1917. p. 114.
37. Bright R. On the functions of the abdomen, and some of the diagnostic marks of its disease. *London Med Gaz* 1833;**12**:378–84 (Gulstonian Lectures, 1833. Lecture II).
38. Fishberg AM. *Hypertension and nephritis*. Philadelphia: Lea & Febiger; 1930. p. 309–10.
39. Grove RD, Hetzle AM. *Vital statistics rates in the United States, 1940–1960*. Washington, DC: U. S. Department of Health, Education and Welfare; 1968. p. 79–82. PHS publication no. 1677.
40. Osler W. *The principles and practice of medicine*. New York: D. Appleton; 1892. p. 750.
41. Kimmelstiel P, Williams C. Intercapillary lesions of the glomeruli of the kidney. *Am J Pathol* 1936;**12**:83–96.
42. Strauss MB, Welt LG, editors. *Diseases of the kidney*. Boston: Little, Brown and Company; 1963.
43. Black D, editor. *Renal disease*. ed. 3. Oxford: Blackwell; 1972.
44. Cameron JS. The discovery of diabetic nephropathy: from small print to centre stage. *J Nephrol* 2006;**19**(10 Suppl):S75–87.
45. Freedman BI, Kopp JB, Langfeld CD, Genovese G, Friedman DJ, Nelson GW, Winkler CA, Bowden DW, Pollak MR. The APOL1 gene and nondiabetic nephropathy in African Americans. *J Am Soc Nephro* 2010;**21**:1422–6.
46. Peitzman SJ. *Dropsy, dialysis, transplant: a short history of failing kidneys*. Baltimore: Johns Hopkins University Press; 2007.
47. Peitzman SJ. Thomas Addis (1881–1949): mixing patients, rats, and politics. *Kidney Int* 1990;**37**:833–40.
48. Wasserstein A. Changing patterns of medical practice: protein restriction for chronic renal failure. *Ann Intern Med* 1993;**119**:79–85.
49. Kopple J. History of dietary protein therapy for the treatment of chronic renal disease from the mid 1800s until the 1950s. *Am J Nephrol* 2002;**22**:278–83.
50. Klahr S, Levey A, Beck G, Caggiula A, Hunsicker L, Kusek J, et al for the Modification of Diet in Renal Disease Study Group. The effects of dietary protein restriction and blood-pressure control

on the progression of chronic renal disease. *N Engl J Med* 1994;**330**: 877–84.
51. Mitch WE, Walser M, Buffington GA, Lemann J. A simple method for estimating progression of chronic renal failure. *Lancet* 1976;**2**: 1326–8.
52. Mitch W, editor. *The progressive nature of renal disease*. New York: Churchill Livingstone; 1986.
53. T.H. Maren, "Diuretics and renal drug development," in Gottschalk et al, Renal physiology, pp. 407–435.
54. Kaiser RM. The introduction of the thiazides: a case study in twentieth-century therapeutics,. In: Higby GJ, Stroud EC, editors. *The inside Story of medicines: a symposium*. Madison, Wisconsin: American Institute of the History of Pharmacy; 1997.
55. Blantz R. Reflections on the past, transitions to the future: the American society of nephrology. *J Am Soc Nephrol* 2003;**14**: 1695–703.
56. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease. *Am J Kidney Dis* 2002;**39**(2 suppl. 1): S1–266.
57. Parker III TF, Blantz R, Hostetter T, Himmelfarb J, et al. The chronic kidney disease initiative. *J Am Soc Nephrol* 2004;**15**:708–16.
58. Couser W. ISN and the 'new nephrology'. *Nat Clin Pract Nephrol* 2006;**2**:541.
59. Collins A, et al. World kidney day: an idea whose time has come. *J Am Soc Nephrol* 2006;**17**:600–1.
60. Moynihan R, Glassock R, Dous J. Chronic kidney disease controversy: how expanding definitions are unnecessarily labeling many people as diseased. *BMJ* 2013;**347**:f 4298.
61. Levin A, Stevens PE. For the Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members: Evaluation and Management of Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline. *Ann Intern Med* 2013;**158**: 825–30.
62. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:1–150.

CHAPTER

3

Classification of Chronic Kidney Disease—Historic Perspective: From Insufficiency and Failure to Chronic Kidney Disease

Joseph A. Vassalotti

Division of Nephrology, Department of Medicine, Icahn School of Medicine at Mount Sinai, and National Kidney Foundation, Inc., New York, NY, United States

Abstract

Chronic kidney disease (CKD) was introduced in 2002 as a set of clinical practice guidelines (CPGs) that defined the term, stratified it into stages on the basis of severity, and described its clinical course and complications. The result has been a paradigm shift which has not only transformed nephrology as a discipline but also affected the practice of medicine in general. A practical list of the most common risk factors to target for CKD testing includes diabetes, hypertension, family history of kidney failure, and age 60 years and older. The estimated GFR and urinary albumin:creatinine ratio guide detection, assess prognosis, and determine management. The majority of care for CKD patients will necessarily be delivered by primary care clinicians, as CKD is common, with a prevalence of approximately 10−15% of the population of industrialized nations. Nephrology referral is recommended for advanced CKD and is essential for preparation for renal replacement therapy and the delivery of optimal care during patients' transitions to kidney failure. Preliminary data support an impact of the CKD CPG, increasing clinical research and improving patient management. Health services research in the coming years will more clearly characterize the impact of the CKD CPG on patient outcomes.

INTRODUCTION

The treatment of end-stage renal disease (ESRD) with dialysis ultimately focused attention on the broader and more prevalent issue of chronic kidney disease (CKD). Started successfully by Willem Kolff in Kampen, the Netherlands, as an exploratory effort to sustain the life of acute kidney injury (AKI) patients in the years that followed World War II, dialysis then began to disseminate to other developed nations.[1] In the US, Shana Alexander's grim article in *Life* magazine in 1962, "They Decide Who Lives, Who Dies," described the medical miracle as well as the moral burden of a small committee that determined the allocation of scarce hemodialysis (HD) treatment slots.[2,3] Seattle's "life or death committee" was instructed to reject children and those over the age of 45 years for treatment.[2] The deliberations of this group of seven individuals regarding the selection of patients for treatment were chillingly arbitrary. By the mid-1960s, there were fewer than 800 Americans sustained by HD compared with 10,000 qualified patients.[1] This led the US government to commission a group chaired by the eminent renal physiologist Carl Gottschalk, charged with informing kidney failure treatment policy.[3] The 1967 report of the committee on CKD presciently used the term CKD for the first time.[4] "Prevention is obviously preferable to treatment of disease. Unfortunately, knowledge concerning the causes…is limited and this is an area in which an expanded research effort is required." The Gottschalk report recommended "a national treatment program aimed at providing chronic dialysis and/or transplantation for all of the American population for whom it is medically indicated."[4]

Dialysis and kidney transplantation evolved in the 1970s into a life-saving therapy for patients whose CKD had progressed to kidney failure.[3] For most of

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00003-6

the three decades that followed, the problem of kidney disease came to be viewed in the context of ESRD. As a result, what guided the research agenda and preoccupied national health agencies were the complications, costs, and disparities in access to dialysis for ESRD patients, who comprised less than 0.1% of the population. As administrative data from national dialysis registries accrued in the 1980s, it became evident that the care of patients with ESRD should have started in advance of preparation for renal replacement therapy (RRT), before the patients sustained the ravaging consequences of progressive loss of kidney function. This new concern at the turn of the millennium prompted the initial efforts at the definition, classification, and evaluation of CKD.[5–7]

Little can be done to promote patient awareness of a condition if the clinicians who care for the patients cannot achieve consensus on nomenclature, definition, or classification. This problem of confusing terminology was perhaps best described by Hsu and Chertow who listed 23 designations (Table 3.1) used to describe CKD in the American Society of Nephrology 1998 and 1999 abstracts.[8] Interestingly, Gottschalk's influential health policy report was neglected by nephrologists, because CKD was not included in the designations. In addition to inconsistent terminology, these 23 names were associated with a variety of definitions of kidney disease.[8]

TABLE 3.1 Terms Used to Describe States of Reduced Glomerular Filtration Rate in 1998 and 1999 American Society of Nephrology Abstracts[8]

1. Chronic renal failure
2. Chronic renal insufficiency
3. Mild renal insufficiency
4. Moderate chronic renal insufficiency
5. Moderate or advanced renal insufficiency
6. Severe renal insufficiency
7. Renal dysfunction
8. Severe renal dysfunction
9. Decreased renal function
10. Pre-end-stage renal disease
11. Low clearance (predialysis) patients
12. Pre-uremic
13. Renal failure
14. Renal disease
15. Renal insufficiency
16. Predialysis
17. Mildly elevated serum creatinine (S[Cr])
18. Chronic renal failure patients not on dialysis
19. Pre-end-stage chronic renal failure
20. Pre-end-stage renal disease chronic renal failure
21. Mild renal failure
22. Chronic renal disease
23. Chronic renal failure requiring dialysis

Reprinted with permission from Reference 8.

DEFINITION AND CLASSIFICATION OF CKD

In 2002, the Kidney Disease Outcomes Quality Initiative (KDOQI) workgroup co-chaired by Andrew Levey and Josef Coresh published the first guideline for a working definition of CKD, independent of the cause of the disease, based on the presence of either kidney damage (proteinuria, abnormal kidney biopsy, or imaging studies) or a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 for more than 3 months.[5] This clinical practice guideline (CPG) also proposed a classification of CKD based on severity, determined by the level of kidney function calculated from the S[Cr] and expressed as the estimated GFR (eGFR). The KDOQI guideline proposed the classification of CKD into five stages. Stages 1 and 2 represent covert disease requiring the presence of kidney injury (proteinuria, abnormal biopsy, or imaging studies). Overt disease is present when the eGFR is less than 60 mL/min/1.73 m^2 and is categorized into stages 3 (eGFR 30–59 mL/min/1.73 m^2), 4 (eGFR 29–15 mL/min/1.73 m^2), and 5 (eGFR <15 mL/min/1.73 m^2). The conceptual model of CKD used in proposing this classification is shown in Figure 3.1.[9] The five stages of CKD do

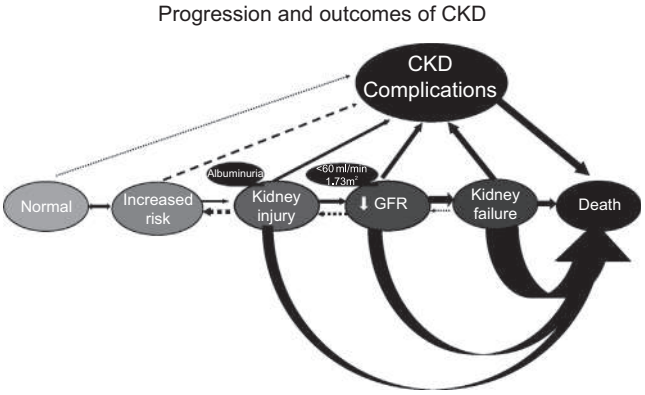


FIGURE 3.1 A conceptual model of the course, complications, and outcomes of chronic kidney disease (CKD). The ellipses represent the progressive stages and complications of CKD. The first two ellipses are antecedent stages representing cohorts at increased risk of developing CKD. The next two ellipses are flagged for the two hallmarks used in the definition and staging of CKD: albuminuria and a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2. The increasing darker shading of the ellipses represents progressive worsening stages of the disease. The ellipse at the top indicates the complications of CKD (anemia, mineral and bone disorders, hypertension, hyperparathyroidism). The arrows at the bottom indicate the risk multiplier effect of CKD on the outcome of coexisting comorbidities, principally cardiovascular disease. The gradually increasing thickness of the arrows connecting the ellipses represent the increased risk of the complications and multiplier effect of CKD as the disease progresses from one stage to the next. The dotted arrows connecting the ellipses indicate the potential for improvement from one stage to its preceding stage, due to treatment or variable natural history of the primary kidney disease. *Modified from Reference 9 with permission.*

not appear in this figure. Rather, stages 1 and 2 are grouped together and implicitly represented in the ellipse labeled "kidney injury" and flagged for albuminuria. Stages 3 and 4 are in the ellipse labeled "decreased GFR" and flagged <60 mL/min/1.73 m^2. The KDOQI guidelines were a major step forward in nephrology as they provided a uniform definition of CKD that replaced the inchoate, ambiguous, and descriptive terms that had been used previously. The common terminology and standardized classification provided new tools whereby kidney disease could be studied and the results compared across different parts of the world.[5,7]

In defining CKD as kidney damage for at least 3 months, the guidelines set the stage for the identification of another form of kidney disease, the potentially reversible form of AKI of less than 3 months' duration that is now the subject of its own guidelines.[10] Familiarity with AKI is essential for the care of CKD patients who are at high risk for development of AKI. CKD patients with AKI sustain poor morbidity and mortality outcomes and undergo the additional loss of residual kidney function and accelerated progression to ESRD.[10–12]

Based on available evidence then, the KDOQI guidelines documented the increased number of systemic complications (cardiovascular disease [CVD], hypertension, metabolic acidosis, mineral and bone disorders, and anemia), morbidity and mortality associated with declining eGFR, and described the greater risk of death from CVD than from progression to kidney failure and ESRD. During the decade that followed, epidemiologic data have validated, refined, and provided convincing evidence that CKD is common, underdiagnosed, treatable, and a major public health problem worldwide. CKD is more common than had been appreciated until then. The estimated prevalence of CKD in the general population is 10–15% and increases in high-risk populations (diabetic, hypertensive, obese, seniors), racial and ethnic minority groups (Hispanic Americans, African Americans, Asians-Pacific Islanders, American Indians), and in those with specific genetic predisposition.[13,14] There is now convincing evidence that the presence and severity of CKD adversely affects the outcome of other prevalent chronic diseases, notably CVD, diabetes, hypertension, and obesity. The reciprocity of these major chronic diseases in their interaction with CKD can be viewed as an overlap phenomenon whereby the presence of CKD emerges as a risk multiplier of the morbidity and mortality of other major chronic diseases, with the magnitude of detrimental effect related to the severity of CKD. Hence, it is important not only to detect the presence of CKD in other chronic diseases but also to evaluate its severity and progression, to estimate the impact of CKD as a modifier of outcomes of the underlying comorbid illnesses.[13,14]

Awareness of CKD

The guideline was a first step to promote awareness of CKD. Diseases for patients and public are defined to some degree by their treatment. The lay perception of dialysis as encompassing the disease was prominent before 2002 and may persist to some degree to this day. Among the general public, knowledge of kidneys and what they do is uncommon. Additionally, national surveys in the US suggest that CKD awareness among affected patients is only approximately 10%.[14,15] Moreover, perceived susceptibility to CKD is also low, including among low-income Americans with hypertension. The wisdom of the unifying simple name, CKD, including both elements of kidney function and kidney damage, has withstood the test of time. The workgroup understood the importance of promoting public awareness by selecting the word "kidney" of Middle English origin as immediately understood by patients in contrast to other terms such as "renal" and "nephrology."[5]

Limitations of the CKD Definition and Classification

By any criteria, the paradigm shift created by the 2002 KDOQI guideline for the definition and classification of CKD is a milestone in the evolution of nephrology, but was not without its limitations. Despite the effort exerted on developing the evidence base of the proposed classification, it was necessarily limited by the meager information then available. The guideline transformed the disease from a concern of nephrologists to one of importance to all clinicians, public health professionals, and clinical researchers. This broadening concept of kidney disease was, and to some degree remains, uncomfortable for nephrology, a clinical specialty focused on advanced disease and RRT. Thus, criticism of the definition and classification of CKD came mostly from nephrologists. These concerns included overdiagnosis of CKD supported by implausibly high prevalence, inaccurate methodology for eGFR determination and urinary studies, definition and classification independent of etiology, and labeling normal loss of kidney function with aging as a disease.[16,17] This controversy was an important derivative of the initial effort that provided the stimulus for new research and the accrual of new information necessary for guideline refinement.

Methodological issues associated with the initial definition of CKD were addressed in the following years and to some extent resolved. S[Cr] assays were standardized using isotope dilution mass spectroscopy reference measurement, the equation to calculate eGFR refined, and clinical laboratories integrated the reporting of eGFR in their results worldwide. The new

CKD Epidemiology Collaboration (CKD-EPI) creatinine equation of 2009 has proved more reliable in predicting morbidity and mortality outcomes of CKD.[18,19] Recently, serum cystatin C levels, in addition to creatinine levels, have been integrated into the formulas used for the estimation of GFR. The standardization and reporting of urinary albumin level is under investigation and awaits refinement.[19]

Overdiagnosis of CKD remains especially controversial, particularly in seniors. The reduction in quality-adjusted life years associated with a false-positive CKD diagnosis was considered by one interesting study that used Monte Carlo microsimulations in the transitions between six conditions: normal, false-positive CKD, true-positive or detected CKD, undetected CKD, chronic kidney failure, and death.[20] This study used the 2002 classification into stages and the eGFR by the Modification of Diet in Renal Disease (MDRD) Study equation. The assessment of the cost-effectiveness of eGFR reporting vs. S[Cr] reporting alone by the authors depends on the accuracy of the model. The assumption of one outpatient nephrology consultation for all detected and false-positive CKD may not be realistic. Nevertheless, the potential negative consequences of a patient being labeled with CKD should be addressed through ongoing investigation.

Apart from data on epidemiology and outcomes of CKD, the new evidence has revealed a strong graded and consistent relationship between the severity of the two hallmarks of CKD: increased albuminuria and reduced eGFR.[21,22] As a result the Kidney Disease: Improving Global Outcomes (KDIGO) group released a new guideline in 2012 for the staging of CKD that integrates albuminuria as a determinant of severity of the disease.[23] The new guideline maintains the definition of CKD as abnormalities of kidney structure or function, present for greater than 3 months, with implications for health of the individual, and refines the classification of CKD based on cause, eGFR, and albuminuria categories (CGA). The classification of CKD by the level of eGFR and albuminuria (the GA of CGA) and their impact on prognosis is shown in Figure 3.2.[23] Cause (C) is based on the presence and absence of systemic diseases and the location of the renal lesion (glomerulus, tubule, vasculature, cystic, genetic). Although albuminuria is now included in the staging of CKD, the evaluation of the individual patient with CKD should include other abnormalities in urinalysis that may be equally important and affect outcome of CKD, especially hematuria.[24]

The importance of considering the cause (the C of CGA) of CKD, now part of the staging, is highlighted in the conceptual model of CKD (Figure 3.1).[9] The dotted arrows in the figure reflect the potential for reversibility at each stage of CKD. This improvement may be part of the natural course of the cause of the kidney disease, but improvement may also be the result of early detection and proper treatment of individual cases. Thus, a patient

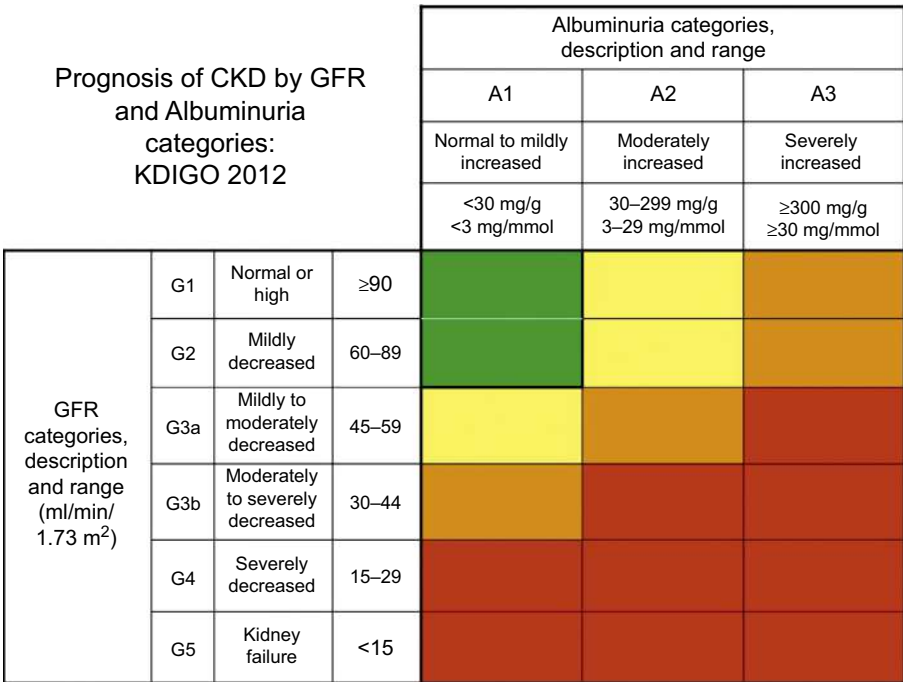


FIGURE 3.2 Staging and prognosis of chronic kidney disease (CKD) by glomerular filtration rate (GFR) and albuminuria. Green = low risk. If no other marker of kidney disease is present such as imaging or biopsy findings, then there is no CKD. Yellow = moderately increased risk. Orange = high risk. Red = very high risk. *Reproduced with permission from Reference 23.*

with severe hypertension and congestive heart failure, who presents with CKD and AKI requiring treatment with dialysis, can recover sufficient kidney function after control of the blood pressure and improvement of cardiac function to cease requiring dialysis, regressing to stage G3b or G4 CKD. The same argument can be made for all CKD patients whose kidney function is aggravated by poor management or that of the comorbid condition with which it overlaps, especially diabetes and hypertension. Improvement of kidney function with regression to an earlier stage is also achieved by proper therapy (for example, steroids, immunosuppression) in those with primary glomerular disease and the reduction of the magnitude of albuminuria with RAAS inhibitors. Finally, in those whose loss of kidney function progresses, it is essential to monitor and circumvent the complications of progressive CKD. The 2012 CKD CPG reemphasizes the importance of these complications, as well as the importance of their management and the need for early detection and intervention. The 2012 CKD CPG continues the trend of the original guidelines to shift the focus of care from exclusively nephrologists to primary care practitioners. A principal issue for clinicians is which population to test for CKD.

GENERAL POPULATION CKD SCREENING

There is insufficient evidence to support general population or mass screening for CKD, according to the US Preventive Services Task Force (USPSTF) and the American College of Physicians.[25,26] A fundamental cost-effectiveness study of CKD screening used a decision tree model to assess dipstick 1+proteinuria as the indication for therapy with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in the general population.[27] The prevalence of CKD stages was based on National Health and Nutrition Examination Survey (NHANES) III, and transitions from each stage to ESRD or death were estimated based on the presence or absence of diabetes, hypertension, and proteinuria. Risks and costs of the screening included additional tests (such as ultrasound or kidney biopsy), physician visits, and adverse effects of interventions (ACEIs, ARBs, or kidney biopsies). The risk reductions for all-cause mortality and ESRD were conservatively estimated as 23% and 30%, respectively, based on previous publications. This widely cited US study concluded that mass screening for proteinuria was unfavorable and costs $282,818 per quality-adjusted-life-year (QALY), with an incremental cost of $616 and a gain of 0.0022 QALY per person.[27] The Centers for Disease Control and Prevention (CDC) CKD initiative built on some of the assumptions of this study, with a similar but more complex model, adding cardiovascular morbidity (angina, myocardial infarction, and stroke), and using the more sensitive albumin:creatinine ratio (ACR) $\geq$ 30 mg/g test as the indication for ACEI or ARB therapy.[28] The CDC study confirmed general population CKD screening is not cost-effective.

TARGETED SCREENING

Both CKD guidelines recommended targeted screening for CKD rather than mass screening. Clinical and sociodemographic factors for susceptibility to and initiation of CKD were described in the original 2002 KDOQI guidelines (Table 3.2).[5] The 2012 KDIGO CKD update recommends regular testing of high-risk groups—those with diabetes, hypertension, CVD, structural renal tract disease, multisystem diseases with potential kidney involvement such as systemic lupus erythematosus, a family history of kidney failure, hereditary kidney disease, the elderly, those receiving potentially nephrotoxic drugs or those opportunistically found to have hematuria or proteinuria. A practical list of the most common risk factors is diabetes, hypertension, age 60 years or older, CVD, family history of CKD, and those with racial and ethnic indications. In

TABLE 3.2 Potential Risk Factors for Susceptibility to and Initiation of Chronic Kidney Disease

Clinical Factors	Sociodemographic Factors
Diabetes	Older age
Hypertension	US ethnic minority status (African American, Hispanic, Asian or Pacific Islander, and American Indian)
Cardiovascular diseases	
Obesity	Exposure to certain chemical and environmental conditions
Autoimmune diseases	
Systemic infections	Low income/education
Urinary tract infections	
Urinary stones	
Lower urinary tract obstruction	
Neoplasia	
Family history of chronic kidney disease	
Recovery from acute kidney injury	
Reduction in kidney mass	
Exposure to certain drugs	
Low birth weight	

Reprinted with permission from Reference 5.

certain parts of the world, environmental exposures and nephrotoxins play a role. Herbal exposure or medicinal use results in aristolochic-acid nephropathy as a common regional cause of CKD in Asia and the Balkans.[29] Occupational heat exposure, water and solute loss in combination with nephrotoxin exposure is the leading hypothesis for the cause of Mesoamerican nephropathy.[30–32]

Targeted Screening: Diabetes, Hypertension, and Old Age

CKD risk conditions were assessed in a 1999–2004 NHANES population of over 15 thousand subjects with weighted logistic regression and a branching diagram for those under 60 years of age to evaluate eGFR <60 mL/min/1.73 m^2 and ACR >30 mg/g distribution.[33] The study revealed a prevalence of CKD of 39% for those aged over 60 years and older compared to 9.3% in those aged 20–59 years, supporting the importance of screening seniors. In individuals aged 20–59 years, CKD prevalence was greater for participants with diabetes (33.8%) than for those without diabetes (8.2%). Using hypertension in the decision tree detected CKD in more young participants with both diabetes and hypertension (43%) than for diabetic participants without hypertension (25.5%), while that of nondiabetic participants with hypertension yielded 15.2% vs. 6.8% for nondiabetics without hypertension. The CDC cost-effectiveness analysis also supported screening populations with diabetes and hypertension.[28] Hence, the recommendation is to target the population with diabetes, hypertension, and those 60 years and older for screening.

In a 1995–1997 cross-sectional survey of more than 65,000 Norwegian individuals assessed for risk factors and eGFR but not ACR, 3069 (4.7%) had an eGFR <60 mL/min/1.73 m^2, requiring 20.6 people (95% confidence interval (CI) 20.0–21.2) to be screened to identify one case.[34] Targeting diabetes, hypertension, and age greater than 55 years required screening 37.1% of the general population to detect 93.2% (95% CI 92.4%–94.0%) of individuals with CKD stages 3–5, with the number needed to screen 8.7 individuals (95% CI 8.5–9.0) to identify one case.[34] These conclusions of the Norwegian study are remarkably consistent with those of the NHANES analysis.

Targeted Screening: CVD

The interactions of CKD with CVD led the American Heart Association in collaboration with the National Kidney Foundation to recommend CKD screening of all patients with CVD.[35] However, in the NHANES study, the addition of CVD as a risk factor did not contribute significantly to the CKD screening yield of people with diabetes, hypertension, and age 60 and older.[33] In the Norwegian cross-sectional study, broadening the scope with CVD in addition to diabetes and hypertension increased identification of CKD from 44.2% to 57.5%. The alternative addition of age greater than 55 years improved the detection of CKD from 44.2% to 93.2%.[34] Thus, the prevalence of self-reported CVD in young individuals without diabetes and hypertension is probably too low (1.9% in the NHANES 1999–2004 population under age 60 years) to qualify CVD as an additional primary risk factor. Taken together, these studies suggest that if screening for CKD among the top three risk conditions (diabetes, hypertension, age 60 and older) is widely applied, screening of CVD patients without those conditions does not contribute significantly to the detection of kidney disease in the population.

Targeted Screening: Family History of CKD

Data on family history of CKD have not been collected in NHANES, and most of the available epidemiologic data derive from the subset of CKD patients treated with HD, making it difficult to assess the significance of this as a risk factor. Several regional US studies of ESRD patients have demonstrated a positive family history of ESRD as a significant risk factor for CKD, even after excluding etiologies with Mendelian inheritance.[36,37] Regional US ESRD data show that 22.8% (5901/25,883) of in-center HD patients report having a family history of ESRD.[37] There were positive associations for female gender, earlier age at ESRD onset, and a negative association with white race. Another study from this region showed that African Americans treated in HD units were 6 times more likely to have a family history of ESRD, yet they were less likely (37 vs. 50%) than individuals of other races to recognize the importance of family history as a CKD risk condition.[38] Although family history of CKD is clearly important in selected populations, it requires further study before it can be broadly adopted as a primary target group in screening for CKD.

Targeted Studies: Ethnic and Racial Minorities

Disparities in the prevalence of CKD affect African Americans, Hispanics, Asian-Pacific Islanders, and American Indians who experience a higher incidence of ESRD than whites. Although the reasons for these disparities are complex, the higher prevalence of type-2 diabetes and hypertension in these ethnic and racial groups are important contributors. Genetic factors may

also be contributors, particularly in African Americans in whom APOL-1 gene variants or gene−environment interactions play a role in susceptibility to CKD.[39] Therefore, targeting diabetes and hypertension in screening for CKD will substantially address the disparities observed in these vulnerable populations.

IDENTITY OF CKD IN PRIMARY CARE

There is little agreement among practitioners regarding a number of pivotal areas, including the definition of CKD (particularly for the elderly with eGFR of 45−60 mL/min/1.73 m^2 in the absence of albuminuria or stage G3a, A1),[16,17] the key elements of primary care management of stages 1−3 CKD, the indications for nephrology consultation,[40] and the scope of the respective roles and responsibilities of the primary care clinician and the specialist following consultation. In the absence of consensus in the therapeutic community, CKD has less of a clinical identity for detection and management than the longer-established chronic diseases such as diabetes and dyslipidemia. First, the distinction between making a diagnosis of CKD and needing to refer a patient to a nephrologist is underappreciated. Secondly, the majority of patients in a primary care practice will need to be managed without nephrology consultation. Lastly, one approach to defining the importance of detection and management of CKD in primary care is to focus on blood pressure control, diabetes management, and patient safety.

TABLE 3.3 Factors to Consider in the Implementation of Individualized Blood Pressure Targets in Chronic Kidney Disease Method of Blood Pressure Assessment (Office, Home, 24-hour Ambulatory)

Cardiovascular risk
Albuminuria
Age
Risk of adverse effects of low BP target (hemodynamic acute kidney injury, falls, syncope)
Orthostatic blood pressure (seniors, diabetic neuropathy)
Shared decision-making

Blood Pressure Control in CKD

Cardiovascular risk reduction is the major incremental benefit of the 2017 CPG recommendation for a lower blood pressure target of ≤130/80 mmHg,[41] based on SPRINT[42] and the standard glycemic arm of the ACCORD BP[43] trial results. Importantly, a target for each patient should be individualized with a suggested approach that incorporates the method of blood pressure measurement with cardiovascular benefit and side effects (Table 3.3). The SPRINT protocol included monthly visits during the titration phase to achieve the lower BP target, making more frequent visits at least initially a consideration for clinical implementation. Based on high level evidence, ACEIs or ARBs should be used for A3 level albuminuria and hypertension.[23,41] Figure 3.3[44] describes potential combinations for the first

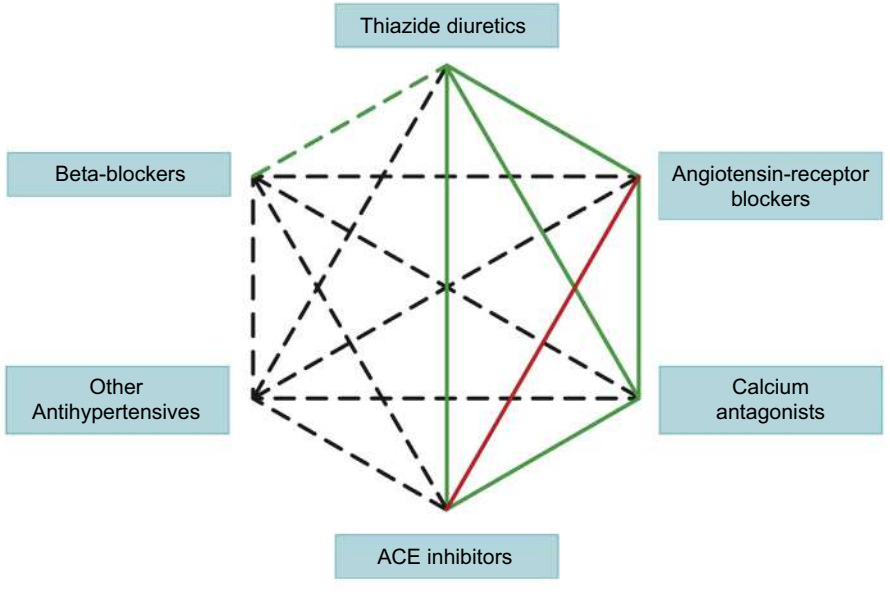


FIGURE 3.3 Possible combinations of classes of antihypertensive drugs. Green continuous lines: preferred combinations; green dashed line: useful combination (with some limitations); black dashed lines: possible but less well-tested combinations; red continuous line: not recommended combination. Dihydropyridine calcium antagonists should normally be combined with beta-blockers. *Reprinted with permission from Reference 44.*

three drugs, incorporating avoidance of dual ACEI and ARB therapy, based on safety signals for AKI and hyperkalemia in randomized trials. For resistant hypertension in CKD, mineralocorticiod receptor antagonists are recommended as fourth line drug therapy, based in part on the results of the PATHWAY-2 trial. The presence of obstructive sleep apnea and counseling regarding high dietary sodium intake as well as other lifestyle changes should be considered.[45] The achievement of an individualized BP target of less than 130/80 or 140/90 mm Hg could arguably be the single most important intervention to slow CKD progression and reduce both cardiovascular events and cardiovascular mortality.

Diabetes Management in CKD

Based on trial data, a hemoglobin A_{1c} (HbA_{1c}) target of approximately 7% is recommended in CKD, with a higher target for those with limited life expectancy, or an increased risk of developing hypoglycemia.[46] In addition to cardiovascular risk reduction, the benefits of glycemic control in CKD include reduced incident and progressive albuminuria and reduced loss of kidney function over time. Metformin is considered the first-line agent for type-2 diabetes but should be avoided at eGFR less than 30 mL/min/1.73 m^2, according to the FDA, because of the risk of development of lactic acidosis.[47] In addition, recent studies (EMPA-REG OUTCOME,[48] CANVAS Program,[49] and DECLARE[50] randomized trials) have demonstrated the antidiabetic drug class sodium-glucose co-transporter-2 (SGLT-2) inhibitors may play a unique role in the treatment of diabetes to slow loss of eGFR compared with placebo and reduce incidence and worsening of albuminuria. This drug class also has efficacy in reducing heart failure admissions, a complication that is enriched in populations with low levels of eGFR. Future investigations (CREDENCE & DAPA-CKD) and regulatory decisions are needed to address current FDA package inserts that restrict the use of these agents for lower levels of kidney function (eGFR <45 mL/min/1.73 m^2 for canagliflozin and empagliflozin and <60 mL/min/1.73 m^2 for dapagliflozin), and incorporate the risk of amputation and other side effects to more precisely define the population that will benefit. Lastly, the EMPA-Kidney study will test the efficacy of reducing CKD progression and cardiovascular mortality of empagliflozin in a randomized double-blind placebo-controlled trial of 5,000 people with CKD, with or without diabetes.[51]

Patient Safety in CKD

Patient safety hazards posed by CKD include drug prescription errors, contrast exposure, electrolyte disorders, inadequate CVD detection and management, and

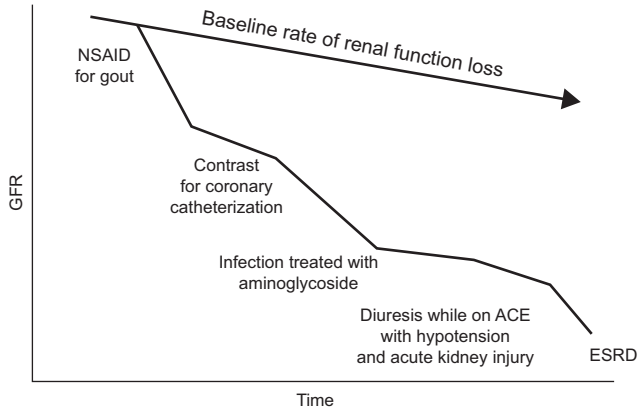


FIGURE 3.4 A theoretical patient with chronic kidney disease (CKD) is subject to several events that might be classified as preventable and related to patient safety. These events contribute to an accelerated rate of kidney function decay. Abbreviations: *ACE*, angiotensin-converting enzyme; *ESRD*, end-stage renal disease; *GFR*, glomerular filtration rate; *NSAID*, nonsteroidal antiinflammatory drug. *Reprinted with permission from Reference 52.*

therapeutic errors in managing effective arterial circulatory volume.[45,52–54] These hazards often result in hospitalization and AKI. Multiple insults leading to AKI are potentially preventable (Figure 3.4).[52] For example, arguably, intravenous therapy with either isotonic sodium chloride or sodium bicarbonate can reduce the risk of contrast-induced AKI in patients at risk, but acetylcysteine is of no benefit.[10,55] Medication dosing that considers the level of eGFR is the most actionable patient safety hazard, as many drugs are cleared by the kidneys.[23,52] Medications that require caution in prescribing include antihypertensive agents, analgesics (NSAIDs and opioids), antimicrobials, hypoglycemics, dyslipidemia therapy (statins and fibrates), chemotherapeutic agents (for example, cisplatin, melphelan, and methotrexate), anticoagulants (direct oral anticoagulants, low-molecular weight heparins, oral thrombin inhibitors, oral Factor Xa inhibitors, and warfarin), and others.[23,56] Vascular injury that limits options for subsequent HD access frequently occurs in the course of hospitalization of CKD patients and should be avoided.[57] Patient safety is a particularly important consideration in the elderly with CKD in whom comorbidities, frailty, and personal preferences may make conservative management a reasonable approach.

CLINICAL RESEARCH

Assessing the impact of the CKD guideline on clinical research is difficult to quantify, but a few of many potential examples follow. PubMed citations for the acronym CKD between 2001 and 2018, a crude surrogate marker of influence, have grown dramatically from 9 to 3,461,

respectively. Impressive progress has been made in what is perhaps the largest clinical research collaboration ever in nephrology, the CKD Prognosis Consortium.[21,22,58] International diagnosis codes incorporated the definition and classification of CKD into stages (585.X & N18.X), by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM),[59] presenting new opportunities for clinical research. Health services research can assess the impact of eGFR reporting and detection of CKD on care and outcomes.

Estimated GFR Reporting

Adoption of eGFR reporting worldwide resulted in an immediate form of clinician education regarding kidney function following every S[Cr] test, which in some cases included CKD guideline content. However, the impact of the CKD CPG is still in early phases of assessment. Clinical decision support is the implementation method of the future to bridge the gap between the evidence synthesized by CPGs and patient care delivered through the electronic health record in a cyclical process.[60]

Kagoma and colleagues evaluated the implementation of one of the key recommendations of the first CKD guideline[61]: to assess kidney function with eGFR in routine clinical practice, reserving 24-hour urine creatinine clearance collections for confirmatory testing.[5] The monthly prevalence of 24-hour urine collections in an adult population of more than 8 million patients in the province of Ontario, Canada, from 1999 to 2009 was used to investigate the impact of two major interventions: the CPG publication in February 2002 and the introduction of eGFR reporting in all outpatient laboratories in January 2006. The authors assumed a 3-month lag period following each of these events to assess variation based on previous publications.[62,63] Each eGFR value, based on the MDRD Study equation, was accompanied by one of five corresponding prompts relating the level of kidney function to CKD. For example, results between 30 and 60 mL/min/1.73 m^2 were followed by "consistent with moderate chronic kidney disease if result confirmed by repeat assessment, with persistence for 3 months or more."[61] This form of clinical decision support assists interpretation with direct incorporation into the clinical workflow for each laboratory result. The results from Canada's most highly populated province showed no significant change following the publication of the KDOQI CKD guideline, but a 23.5% reduction in 24-hour urine collections after eGFR reporting with prompts, from 44.6 to 34.1 per 100,000 population, which remained significant after adjustment for sex and age ($p < 0.0001$). The obvious benefits are improved patient convenience and increased accuracy of kidney function assessment for clinical practice, using eGFR rather than creatinine clearance. The estimated cost benefit was small, $5651 per month in reduced laboratory fees for 24-hour urine testing, based on a per-test cost of $10.35. The inability to distinguish the impact of eGFR reporting from the impact of the prompt is worth noting. An ongoing area of investigation is the assessment of the cost-effectiveness of CKD interventions using simulation models, observational data, and clinical trials.

Detection of CKD

Rather than assess the risks and benefits of screening, the important health services research question is whether or not primary care detection of CKD affects outcomes. There will never be a randomized trial of CKD screening, because withholding screening from a control population is neither feasible nor ethical. Preliminary regional data demonstrate that patients who have laboratory evidence of CKD that is detected by their primary care clinician are more likely to have evidence-based care (avoidance of unsafe medications, use of ACEIs or ARBs when indicated, and appropriate referral for nephrology) than individuals who have undiagnosed CKD.[64] An outpatient study by Wyatt et al. from the US Veterans Affairs Medical Center revealed small but significant improvements in CKD detection using administrative data collection for diagnosis codes before and after reporting (14.6–21.5%).[65] Although the comparison between detected and undetected CKD did not influence the achievement of target blood pressure (32.9–34.4%), the use of the appropriate CKD diagnostic code was significantly associated with urinary protein testing (39.8%–54.2%) and use of ACEIs or ARBs.[65]

Drug Prescription Practice and Patient Safety

Three of four studies demonstrated small but statistically significant increases in ACEI or ARB use following eGFR reporting.[63,65,66] The authors of the negative study speculated high baseline rates of these drugs might be a possible explanation for lack of differences.[63] A systematic review of drug prescribing practices that considered the level of kidney function using clinical decision support showed promise overall, with the limitation of heterogeneous design across studies.[67] A UK population study showed over 4000 fewer NSAID prescriptions following eGFR reporting (adjusted odds ratio 0.78). Furthermore, follow-up data confirmed that the 1511 individuals with eGFR <60 mL/min/1.73 m^2 experienced significant improvement in kidney function following withdrawal of NSAIDs.[68]

Nephrology Consultation

In the US, in 2016, late referral for nephrology services remains surprisingly common, as 35.4% of incident dialysis patients had little or no prior nephrology care before initiating dialysis, and only 36.8% received care from a nephrologist for at least 12 months before the start of RRT.[69] The effects of eGFR reporting on nephrology consultation may not be the best metric at this juncture in the absence of consensus,[40] despite comprehensive CPG recommendations (Table 3.4).[23] A recent systematic review of the impact of eGFR reporting with and without clinical decision support demonstrated an overall increase in nephrology consultations in the range of 13%–270% from 13 of 16 studies.[66] Most studies also showed a change in the distribution of patients, including more elderly and women, as would be expected on the basis of the variables of the eGFR equation. In the publications that provided data, there was a trend for a decrease in stages 1 and 2 consultations with increases in referrals in stages 3 to 5.[66] Studies were heterogeneous with regard to the predefined use of appropriate nephrology consultation indications. One study used discharge from nephrology care within one year of consultation as the definition of an inappropriate use of resources.[66] Two studies evaluated changes in the timing of referral relative to the onset of ESRD following reporting, but the assessment was complicated by the use of significantly different definitions of early and late consultation.[66]

These preliminary studies are encouraging regarding an overall trend for a benefit of detection of CKD and eGFR reporting following the guideline publication. Additional data are needed on the impact of eGFR reporting and CKD diagnosis on patient and public awareness of CKD and its risk factors and outcomes.[70] Evaluation of the impact of reporting will be essential for the refinement of methods of estimating GFR, such as the CKD-EPI creatinine equation, CKD-EPI cystatin C equation, and the CKD-EPI creatinine+cystatin C equation. Patient safety will be important to investigate further, but the metrics will need to be more precisely defined. What the impact of eGFR reporting is on the timing of dialysis initiation remains to be determined. Will there be an influence of reporting when enough time has elapsed to accrue adequate hard endpoints for cardiovascular events, onset of ESRD, and mortality? Future studies of eGFR reporting should further explore the impact of clinical decision support based on the level of kidney function.

TABLE 3.4 Recommended Referral to Specialist Kidney Care for People With Chronic Kidney Disease (CKD) in the Following Circumstances (Kidney Disease: Improving Global Outcomes Guideline Statement 5.1.1)

Acute kidney injury or abrupt sustained fall in glomerular filtration rate (GFR)
GFR <30 mL/min/1.73 m^2
Persistent albuminuria (albumin:creatinine ratio >300 mg/g)
Rapid progression is defined as a sustained decline in estimated GFR of more than 5 mL/min/1.73 m^2 per year (for other definitions of progressive CKD see guideline statement 2.1.3)
Urinary red cell casts, RBC >20 per HPF
CKD and hypertension refractory to treatment with 4 or more antihypertensive agents
Persistent abnormalities of serum potassium (S[K])
Recurrent or extensive nephrolithiasis
Hereditary kidney disease

Reprinted with permission from Reference 23.

CONCLUSION

The 2002 CKD guideline expanded the scope of kidney disease from a nephrology focus on advanced disease to additionally encompass earlier detection and management for primary clinicians. The first CKD CPG inspired clinical research activities and transformed the public health agenda. The 2012 evaluation and management of CKD guideline maintained the 2002 definition and further refined the classification. Preliminary data suggest benefits of eGFR reporting and detection of CKD by clinicians. Future studies will determine the importance of the guideline refinement on patient outcomes, particularly regarding albuminuria. The clinical case for the importance of CKD classification and terminology on outcomes is presented, but a financial case for return on investment of CKD interventions will be required to convince health system decision-makers to broadly implement CKD quality improvement and population health interventions.

Acknowledgments

Garabed Eknoyan generously provided advice on content, historical context, critical review, and constructive comments during chapter preparation.

References

1. Kolff WJ. Lasker Clinical Medical Research Award. The artificial kidney and its effect on the development of other artificial organs. *Nat Med* 2002;**8**(10):1063–5.
2. Alexander S. They decide who lives who dies: medical miracle puts moral burden on small committee. *Life* 1962;**53**:102–25.

3. Blagg CR. The early history of dialysis for chronic renal failure in the United States: a view from Seattle. *Am J Kidney Dis* 2007;**49**(3): 482–96.
4. *Committee on chronic kidney disease, report of the committee on chronic kidney disease*. Washington: U.S: Bureau of the Budget; 1967.
5. National Kidney Foundation. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**(Suppl. 1):S1–266.
6. Peitzman S. *Dropsy, dialysis, transplant: a short history of failing kidneys*. Baltimore, MD: Johns Hopkins University Press; 2007.
7. Eknoyan G. A decade after the KDOQI CKD guidelines: a historical perspective. *Am J Kidney Dis* 2012;**60**(5):686–8.
8. Hsu CY, Chertow GM. Chronic renal confusion: insufficiency, failure, dysfunction, or disease. *Am J Kidney Dis* 2000;**36**(2):415–8.
9. Eknoyan G. Chronic kidney disease definition and classification: the quest for refinements. *Kidney Int* 2007;**72**(10):1183–5.
10. Palevsky PM, Liu KD, Brophy PD, Chawla LS, Parikh CR, Thakar CV. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am J Kidney Dis* 2012; **61**(5):649–72.
11. Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. *Kidney Int* 2011;**79**(12):1361–9.
12. Cerdá J, Lameire N, Eggers P, Pannu N, Uchino S, Wang H. Epidemiology of acute kidney injury. *Clin J Am Soc Nephrol* 2008;**3**(3): 881–6.
13. Couser WG, Remuzzi G, Mundi S, Tonelli M. The contribution of chronic kidney disease to the global burden of noncommunicable diseases. *Kidney Int* 2011;**80**(12):1258–70.
14. The Centers for Disease Control and Prevention. Chronic Kidney Disease Surveillance System. https://nccd.cdc.gov/ckd/default.aspx.
15. Tuot DS, Plantinga LC, Hsu C, Jordan R, Burrows NR, Hedgeman E, for the Centers for Disease Control Chronic Kidney Disease Surveillance Team. Chronic kidney disease awareness among individuals with clinical markers of kidney dysfunction. *Clin J Am Soc Nephrol* 2011;**6**(8):1838–44.
16. Bauer C, Melamed ML, Hostetter TH. Staging of chronic kidney disease: time for a course correction. *J Am Soc Nephrol* 2008;**19**(5): 844–6.
17. Glassock RJ, Winearls C. An epidemic of chronic kidney disease: fact or fiction? *Nephrol Dial Transplant* 2008;**23**(4):1117–21.
18. Levey AS, Stevens LA, Schmid CH, Chen J, Horio M, Imai E, for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**(9):604–12.
19. Matsushita K, Mahmood BK, Woodward M, Emberson JR, Jafar TH, Jee SH. Comparison of risk prediction using CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *J Am Med Assoc* 2012;**307**(18):1941–51.
20. den Hartog JR, Reese PP, Cizman B, Feldman HI. The costs and benefits of automatic estimated glomerular filtration rate reporting. *Clin J Am Soc Nephrol* 2009;**4**(2):419–27.
21. Van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2011;**79**(12):1341–52.
22. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Gansevort RT. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. *Kidney Int* 2011;**80**(9):17–28.
23. KDIGO 2012. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013;(Suppl. 3):1–150.
24. Moreno JA, Martin-Cleary C, Gutierrez E, Rubio-Navarro A, Ortiz A, Praga M. Haematuria: the forgotten CKD factor. *Nephrol Dial Transplant* 2012;**27**(1):28–34.
25. Moyer VA, US Preventive Services Task Force. Screening for chronic kidney disease: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 2012;**157**(8):567–70.
26. Qaseem A, Hopkins RH, Sweet DE, Starkey M, Shekelle P. Screening, monitoring, and treatment of stage 1 to 3 chronic kidney disease: a clinical practice guideline from the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med* 2013;**159**(12):835–47.
27. Boulware LE, Jaar BG, Tarver-Carr ME, Brancati FL, Powe NR. Screening for proteinuria in U.S. adults – a cost effective analysis. *J Am Med Assoc* 2003;**290**(23):3101–14.
28. Hoerger TJ, Wittenborn JS, Segel JE, Burrows NR, Imai K, Eggars P, Centers for Disease Control and Prevention CKD Initiative. A health policy model of CKD: 2. the cost- effectiveness of microalbuminuria screening. *Am J Kidney Dis* 2010;**55**(3):463–73.
29. Gökmen MR, Cosyns JP, Arlt VM, Stiborova M, Phillips DH, Schmeiser HH. The epidemiology, diagnosis, and management of aristolochic acid nephropathy: a narrative review. *Ann Intern Med* 2013;**158**(6):469–77.
30. Wesseling C, Crowe J, Hogstedt C, Jakobsson K, Lucas R, Wegman DH. Resolving the enigma of the Mesoamerican nephropathy: a research workshop summary. *Am J Kidney Dis* 2014;**63**(3): 396–404.
31. Lunyera J, Mohottige D, VonIsenburg M, Jeuland M, Patel UD, Stanifer JW. CKD of uncertain etiology: a systematic review. *Clin J Am Soc Nephrol* 2016;**11**(3):379–85.
32. Johnson RJ, Wesseling C, Newman LS. Chronic kidney disease of unknown origin in agricultural communities. *N Engl J Med* 2019; **380**:1843–52.
33. Collins AJ, Vassalotti JA, Wang C, Li S, Gilbertson DT, Liu J. Who should be targeted for CKD screening? Impact of diabetes, hypertension, and cardiovascular disease. *Am J Kidney Dis* 2009;**53**(S3): S71–85.
34. Hallan SI, Dahl K, Oien CM, Grootendorst DC, Aasberg A, Homen J. Screen strategies for chronic kidney disease in the general population: follow-up of cross-sectional health survey. *BMJ* 2006;**333**(7577):1047–51.
35. Brosius FC, Hostetter TH, Kelepouris E, Mitsnefes MM, Moe SM, Moore MA. Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: a science advisory from the American Heart Association Kidney and Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: developed in collaboration with the National Kidney Foundation. *Circulation* 2006;**114**:1083–7.
36. Lei HH, Perneger TV, Klag MJ, Whenton PK, Coresh J. Familial aggregation of renal disease in a population-based case-control study. *J Am Soc Nephrol* 1998;**9**(7):1270–6.
37. Freedman BI, Volkova NV, Satko SG, Krisher J, Jurkovitz C, Soucie JM. Population-based screening for family history of end-stage renal disease among incident dialysis patients. *Am J Nephrol* 2005;**25**(6):529–35.
38. Jurkovitz C, Hylton TN, McClellan WM. Prevalence of family history of kidney disease and perception of risk for kidney disease: a population-based study. *Am J Kidney Dis* 2005;**46**(1):11–7.
39. Parsa A, Kao WHL, Xie D, Astor BC, Li M, Hsu CY, et al. APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med* 2013;**369**(23):2183–96.
40. De Coster C, McLaughlin K, Noseworthy TW. Criteria for referring patients with renal disease for nephrology consultation: a review of the literature. *J Nephrol* 2010;**23**(4):399–407.

41. Whelton PK, Carey RM, Aronow WS, Casey Jr DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith Jr SC, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams Sr KA, Williamson JD, Wright Jr JT. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Circulation* 2018;**138**(17):e426–83.
42. SPRINT Research Group, Wright Jr JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff Jr DC, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**(22):2103–16.
43. Beddhu S, Chertow GM, Greene T, Whelton PK, Ambrosius WT, Cheung AK, Cutler J, Fine L, Boucher R, Wei G, Zhang C, Kramer H, Bress AP, Kimmel PL, Oparil S, Lewis CE, Rahman M, Cushman WC. Effects of intensive systolic blood pressure lowering on cardiovascular events and mortality in patients with type 2 diabetes mellitus on standard glycemic control and in those without diabetes mellitus: reconciling results from ACCORD BP and SPRINT. *J Am Heart Assoc* 2018;**7**(18):e009326.
44. ESH/ESC Task Force for the Management of Arterial Hypertension. 2013 practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens* 2013;**31**(10):1925–38.
45. Sinha AD, Agarwal R. Clinical pharmacology of antihypertensive therapy for the treatment of hypertension in chronic kidney disease. *Clin J Am Soc Nephrol* 2018. https://doi.org/10.2215/CJN.04330418 [Epub ahead of print].
46. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis* 2012;**60**:850–86.
47. FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM494140.pdf.
48. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**(22):2117–28.
49. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR, CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**(7):644–57.
50. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS. DECLARE–TIMI 58 investigators, dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2018. https://doi.org/10.1056/NEJMoa1812389 [Epub ahead of print].
51. U.S. National Library of Medicine, ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03594110?cond=EMPA+Kidney&rank=1.
52. Fink JC, Brown J, Hsu VD, Seliger SL, Walker L, Zhan M. CKD as an underrecognized threat to patient safety. *Am J Kidney Dis* 2009;**53**(4):681–8.
53. Hug BL, Witkowski DJ, Sox CM, Keohane CA, Seger DL, Yoon C. Occurrence of adverse, often preventable, events in community hospitals involving nephrotoxic drugs or those excreted by the kidney. *Kidney Int* 2009;**76**(11):1192–8.
54. Chapin E, Zhan M, Hsu VD, Seliger SL, Walker LD, Fink JC. Adverse safety events in chronic kidney disease: the frequency of "multiple hits". *Clin J Am Soc Nephrol* 2010;**5**(1):95–101.
55. Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin SS, Conner TA, Chertow GM, Bhatt DL, Shunk K, Parikh CR, McFalls EO, Brophy M, Ferguson R, Wu H, Androsenko M, Myles J, Kaufman J, Palevsky PM. PRESERVE trial group, outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med* 2018;**378**(7):603–14.
56. Vassalotti JA, Centor R, Turner BJ, Greer RC, Choi M, Sequist TD, National Kidney Foundation Kidney Disease Outcomes Quality Initiative. A practical approach to detection and management of chronic kidney disease for the primary care clinician. *Am J Med* 2016;**129**(2):153–62.
57. Vassalotti JA, Jennings WC, Beathard GA, Neumann M, Caponi S, Fox CH. Fistula First breakthrough initiative: targeting catheter last in fistula First. *Semin Dial* 2012;**25**(3):303–10.
58. Coresh J. A decade after the KDOQI CKD guidelines: impact on research. *Am J Kidney Dis* 2012;**60**(5):701–4.
59. The National Center for Health Statistics, Centers for Disease Control and Prevention. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM & ICD-10-CM). https://www.cdc.gov/nchs/icd/.
60. Vassalotti JA. The cycle of development, publication, and implementation of clinical practice guidelines for CKD. *Kidney Int* 2012;**81**(12):1159–61.
61. Kagoma YK, Garg AX, Li L, Jain AK. Reporting of the estimated glomerular filtration rate decreased creatinine clearance testing. *Kidney Int* 2012;**81**(12):1245–7.
62. Jain AK, McLeod I, Huo C, Cuerden MS, Akbari A, Tonelli M. When laboratories report estimated glomerular filtration rates in addition to serum creatinines, nephrology consults increase. *Kidney Int* 2009;**76**(3):318–23.
63. Hemmelgarn BR, Zhang J, Manns BJ, James MT, Quinn RR, Ravani P. Nephrology visits and health care resource use before and after reporting estimated glomerular filtration rate. *J Am Med Assoc* 2010;**303**(12):1151–8.
64. Allen AS, Forman JP, Orav EJ, Bates DW, Denker BM, Sequist TD. Primary care management of chronic kidney disease. *J Gen Intern Med* 2011;**26**(4):386–92.
65. Wyatt C, Konduri V, Eng J, Rohatgi R. Reporting of estimated GFR in the primary care clinic. *Am J Kidney Dis* 2007;**49**(5):634–41.
66. Kagoma YK, Weir MA, Iansavichus AV, Hemmelgarn BR, Akbari A, Patel UD. Impact of estimated GFR reporting on patients, clinicians, and health-care systems: a systematic review. *Am J Kidney Dis* 2011;**57**(4):592–601.
67. Tawadrous D, Shariff SZ, Haynes RB, Iansavichus AV, Jain AK, Garg AX. Use of clinical decision support systems for kidney-related drug prescribing. *Am J Kidney Dis* 2011;**58**(6).
68. Wei L, MacDonald TM, Jennings C, Sheng X, Flynn RW, Murphy MJ. Estimated GFR reporting is associated with decreased nonsteroidal anti-inflammatory drug prescribing and increased renal function. *Kidney Int* 2013;**84**(1):174–8.
69. US Renal Data System. *USRDS 2018 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018.
70. Stevens LA, Levey AS. Impact of reporting estimated glomerular filtration rate: it's not just about us. *Kidney Int* 2009;**76**(3):245.

QUESTIONS AND ANSWERS

Question 1

All of the following patients should have random or spot ACR testing at least annually, except?

A. 68-year-old woman with type-2 diabetes onset in 2010
B. 50-year-old man with uncomplicated essential hypertension since 2000
C. 52-year-old man with hypothyroidism and asthma
D. 65-year-old man whose mother required dialysis treatment at age 60
E. 70-year-old woman with osteoarthritis after cardiac catheterization revealing two-vessel coronary artery disease

Answer: C

Diabetes, hypertension, and age 60 years and older are the target conditions to test for CKD.[23,27,28,56]

Question 2

A 58-year-old man presents for initial outpatient visit. He has a long history of hypertension, but has not seen a physician in several years. He no longer takes any medication. On physical examination, BP 152/90 mm Hg, pulse 72 bpm. Physical examination is normal including cardiac lungs and absent peripheral edema. S[Cr] is 1.40 mg/dL. What is the best test for assessment of his kidney function?

A. S[Cr]
B. Cockcroft-Gault eGFR
C. CKD-EPI eGFR
D. 24-hour urine collection
E. Serum cystatin C

Answer: C

The CKD-EPI eGFR is the most accurate and least biased widely available assessment of kidney function for routine clinical practice.[23]

Question 3

A 55-year-old African-American woman with type-2 diabetes for 10 years presents for ambulatory care with BP 150/88 mm Hg, pulse 78 bpm, and body mass index 35 m^2. Physical examination reveals microaneurysms of the retina on fundoscopic examination, normal heart and lungs, obesity, +1 pedal edema, and decreased ankle reflexes.

Laboratory data:

S[K] 4.0 mEq/L
Total carbon dioxide 16 mEq/L
S[Cr] 2.75 mg/dL, CKD-EPI eGFR 22 mL/min/1.73 m^2
Hemoglobin 11.2 g/dL
Hemoglobin A1c 7.6%
ACR 450 mg/g

These test results are confirmed with repeat testing over a 4-month period. Current therapy includes labetalol 100 mg twice daily and metformin 500 mg twice daily. All of the following apply to this patient, except?

A. The patient has C = diabetic nephropathy, G4, A3 using the CGA staging of CKD
B. The patient should be referred for nephrology consultation
C. An ACE inhibitor or ARB should be added to the hypertension regime with S[K] and eGFR monitoring
D. Sodium bicarbonate 650 mg therapy should be initiated
E. Erythropoetin alpha 20,000 units subcutaneously weekly should be initiated

Answer: E

ESA therapy is only recommended after an initial investigation of anemia. In addition, the hemoglobin at which ESA should be initiated is less than 10 g/dL. See Reference 49. All the other answers apply to the patient.[23]

Question 4

For the patient described in Question 3, a patient safety approach to medication management that considers the level of kidney function includes all of the following, except?

A. Avoidance of nonsteroidal antiinflammatory drugs for analgesia
B. Discontinuation of metformin
C. Intravenous sodium chloride to reduce the risk of AKI following iodinated contrast media exposure for acute coronary syndrome
D. Avoidance of aspirin 81 mg daily for cardiovascular prophylaxis
E. Avoidance of sodium phosphate bowel preparations for routine colonoscopy surveillance

Answer: D

The correct answer is D. Routine daily aspirin prophylaxis for cardiovascular disease is not contraindicated in CKD. Nonsteroidal antiinflammatory (ibuprofen, naproxen) use should generally be avoided as it is a cause of AKI in CKD, especially when combined with diuretics or RAAS blockers (Answer A). Metformin risk of lactic acidosis contraindicates its use when the eGFR is less than 30 mL/min/1.73 m^2 (Answer B). For patients with eGFR between 30 to 60 mL/min/1.73 m^2, this biguanine should be used with caution. Intravenous sodium chloride administration is currently controversial

as a therapeutic maneuver in CKD patients receiving intravenous contrast (Answer C). Other considerations to reduce the risk of contrast-induced AKI include avoidance of high osmolar agents, use of the lowest possible contrast dose, and withdrawal of diuretics before and after the procedure. Sodium phosphate oral bowel preparations should be avoided, because these are associated with acute phosphate nephropathy in CKD and in diabetic patients with normal kidney function treated with RAAS blockers (Answer E). See References 23,52 and 56.

Question 5

All of the following adult patients with laboratory data and characteristics below should be referred for nephrology consultation, except?

A. Initial visit: eGFR 26 and 3 month visit: eGFR 28 (mL/min/1.73 m^2)
B. Initial visit: eGFR 55 and 3 months later eGFR 43 (mL/min/1.73 m^2)
C. Initial visit: ACR 450 and 3 months later: ACR 355 (mg/g) on both dates the eGFR >60 mL/min/1.73 m^2
D. Initial visit: eGFR >60 and 3 months later: eGFR >60 (mL/min/1.73 m^2) with personal history of autosomal dominant polycystic kidney disease
E. Initial visit: eGFR 42 and 3 months later: eGFR 44 (mL/min/1.73 m^2)

Answer: E

The correct answer is E. This patient has G3b CKD with no indication for nephrology referral. Answer B is incorrect as the eGFR trend reflects rapid progression of CKD, which is defined as a sustained decline of more than 5 mL/min/1.73 m^2 per year. Answers A and C are incorrect with low eGFR and severe albuminuria as indications for nephrology referral, respectively. Answer D is incorrect as a hereditary cause of CKD.

See Table 3.3 and Reference 23.

Question 6

Observational studies of early as compared with late nephrology referral have demonstrated which of the following?

A. Reduced 1-year mortality (11 vs. 29%, p value 0.028)
B. Reduced mean hospital days (13.5 vs. 25.3 days, p 0.0007)
C. Higher serum albumin at the initiation of dialysis or kidney transplantation (3.62 vs. 3.40 g/dL, p 0.0001)
D. Higher hematocrit at the initiation of dialysis or kidney transplantation (30.54 vs. 29.71%, p 0.013)
E. All of the above.

Answer: E

All of the above are associated with early as compared with late nephrology referral.[23]

CHAPTER

4

Assessing Kidney Function

Pierre Delanaye[a], *Christine A. White*[b], *Natalie Ebert*[c], *Andrew D. Rule*[d]

[a]Department of Nephrology-Dialysis-Transplantation, University of Liège, Liège, Belgium; [b]Division of Nephrology, Queen's University, Kingston, ON, Canada; [c]Charité University Hospital, Institute of Public Health, Berlin, Germany; [d]Division of Nephrology and Hypertension and Division of Epidemiology, Mayo Clinic, Rochester, MN, United States

Abstract

Glomerular filtration rate (GFR) is used to characterize kidney function. Its underlying determinants, nephron number and single nephron GFR, better characterize kidney function but are not easy to measure in patients. Using GFR to characterize chronic kidney disease (CKD) requires an understanding of its physiological variation, as well as its decline with healthy aging. The measurement of GFR is based on the urinary or plasma clearance of an ideal or near ideal exogenous marker such as inulin, iohexol, or iothalamate. This requires infrastructure, expense, and patient burden that are not feasible in most clinical settings. Endogenous circulating markers cleared primarily by glomerular filtration, particularly creatinine, are more practical and useful to detect level and loss of kidney function. Estimated GFR can improve the interpretation and application of endogenous markers of GFR. However, estimated GFR still reflects the biology of the underlying markers, which may be unrelated to kidney structure and function. There is not one GFR estimating equation that accurately estimates GFR in all clinical settings, optimally predicts CKD outcomes, and performs the same as measured GFR in its association with CKD risk factors and outcomes.

KIDNEY FUNCTION

The kidneys are essential to maintain homeostasis in the body. Kidneys have two main roles: eliminating catabolic-induced wastes and regulating the water-sodium equilibrium. In addition, the kidney has several endocrine roles, including erythropoiesis and maintenance of phosphorus–calcium balance. Other functions of the kidney include tubular reabsorption of nutrients and proteins, tubular secretion of metabolic wastes, and prevention of crystallization and stone formation in supersaturated urine. However, the term "kidney function" is often used to describe the glomerular filtration rate (GFR) alone because it is perceived to be the best global marker of kidney function. Chronic kidney disease (CKD) has primarily been defined and classified using GFR to define kidney function.

Glomerular Filtration Rate

The concept of GFR is best understood by first explaining the concept renal clearance.[1,2] The renal clearance of a plasma solute is defined as the volume of plasma cleared of this solute by the kidneys per unit time. Clearances are thus flow rates (mL/min). A solute marker with the following characteristics can be considered ideal for measurement of GFR: soluble in the plasma (not bound to protein), metabolically inert, freely filtered through the glomerular filtration barrier, neither secreted nor reabsorbed by the tubules, and only excreted by glomerular filtration.[2] Lower GFR is associated with metabolic complications of CKD (many of which reflect other functions of the kidney).[3] Lower GFR is also a risk factor for cardiovascular morbidity and mortality.[4,5] Clinical practice guidelines have used GFR (along with albuminuria) to define and stage CKD. In particular, CKD has been defined by a GFR less than 60 mL/min/1.73 m^2 (Table 4.1) with a normal GFR defined as 90 mL/min/1.73 m^2 or higher.[7]

Normal GFR levels have been thoroughly studied in healthy young adults. Homer W. Smith found a mean measured GFR of 127 mL/min/1.73 m^2 and 118 mL/min/1.73 m^2 for men and women, respectively.[8] Laurence G. Wesson found the values were 130 mL/min/1.73 m^2 and 120 mL/min/1.73 m^2 for men and women, respectively.[9] More contemporary studies have found somewhat lower mean GFR values in healthy young adults, i.e. around 100–110 mL/min/1.73 m^2.[10–14] Smith and Wesson observed a significant difference according to gender.[8,9] However, gender

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00004-8

TABLE 4.1 GFR Categories for CKD Classification According to the KDIGO Guidelines[6]

Term	GFR Category	GFR (mL/min/1.73 m^2)
Normal or high	G1	90 and higher
Mildly decreased	G2	60–89
Mildly to moderately decreased	G3a	45–59
Moderately to severely decreased	G3b	30–44
Severely decreased	G4	15–29
Kidney failure	G5	<15

CKD, chronic kidney disease; *GFR*, glomerular filtration rate.
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

differences have been very small or not observed in more contemporary studies.[10–12] Normal GFR values do not significantly differ between healthy whites and African Americans.[11]

Physiological Variation in GFR

As with any physiological characteristic, distinguishing normal physiological variation in GFR from pathological disease states is critical.[15] There can be both between-individual and within-individual variations influenced by genetic and environmental factors, as well as variation due to assay error. Several studies have shown GFR variations of up to 10 mL/min following changes in dietary protein or sodium intake.[16,17] A small impact of exercise on GFR is also evident.[17,18] Diurnal variability with GFR in healthy subjects has also been described. Sirota et al. found lower GFR at night compared to the day.[19] Koopman et al. also found nocturnal variation in GFR.[20] The day-to-day variability of GFR (reflecting physiological variation and assay error) has been estimated to be between 4 and 10% in healthy subjects, and 5 and 15% in CKD patients, depending on the method used to measure GFR.[21–23]

Nephron Number and Single Nephron GFR

The underlying determinants of GFR are nephron number (number of nonsclerosed functioning glomeruli) and mean single nephron GFR. Factors that influence variation in nephron number and single nephron GFR have been studied in healthy adults (Table 4.2).[6] Some factors, such as age, associate with lower nephron number, but do not associate with single nephron GFR, resulting in a lower total GFR. Other factors, such as obesity, associate with higher single nephron GFR, but do not associate with nephron number, resulting in a higher total GFR. Importantly, some factors, such as family history of end-stage renal disease (ESRD), associate with both lower nephron number and higher single nephron GFR, such that no association with total GFR is evident. Nephron number is itself determined by nephron endowment (associated with factors such as family history of ESRD and height) minus any loss of nephrons (associated with factors such as age and nephrosclerosis on kidney biopsy).[24]

Determining nephron number and single nephron GFR in clinical practice is not easily accomplished. Nephron number can be determined from the volume of cortex in the kidney (determined from high-resolution kidney imaging with computed tomography) multiplied by the three-dimensional density of glomeruli in the kidney cortex (determined from stereological calculations applied to a kidney biopsy).[24] Single nephron GFR is calculated from total GFR divided by the nephron number.[6] Although these determinants of total GFR are not easily measured in CKD patients, we tend to assume that sustained reductions in GFR are due to reduction in nephron number while increases in

TABLE 4.2 Clinical Factors Associate Differently With Nephron Number and Single Nephron Glomerular Filtration Rate (GFR) (nL/min), but the Net Effect Determines How They Associate With Total GFR (mL/min) in Healthy Adults

Clinical Factor	Nephron Number	Single Nephron GFR	Total GFR
Age	↓	0	↓
Female	↓	0	↓
Obesity	0	↑	↑
Tall height	↑	↑	↑
Uric acid	↓	0	↓
Family history of ESRD	↓	↑	0

ESRD, end-stage renal disease.

GFR are due to increases in single nephron GFR. Enlarged glomeruli and tubules on a kidney biopsy are also reflective of glomeruli that are hyperfiltering (increased single nephron GFR).[6] Interstitial fibrosis in the cortex appears to restrict the ability of remaining glomeruli to enlarge and hyperfilter to compensate for the loss of nephrons.[25]

Age-Related Decline in GFR

GFR declines with normal adult aging.[8–12,26] Davies and Shock demonstrated a continuous decrease in GFR from a mean 123 mL/min/1.73 m^2 at age 20–29 years to a mean 65 mL/min/1.73 m^2 at age 80–89 years (about 10 mL/min per decade of age).[26] Other investigations have found a decline in GFR ranging from 6 to 12 mL/min/1.73 m^2 per decade of age.[10,27,28] There is some uncertainty regarding whether the decline in GFR is constant or accelerates with age. Some studies have shown that the decrease in GFR is relatively constant throughout adulthood,[10,12,29] while others find GFR decline begins[8–10,26,28] or accelerates[10,11] during middle age (approximately 40–59 years). These discrepancies likely reflect differences in how healthy adults are selected for study, particularly in the older age groups where comorbidities are common and difficult to exclude. These studies are cross-sectional, as there are no longitudinal studies following measured GFR in normal adults. A longitudinal study using urinary creatinine clearance found a decrease of 7.5 mL/min per decade of age. There was wide variation in this trend, and one-third actually had an increasing creatinine clearance. However, this analysis did not account for the substantial measurement error that occurs with urinary creatinine clearance or account for increasing creatinine clearance from diseases that cause hyperfiltration (e.g. early diabetes and obesity).[30]

Reference ranges for normal GFR values have been defined using potential kidney donors, though few subjects older than 70 years are studied. The lower reference value (fifth percentile) at 60 years was 64 and 60 mL/min/1.73 m^2 for men and women, respectively.[11] Creatinine-based estimated GFR underestimates GFR in healthy subjects, and the fifth percentile is below 60 mL/min/1.73 m^2 in women by age 50 years and in men by age 55 years[11,31,32] (Figure 4.1). Given the decline in GFR with age, it may be reasonable to expect that the value of the fifth percentile in healthy subjects older than 70 years could be well below 60 mL/min/1.73 m^2. Indeed, a study specifically targeting "healthy for their age" patients older than 70 years found that by age 90 years, the average mGFR was 60 mL/min/1.73 m^2.[10,33] A population-based study found that 48% of adults over age 70 years had a measured GFR <60 mL/min/1.73 m^2.[34]

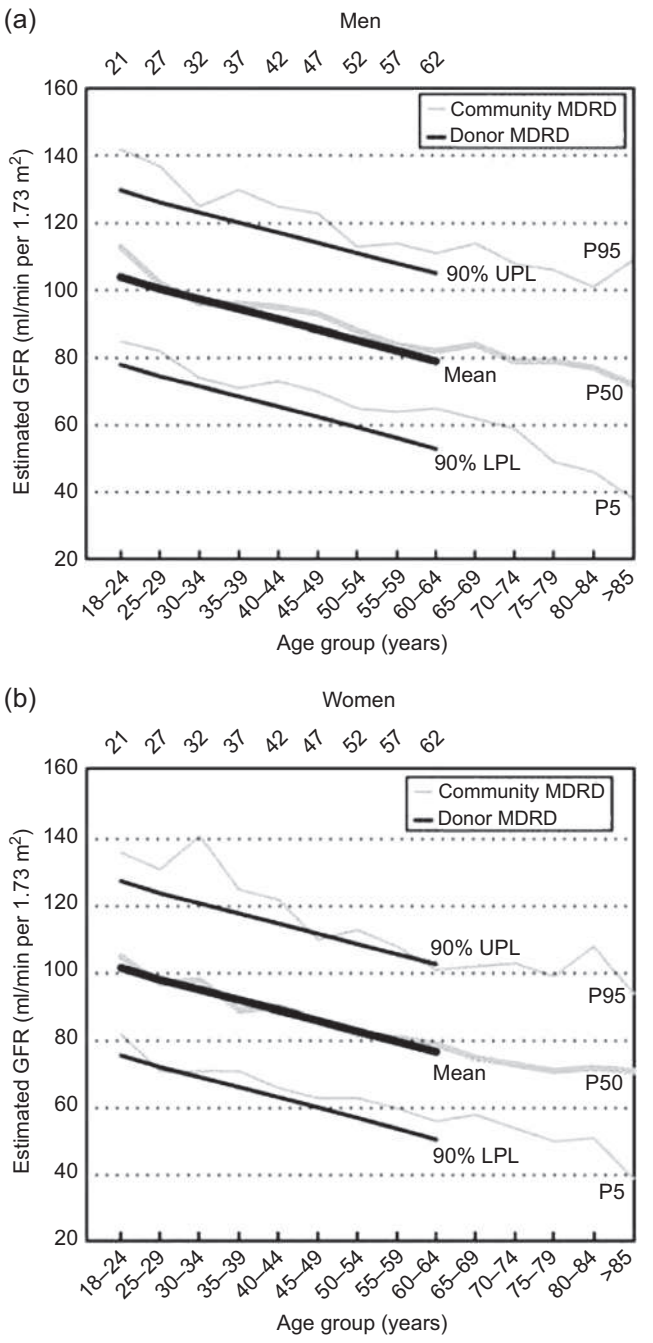


FIGURE 4.1 Comparison of estimated GFR in two different cohorts. Mean, 5th, and 95th percentiles for expected eGFR by MDRD equation in living kidney donors (Estimated MDRD—*black lines*) and eGFR by the MDRD equation in residents from the general community (Nijmegen MDRD—*gray lines*) among different age groups for (a) men and (b) women. *eGFR*, estimated glomerular filtration rate; *GFR*, glomerular filtration rate; *MDRD*, Modified Diet in Renal Disease. *Figure permission obtained from the Nature Publishing Group.*

The cause of this decline in GFR is due to a decline in nephron number without a compensatory increase in single nephron GFR or glomerular volume.[6,24,25] Whether nonrenal factors, such as decreased physiological

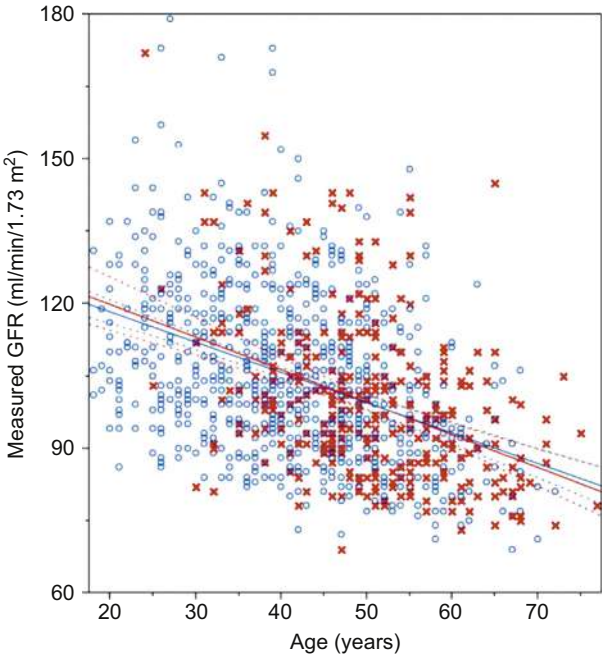


FIGURE 4.2 The relationship between GFR and age in persons with and without nephrosclerosis. The relationship between GFR and age in persons with nephrosclerosis is similar to that in persons without nephrosclerosis. *GFR*, glomerular filtration rate.

demand for GFR with less metabolic waste in the elderly, account for the lack of a compensatory increase in single nephron GFR with aging is unclear. A cause of age-related nephron loss is nephrosclerosis, which is only partially detected either by biopsy (globally sclerosed glomeruli atrophy and disappear) or by cortical volume on CT scan (tubular hypertrophy of remaining nephrons masks the nephron loss).[24] The age-related decline of GFR is not different in patients with more severe nephrosclerosis than expected for age on renal biopsy (Figure 4.2),[27] as there is a compensatory increase in single nephron GFR when nephrosclerosis exceeds that expected for age.[6]

DIRECT MEASUREMENT OF GFR

Exogenous Filtration Markers

Endogenous markers have biological activity that leads to variation in different physiological and pathological states. Thus, exogenous markers are needed to measure GFR. Inulin has been the most validated as an ideal marker. Inulin is a 5200 Da polymer of fructose, which is found in some plants (such as chicory and leek), which use it as energy source.[2] Inulin is freely filtered and not protein-bound.[2,35] The absence of both tubular reabsorption and secretion has been demonstrated in fish and dog models treated with tubular secretion inhibitors,[35,36] and further confirmed with tubular micropuncture studies in a rat model.[37] In humans, an intravenous injection of inulin is fully excreted in the urine, except for negligible amounts found in bile.[38] Because of these validation studies, inulin is an ideal marker for GFR measurement. Nevertheless, inulin is not readily available and is expensive, and assays are not easily standardized.[39] Other exogenous markers used to measure GFR have been generally validated against inulin clearance.

^{51}Cr-EDTA (Ethylenediaminetetra-acetic acid) is an alternative exogenous marker that shows good performance for GFR measurement compared to inulin.[40,41] While detected by radioactive decay, the quantity of ^{51}Cr-EDTA injected is relatively small, and the dose of radiation is very limited. Like ^{51}Cr-EDTA, ^{99}Tc-DTPA (Diethylenetriaminepenta-acetic acid) is an exogenous isotopic marker, but has a shorter half-life, making it less practical than ^{51}Cr-EDTA.[42] One advantage is that ^{99}Tc-DTPA clearance can be coupled with a nephrogram to demonstrate differential function between the two kidneys. However, physiological data to validate ^{99}Tc-DTPA are lacking, and performance may be suboptimal because ^{99}Tc-DTPA can bind to plasma proteins.[43] GFR can also be estimated with external counting using a gamma camera (the "Gates" method), but this method is not accurate enough to be considered a reference method for measuring GFR.[44]

Iothalamate is an iodinated contrast agent derived from tri-iodobenzoic acid. Iothalamate can be measured either by isotopic methods or by different analytical methods that do not require radiation. Many, but not all, studies have suggested iothalamate is secreted by renal tubules or has extrarenal clearance.[16,45–48] This marker is particularly important because iothalamate clearance has been used to develop most of the commonly used creatinine-based equations to estimate GFR. Iohexol is another iodinated contrast agent that can be used to measure GFR without requiring the nuclear medicine infrastructure needed for isotope based markers. Iohexol assays appear to have a low assay error.[49] Some studies showed acceptable performance for iohexol compared to inulin.[50,51] Most studies have shown plasma clearance of iohexol performs similar to other exogenous markers used to measure GFR.[52–55] Dried blood spot testing is possible with iohexol, which may make measured GFR more feasible in more settings.[56]

Methods based on fluorescein-isothiocyanate (FICT) may have the potential to make measured GFR a more convenient test. Inulin can be labeled with FICT,[57] and the clearance of this marker has been measured

transcutaneously[58,59] in rodent models. In humans, FICT conjugated with inulin has been assayed in plasma samples over a 3 h interval to measure GFR *via* its plasma clearance.[60]

Urinary and Plasma Clearance

GFR can be determined from two types of clearance methods. Urinary clearance uses timed urine and plasma samples, and plasma clearance uses only plasma samples. Ideally, for both methods the marker would be infused at a constant rate until a steady state plasma concentration has been achieved. Due to its high molecular weight and viscosity, this is the only way to administer inulin for GFR measurement. This is also often not practical with the time and expense constraints of clinical testing. For urinary clearance, some centers use a single subcutaneous injection of the marker, while others use constant intravenous infusions, but do not wait until steady state is achieved. Clearance is then calculated by the simple calculation: $U \times V/P$ (where U is the urine marker level, V is the urinary flow rate, and P is the plasma marker level).[2] Errors in urine collection, particularly from incomplete bladder emptying, are a limitation and a source of variability (imprecision) of urinary clearances. Averaging the clearance over multiple urine collections is used to decrease test error. Sonographic scanning to assess bladder emptying with bladder catheters as needed can also be helpful.[61]

Plasma clearance methodology has the advantage of not requiring urine collections, but it is more dependent on there being no extrarenal clearance of the marker. Like urinary clearances, a constant infusion is too time consuming to be practical, and a bolus infusion of the marker is given instead. After bolus intravenous injection, plasma concentration decreases in two stages: a rapid decrease that corresponds to the distribution of the marker throughout the extracellular space, and then a slower decrease which corresponds to the renal excretion of the marker by GFR (Figure 4.3).[40] The plasma clearance of the marker is then determined by the ratio of the injected dose and the area under the curve for the modeled rate of marker excretion. Plasma clearances are not accurate in patients with extracellular volume expansion, such as edema or ascites.[40,63] Moreover, the sample timing and the number of samples considered strongly influence the accuracy of the plasma clearance. In severe CKD, the longer the period before the last plasma sample, the more accurate the determination of plasma clearance.[40,64,65] Single sample methods appear to perform reasonably well compared to multiple plasma methods in patients who do not have severe CKD or obesity.[66] Several studies have compared simultaneous urinary and plasma clearances.[63–65] Plasma clearances tend to systematically overestimate urinary clearances because of the small amount of non-GFR clearance for all markers.

Clinical Indications for Measuring GFR

Guidelines have generally relegated the application of measured GFR in CKD as an alternative test in settings where serum creatinine concentration (S[Cr])–based estimated GFR is clearly inaccurate.[7] Studies comparing measured GFR and estimated GFR with clinical endpoint are few and generally limited to CKD

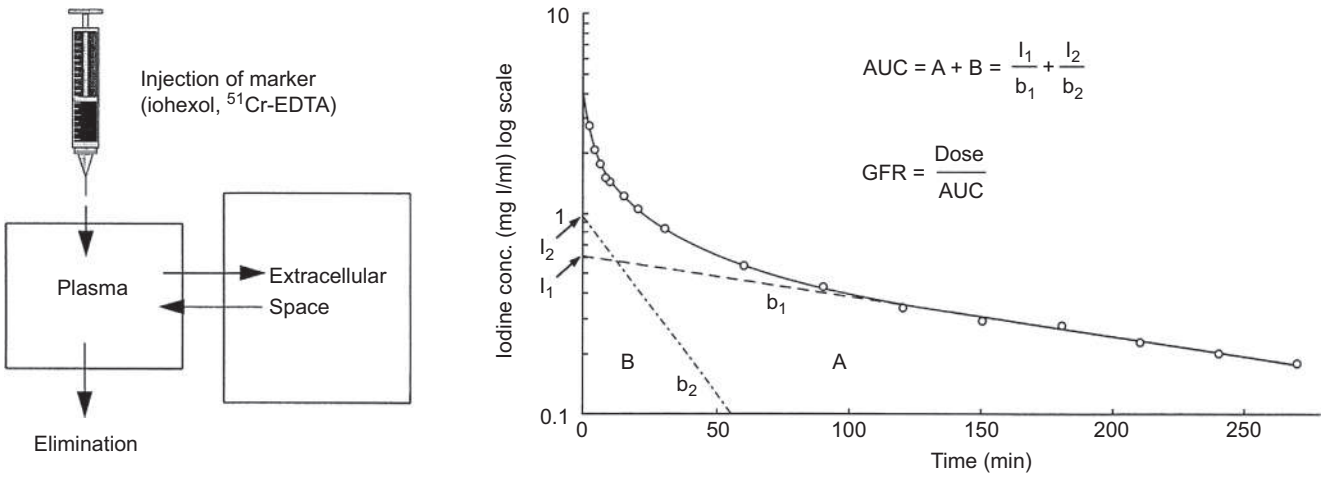


FIGURE 4.3 The two-compartment kinetic model for plasma clearance of iohexol.[62] The plasma concentration of iohexol as a function of time (t) based on all 16 measurements in the period 2–270 min after bolus injection of iohexol. The two-compartment model is mathematically described as the sum of two exponential functions. The elimination rate constants of the two compartments are *b1* and *b2* and the corresponding intercepts on the ordinate are I_1 and I_2 (mg I/mL). Plasma concentration of markers $= I_1\, e^{-b1t} + I_2\, e^{-b2t}$. *AUC*, area under the curve; *GFR*, glomerular filtration rate. *Figure permission obtained from Springer.*

populations. In CKD populations, measured GFR is not a better predictor of metabolic complications than estimated GFR.[3,67] There are generally two indications where measured GFR has been advocated. The first indication is when a very accurate GFR measurement is desired, such as for evaluation of potential living kidney donors or when administering a renally cleared medication with a narrow therapeutic window.[68] The second indication is in settings when estimated GFR is likely to be inaccurate, as discussed in the next section.

ENDOGENOUS FILTRATION MARKERS

Serum Creatinine

For almost a century S[Cr] has been the most widely used endogenous marker of GFR.[35] S[Cr] is assayed using either Jaffe or enzymatic methods, and many different assays are available. Over the past decade, most manufacturers have standardized their assays using reference materials traceable to the gold standard isotope dilution mass spectrometry (IDMS).[69,70] The IDMS traceability has reduced the bias observed between assays for both the Jaffe and enzymatic methods, although Jaffe assays continue to yield higher values than enzymatic ones.[71–73] Differences continue to exist largely due to both endogenous and exogenous interfering factors, which impact differentially on assays provided by different manufacturers. This appears to be less problematic with enzymatic methods that show improved precision over Jaffe methods.[72–74,70]

The two main biological limitations of using S[Cr] as a surrogate for GFR are the tubular secretion of creatinine[75,76] and the dependence of its circulating level on muscular mass.[75,77,78] Circulating creatinine is the catabolic end-product of creatine, which serves as an energy storage molecule for muscles. There is also some degree of extrarenal excretion of creatinine at very low GFR levels.[79] S[Cr] can also increase after ingestion of cooked animal protein.[80,81] S[Cr], like all endogenous filtration markers, has a reciprocal relationship with GFR (Figure 4.4).[75,82] Each doubling of S[Cr] represents an approximately 50% loss of GFR. The same increase in S[Cr] represents a smaller decline in GFR at low GFR levels compared to high GFR levels. This can be clinically useful since smaller changes in GFR become more clinically relevant as GFR declines to low levels.

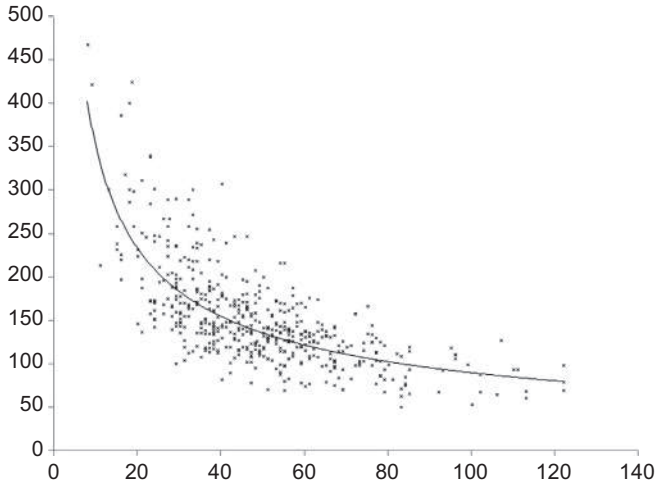


FIGURE 4.4 Relationship between GFR and serum creatinine concentration. *GFR*, glomerular filtration rate. *Figure permission obtained from Christophe Mariat, Saint Etienne, France.*

Urinary Creatinine Clearance

Urinary creatinine clearance, usually calculated from 24-h urine collections, is a relatively easy method to determine GFR, using the standard U x V/P clearance equation. Because of creatinine tubular secretion, creatinine clearance systematically overestimates measured GFR, particularly at low GFR levels.[75,76] Tubular secretion is also quite variable between patients and cannot be directly measured.[75,76] Administration of cimetidine has been used to block creatinine secretion and increase the accuracy of urinary creatinine clearance.[76,83] Perhaps the biggest limitations of creatinine clearance are the high intraindividual variation of creatinine excretion and inaccurate urine collection by patients.[75,78,84,85]

Cystatin C

Cystatin C (CysC) is a 13.3 kDa cysteine proteinase inhibitor[86] produced by nucleated cells.[87] CysC is freely filtered by the glomeruli and then reabsorbed by the proximal tubules, where it is catabolized.[88] A particular advantage of CysC over S[Cr] is that its concentration is less influenced by variations in muscle mass, age, and sex.[89–92] Many additional non-GFR determinants have been described including thyroid disorders, obesity, inflammation, viral load in HIV-infected patients, therapy with glucocorticoids, malignancy, and diabetes.[89,93–98] CysC can be measured by nephelometric, turbidimetric, and ELISA assays, although differences between these have been shown.[99,100] Assay drift over time has also been noted.[100–102] Certified reference material is now available,[103] although significant method-related bias exists between different assays.[104] CysC has emerged as the most prominent nontraditional GFR biomarker, and CysC is included in the diagnostic criteria for CKD in the KDIGO guidelines.[7] CysC has also been shown to be more strongly

associated with adverse nonrenal outcomes, such as death, compared to S[Cr]-based evaluations, even after accounting for mGFR in some cases.[105–108]

BTP

β trace protein (BTP) is a 109 amino acid glycoprotein with multiple isoforms due to variable posttranslational glycosylation. Originally identified in human cerebral spinal fluid,[109] BTP was recognized to be elevated in the serum of patients with CKD in 1997.[110] BTP is produced by numerous cell types, including endothelial, cardiac, CNS, bone, adipose, and kidney.[111] The origin of serum BTP remains uncertain.[111] The renal handling of BTP is also unclear and it seems unlikely given its molecular weight (26–29 kDa) that it is freely filtered. Unlike cysC and β_2-microglobulin (B_2M), BTP is not completely reabsorbed in the tubules. BTP is present in the urine in healthy people.[110]

There are at least two commercial assays (ELISA and nephelometric) used to measure BTP. There are no higher order reference methods or materials available and significant differences between the two assay types have been demonstrated.[112] Although not as well established as for S[Cr] and cysC, there are multiple non-GFR determinants of serum BTP concentration, including age, gender, weight, cardiovascular disease, inflammation, proteinuria, pregnancy and genetic factors.[92,111] This is not surprising given the biologic functions of BTP. BTP catalyzes the conversion of prostaglandin H2 (PGH2) to prostaglandin D2 (PGD2). PGD2 is involved in the inflammatory response, as well as in platelet aggregation, vasodilation, bone remodeling, sleep induction and nociception.[111] Most studies do not suggest BTP to be superior to S[Cr] or CysC as a diagnostic marker of GFR in CKD. BTP may however be a more sensitive marker of early GFR decline than S[Cr].[113–116] BTP has been shown to be a stronger predictor of all cause and cardiovascular mortality than S[Cr] and even, in some cases, than mGFR.[105,106] However, serious analytic impediments to the widespread use of BTP need to be addressed to integrate this interesting biomarker into clinical care.

B_2M

B_2M is a low molecular weight protein (11.8 kDa) expressed on the surface of all cell types.[117] B_2M is freely filtered and then is almost entirely reabsorbed and catabolized in the proximal tubules.[118] Serum B_2M concentrations can be elevated in conditions other than CKD including neoplastic, inflammatory, and infectious illnesses.[119] Systolic blood pressure, C-reative protein, age, gender, total cholesterol, smoking and urine protein excretion have also been shown to be associated with serum B_2M independently of GFR.[92,120] A variety of types of assays are commercially available to quantitate B_2M with differences between them identified.[121] Similarly to CysC and BTP, B_2M has been shown to be more strongly associated with certain adverse outcomes such as death than S[Cr].[105,122]

Nontargeted Metabolomics

There are numerous small molecules in the blood that are cleared by glomerular filtration. Rather than focusing on a specific endogenous filtration marker, a nontargeted metabolomic approach can be used to identify endogenous filtration markers. Various panels of renally cleared metabolites that in combination may improve the estimation of GFR have been identified.[123,124] However, development of such metabolic panels into useful and cost-effective tests for GFR assessment has not yet occurred.

ESTIMATION OF MEASURED GFR

The "Estimated GFR Construct"

Estimated GFR is a statistical model (equation) that estimates measured GFR using endogenous filtration markers and readily available surrogates (primarily age, sex, race, and weight) to model the non-GFR determinants of the marker. The best equation for estimated GFR has been a source of significant debate in the nephrology literature. So far, there have been primarily three different criteria used to evaluate and determine the "best" GFR-estimating equation: (1) Accuracy in estimating measured GFR, (2) Optimal discrimination of clinical outcomes, and (3) Similar association with CKD risk factors and outcomes to that seen with measured GFR. These criteria are often not in agreement regarding the best equation.[125] A major problem is that some markers such as CysC and BTP are actually better than GFR in predicting certain clinical outcomes.[108] Optimally predicting outcomes with kidney function markers is not the same as optimally determining how kidney function predicts outcomes.[126]

There are also specific issues that affect the performance of different equations in estimating measured GFR. GFR estimating equations are population specific. An equation developed using CKD patients will underestimate GFR in potential kidney donors, while an equation developed using potential kidney donors will overestimate GFR in CKD patients[82,127,128] (Figure 4.5). Equations can be developed for estimating GFR in mL/min or in mL/min/1.73 m^2. The former is

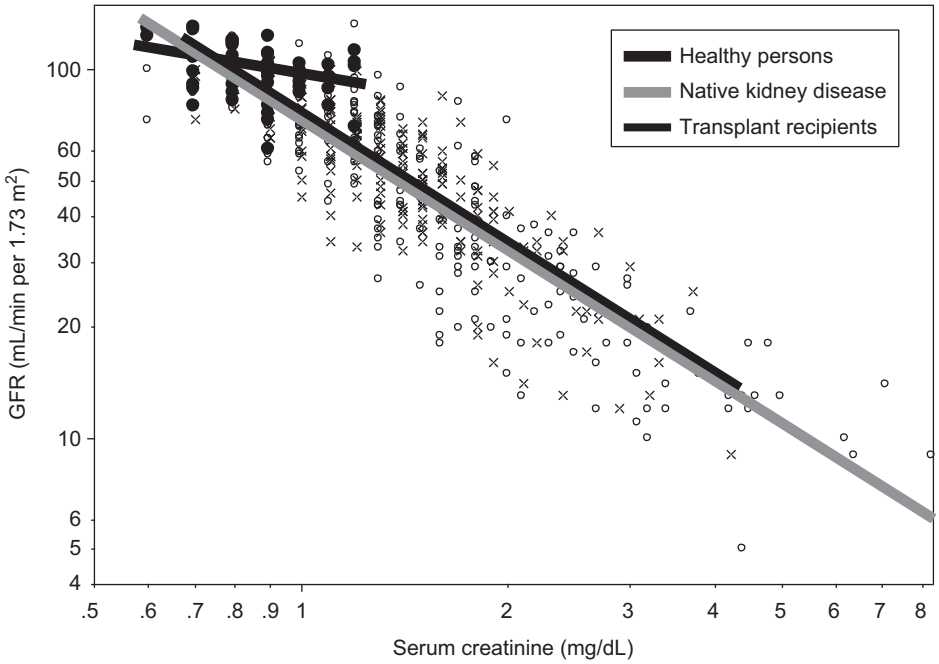


FIGURE 4.5 Relationship between serum creatinine and glomerular filtration rate (GFR) (measured by iothalamate) in healthy, native kidney disease and transplant recipients.[61] The *closed circles* represent healthy persons (n = 50). The *open circles* represent patients with native kidney disease only (n = 204). The *crosses* represent patients with solid organ transplants (n = 206). The regression lines (similar to GFR estimating equations) for all three patient groups (native kidney disease, transplant recipients, and healthy) are shown. *Figure permission obtained from the Nature Publishing Group.*

more relevant for determining drug doses, while the latter is more relevant for staging CKD. Endogenous filtration markers are inherently more correlated with GFR in mL/min/1.73 m^2 than GFR in mL/min. Indexing GFR to body surface area (1.73 m^2) is somewhat misleading in obese patients. The increase in GFR from the increase in single nephron GFR with obesity[129] is masked by the increase in body surface area in obesity.

Commonly used equations have been derived using standardized S[Cr] (Modified Diet in Renal Disease [MDRD] study and Chronic Kidney Disease Epidemiology [CKD-EPI] equations) or were derived in a manner that did not depend on S[Cr] standardization (Cockcroft-Gault equation) (Figure 4.6). Finally, there are numerous differences in GFR measurement protocols, including choice of exogenous markers, which can affect performance of any GFR estimating equation.[130]

Equations Used in Clinical Practice

Most current clinical practice guidelines recommend the S[Cr]-based CKD-EPI equation to estimate GFR in adults,[7] which has replaced the formerly recommended MDRD Study equation.[131] Both equations use the same variables (S[Cr], age, sex, black vs. nonblack race) to estimate measured GFR based on iothalamate clearance and give similar GFR estimates except in patients with lower S[Cr] levels. The S[Cr]-based CKD-EPI equation generally gives higher GFR estimates than the MDRD Study equation, because it was derived using about one-third low-risk patients (such as kidney donors) and two-thirds CKD patients, while the MDRD Study equation was derived using only CKD patients.[132,133] The CKD-EPI equation also models age with a linear function (MDRD Study equation used a logarithmic function), which leads to lower GFR estimates in the elderly.

The Cockcroft-Gault equation estimates urinary creatinine clearance rather than measured GFR.[134] It is imprecise relative to currently used S[Cr]-based equations[135] because it contains a weight variable, which is helpful in estimating GFR in mL/min. It is difficult to avoid anthropomorphic variables such as height and weight for equations that estimate GFR in mL/min instead of mL/min/1.73 m^2. The Cockcroft-Gault equation is still useful in clinical practice for dosing renally excreted drugs that have dosing guidelines based on estimated GFR with the Cockcroft-Gault equation.[136,137] More contemporary estimated GFR equations can substantially improve drug dosing over the Cockcroft-Gault equation once equation-specific dosing guidelines are developed.[138,139]

There are also equations based on cystatin C (with or without S[Cr]) including the CKD-EPI equations, the

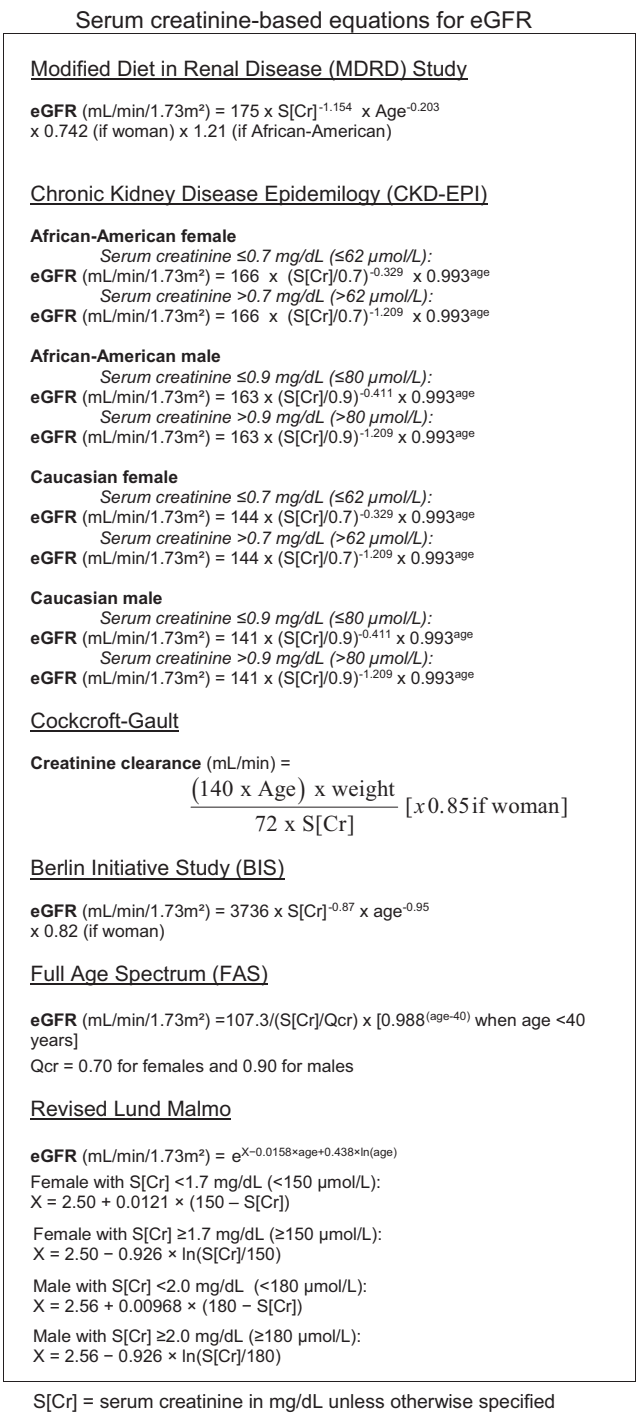


FIGURE 4.6 Creatinine-based equations to estimate glomerular filtration rate.

Full Age Spectrum (FAS) equations,[140] and the Caucasian, Asian, Pediatric, and Adult (CAPA) equation.[141] CysC-based equations perform similar to S[Cr]-based equations but combining S[Cr] and CysC improves the estimation of measured GFR, particularly in children and older adults. Interestingly, CysC has been shown to perform better than S[Cr] in predicting cardiovascular morbidity and mortality.[142–144] This does not necessarily make CysC or CysC-based estimated GFR a superior method for determining GFR, because better discrimination of outcomes can be due to the non-GFR determinants of CysC, such as inflammation and atherosclerosis.[145,146] In particular, S[Cr]-based estimated GFR is generally less biased in its associations with CKD risk factors and outcomes than CysC-based estimated GFR.[108,147,148] Several equations based on BTP or B_2M have also been proposed by different studies.[149–151] However, these equations have been developed from limited samples and have not shown an improvement in estimating GFR over S[Cr] and CysC-based equations in children or adults.[152–156]

All S[Cr]-based and adult-derived equations are inaccurate in children and adolescents.[157] In children, S[Cr] increases with age due to increases in muscle mass, while GFR also increases with age as kidneys grow in size. Reliability and standardization of endogenous filtration markers is particularly critical as their concentrations are lower in children than in adults.[158,159] The most popular equation in children remains the Schwartz equation (based on S[Cr] and height), especially the 2009 version, which has been developed with a standardized enzymatic IDMS-traceable assay, and validated against measured GFR by iohexol clearance.[160] CysC-based equations have also been developed.[161] CysC-based equations developed for use in children have been shown to be more accurate than S[Cr]-based equations.[162]

Ethnicity

Muscle mass and creatinine tubular secretion can differ by race or ethnicity.[163] This has been well described in assessing kidney function between white and African American patients.[75,95] The MDRD study equation was the first to include a race coefficient for African American *relative to* white subjects.[132] There is evidence that this race coefficient is less accurate and even inappropriate in low-risk populations.[164,165] Estimated GFR using the race coefficient leads to determination of a lower prevalence of CKD in African Americans than whites, despite the considerably higher risk of ESRD in African Americans. The African American coefficient may not be accurate in other black populations in Africa, Europe, Caribbean, or indigenous Australians.[165–168]

There are a variety of proposed race coefficients for the MDRD Study and CKD-EPI equations in Asian populations, but these studies lacked a white reference group. Thus, methodological differences between studies may explain these race coefficients.[169–171]

Older Adults

Older adults require special consideration in the context of GFR assessment. Older age leads to GFR decline from nephron loss in healthy adults,[24] and it is the strongest predictor of CKD.[27] The CKD-EPI equations were developed from a cohort that included a small proportion of patients older than 70 years. Both the CKD-EPI and the MDRD study equations overestimate measured GFR in older adults with CKD[34] (Figure 4.7). These results are explained by sarcopenia, which affects the relationship between S[Cr] and GFR and is not modeled correctly across the full adult age spectrum. Addition of CysC into estimating equations increases accuracy and precision for estimating measured GFR in older adults.[34,140,172] From a population-based sample of adults aged 70 years and older, the Berlin Initiative Study (BIS) developed two equations, one based on S[Cr] (BIS1) and the other based on both S[Cr] and CysC (BIS2).[34] While some external validation studies confirmed the improved accuracy of the BIS equation in older adults,[172–174] others did not.[175] The S[Cr] and CysC–based FAS equation, the CAPA equation, and the Revised Lund Malmo equations have also been shown to perform well in older adults.[140,172]

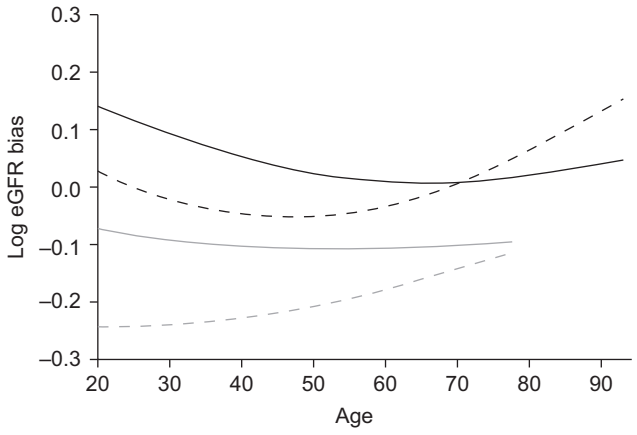


FIGURE 4.7 Bias between estimated and measured glomerular filtration by age (years) and population (healthy vs. chronic kidney disease [CKD]).[125] Mean bias calculated for log eGFR—log mGFR is depicted. The creatinine-based Chronic Kidney Disease Epidemiology (CKD-EPI) equation is represented by the solid smoother curves, and the Modified Diet in Renal Disease (MDRD) equation is represented by the dashed smoother curves. Native CKD and transplant recipients (n = 4558) are represented by the black curves, and the potential kidney donors and postnephrectomy kidney donors (n = 680) are represented by the gray curves. In CKD patients, the CKD-EPI equation tended to overestimate GFR more in younger adults, whereas the MDRD equation tended to overestimate GFR more in older adults, though both overestimate GFR in the very elderly. *GFR*, glomerular filtration rate. *Figure permission obtained from the American Society of Nephrology.*

Limitations of Estimated GFR

The MDRD and CKD-EPI equations were developed from cohorts that contained all or mostly CKD patients.[132,133,176] CKD patients have lower muscle mass than healthy subjects, leading to underestimation of GFR in low-risk populations, such as predonation or postdonation kidney donors.[127] Among hospitalized patients with muscle wasting, caution is needed with interpreting estimated GFR.[177,178] Other settings where creatinine generation is not well modeled by S[Cr]-based equations include obese,[179] anorectic,[180] critically ill,[177] and hyperfiltering patients.[181] As with any endogenous filtration marker, GFR-estimating equations are more accurate in the steady state than in acute kidney injury. GFR-estimating equations do not always correctly reflect the slopes of measured GFR.[181–184] Thus, in certain settings, such as dosing of nephrotoxic drugs or determining eligibility for kidney donation, direct measurement of GFR can be useful given the limitations of estimated GFR.[55]

CONCLUSIONS

Abnormal loss of kidney function identifies CKD, and kidney function is primarily determined using GFR. There are inherent problems with over-reliance on either measured GFR or estimated GFR to characterize kidney function. Other characterizations of kidney function are also useful to identify CKD, such as albuminuria despite the glomerular filtration barrier and tubular reabsorption. Future novel, practical tests that characterize additional aspects of kidney function may help better identify and classify CKD.

References

1. Möller E, McIntosh JF, Van Slycke DD. Studies of urea excretion. II. Relationship between urine volume and the rate of urea excretion by normal adults. *J Clin Invest* 1929;**6**(3):427–65.
2. Smith HW. *The kidney: structure and function in health and disease*. New York: Oxford University Press Inc; 1951.
3. Moranne O, Froissart M, Rossert J, Gauci C, Boffa JJ, Haymann JP, et al. Timing of onset of CKD-related metabolic complications. *J Am Soc Nephrol* 2009;**20**(1):164–71.
4. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**(13):1296–305.
5. Matsushita K, van d V, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;**375**(9731):2073–81.
6. Denic A, Glassock RJ, Rule AD. Single-nephron glomerular filtration rate in healthy adults. *N Engl J Med* 2017;**377**:1203–4.

7. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; **3**(1):1−150.
8. Smith HW. Comparative physiology of the kidney. In: Smith HW, editor. *The kidney: stucture and function in health and disease*. New York: Oxford University press; 1951. p. 520−74.
9. Wesson LG. Renal hemodynamics in physiologic states. In: Wesson LG, editor. *Physiology of the human kidney*. New York: Grune & Stratton; 1969. p. 96−108.
10. Delanaye P, Schaeffner E, Ebert N, Cavalier E, Mariat C, Krzesinski JM, et al. Normal reference values for glomerular filtration rate: what do we really know? *Nephrol Dial Transplant* 2012; **27**(7):2664−72.
11. Poggio ED, Rule AD, Tanchanco R, Arrigain S, Butler RS, Srinivas T, et al. Demographic and clinical characteristics associated with glomerular filtration rates in living kidney donors. *Kidney Int* 2009;**75**(10):1079−87.
12. Rule AD, Gussak HM, Pond GR, Bergstralh EJ, Stegall MD, Cosio FG, et al. Measured and estimated GFR in healthy potential kidney donors. *Am J Kidney Dis* 2004;**43**(1):112−9.
13. Pottel H, Hoste L, Yayo E, Delanaye P. Glomerular filtration rate in healthy living potential kidney donors: a meta-analysis supporting the construction of the full age spectrum equation. *Nephron* 2017;**135**:105−19.
14. Pottel H, Delanaye P, Weekers L, Selistre L, Goffin K, Gheysens O, Dubourg L. Age-dependent reference intervals for estimated and measured glomerular filtration rate. *Clin Kidney J* 2017;**10**:545−51.
15. Ricos C, Cava F, Garcia-Lario JV, Hernandez A, Iglesias N, Jimenez CV, et al. The reference change value: a proposal to interpret laboratory reports in serial testing based on biological variation. *Scand J Clin Lab Invest* 2004;**64**(3):175−84.
16. Visser FW, Muntinga JH, Dierckx RA, Navis G. Feasibility and impact of the measurement of extracellular fluid volume simultaneous with GFR by 125I-iothalamate. *Clin J Am Soc Nephrol* 2008; **3**(5):1308−15.
17. Wilkinson J, Fleming JS, Waller DG. Effect of food and activity on the reproducibility of isotopic GFR estimation. *Nucl Med Commun* 1990;**11**(10):697−700.
18. Merrill AJ, Cargill WH. The effect of exercise on the renal plasma flow and filtration rate of normal and cardiac subjects. *J Clin Invest* 1948;**27**(2):272−7.
19. Sirota JH, Baldwin DS, Villarreal H. Diurnal variations of renal function in man. *J Clin Invest* 1950;**29**(2):187−92.
20. Koopman MG, Koomen GC, Krediet RT, de Moor EA, Hoek FJ, Arisz L. Circadian rhythm of glomerular filtration rate in normal individuals. *Clin Sci (Lond)* 1989;**77**(1):105−11.
21. Brochner-Mortensen J, Rodbro P. Selection of routine method for determination of glomerular filtration rate in adult patients. *Scand J Clin Lab Invest* 1976;**36**(1):35−43.
22. Delanaye P, Cavalier E, Froissart M, Krzesinski JM. Reproducibility of GFR measured by chromium-51-EDTA and iohexol. *Nephrol Dial Transplant* 2008;**23**(12):4077−8.
23. Gaspari F, Perico N, Matalone M, Signorini O, Azzollini N, Mister M, et al. Precision of plasma clearance of iohexol for estimation of GFR in patients with renal disease. *J Am Soc Nephrol* 1998;**9**(2):310−3.
24. Denic A, Lieske JC, Chakkera HA, Poggio ED, Alexander MP, Singh P, et al. The substantial loss of nephrons in healthy human kidneys with aging. *J Am Soc Nephrol* 2017;**28**:313−20.
25. Denic A, Mathew J, Nagineni VV, Thompson RH, Leibovich BC, Lerman LO, et al. Clinical and pathology findings associate consistently with larger glomerular volume. *J Am Soc Nephrol* 2018;**29**(7):1960−9.
26. Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J Clin Invest* 1950;**29**(5):496−507.
27. Rule AD, Amer H, Cornell LD, Taler SJ, Cosio FG, Kremers WK, et al. The association between age and nephrosclerosis on renal biopsy among healthy adults. *Ann Intern Med* 2010;**152**(9): 561−7.
28. Back SE, Ljungberg B, Nilsson-Ehle I, Borga O, Nilsson-Ehle P. Age dependence of renal function: clearance of iohexol and p-amino hippurate in healthy males. *Scand J Clin Lab Invest* 1989;**49**(7):641−6.
29. Slack TK, Wilson DM. Normal renal function: CIN and CPAH in healthy donors before and after nephrectomy. *Mayo Clin Proc* 1976;**51**(5):296−300.
30. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc* 1985; **33**(4):278−85.
31. Wetzels JF, Kiemeney LA, Swinkels DW, Willems HL, den Heijer M. Age- and gender-specific reference values of estimated GFR in Caucasians: the Nijmegen biomedical study. *Kidney Int* 2007;**72**(5):632−7.
32. Glassock RJ, Rule AD. The implications of anatomical and functional changes of the aging kidney: with an emphasis on the glomeruli. *Kidney Int* 2012;**82**(3):270−7.
33. Fehrman-Ekholm I, Skeppholm L. Renal function in the elderly (>70 years old) measured by means of iohexol clearance, serum creatinine, serum urea and estimated clearance. *Scand J Urol Nephrol* 2004;**38**(1):73−7.
34. Schaeffner ES, Ebert N, Delanaye P, Frei U, Gaedeke J, Jakob O, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. *Ann Intern Med* 2012;**157**(7):471−81.
35. Shannon JA. The renal excretion of creatinine in man. *J Clin Invest* 1935;**14**(4):403−10.
36. Richards AN, Westfall BB, Bott PA. Renal excretion of inulin, creatinine, and xylose in normal dogs. *Proc Soc Exp Biol Med* 1934;**32**:73.
37. Gutman Y, Gottschalk C, Lassiter WE. Micropuncture study of inulin absorption in the rat kidney. *Science* 1965;**147**:753−4.
38. Schanker LS, Hogben CA. Biliary excretion of inulin, sucrose, and mannitol: analysis of bile formation. *Am J Physiol* 1961;**200**: 1087−90.
39. Delanaye P, Thibaudin L, Souvignet M, Maillard N, Alamartine E, Rozet E, et al. Comparison of acid and enzymatic methods for inulin dosage: analytical performances and impact on glomerular filtration rate evaluation. *Clin Chim Acta* 2012;**413**(5−6):556−60.
40. Brochner-Mortensen J. A simple method for the determination of glomerular filtration rate. *Scand J Clin Lab Invest* 1972;**30**(3): 271−4.
41. Medeiros FS, Sapienza MT, Prado ES, Agena F, Shimizu MH, Lemos FB, et al. Validation of plasma clearance of 51Cr-EDTA in adult renal transplant recipients: comparison with inulin renal clearance. *Transpl Int* 2009;**22**(3):323−31.
42. Owen JE, Walker RG, Willems D, Guignard PA, d'Apice AJ. Cadmium telluride detectors in the external measurement of glomerular filtration rate using 99mTc-DTPA (Sn): comparison with 51Cr-EDTA and 99mTc-DTPA (Sn) plasma sample methods. *Clin Nephrol* 1982;**18**(4):200−3.
43. Jeghers O, Piepsz A, Ham HR. What does protein binding of radiopharmaceuticals mean exactly? *Eur J Nucl Med* 1990; **17**(3−4):101−2.

44. Xie P, Huang JM, Liu XM, Wu WJ, Pan LP, Lin HY. (99m)Tc-DTPA renal dynamic imaging method may be unsuitable to be used as the reference method in investigating the validity of CDK-EPI equation for determining glomerular filtration rate. *PLoS One* 2013;**8**(5):e62328.
45. Back SE, Krutzen E, Nilsson-Ehle P. Contrast media as markers for glomerular filtration: a pharmacokinetic comparison of four agents. *Scand J Clin Lab Invest* 1988;**48**(3):247–53.
46. Botev R, Mallie JP, Wetzels JF, Couchoud C, Schuck O. The clinician and estimation of glomerular filtration rate by creatinine-based formulas: current limitations and quo vadis. *Clin J Am Soc Nephrol* 2011;**6**(4):937–50.
47. Perrone RD, Steinman TI, Beck GJ, Skibinski CI, Royal HD, Lawlor M, et al. Utility of radioisotopic filtration markers in chronic renal insufficiency: simultaneous comparison of 125I-iothalamate, 169Yb-DTPA, 99mTc-DTPA, and inulin. The Modification of Diet in Renal Disease study. *Am J Kidney Dis* 1990;**16**(3): 224–35.
48. Ott NT. A simple technique for estimating glomerular filtration rate with subcutaneous injection of (125I)lothalamate. *Mayo Clin Proc* 1975;**50**(11):664–8.
49. Cavalier E, Rozet E, Dubois N, Charlier C, Hubert P, Chapelle JP, et al. Performance of iohexol determination in serum and urine by HPLC: validation, risk and uncertainty assessment. *Clin Chim Acta* 2008;**396**(1–2):80–5.
50. Gaspari F, Perico N, Ruggenenti P, Mosconi L, Amuchastegui CS, Guerini E, et al. Plasma clearance of nonradioactive iohexol as a measure of glomerular filtration rate. *J Am Soc Nephrol* 1995;**6**(2): 257–63.
51. Sterner G, Frennby B, Mansson S, Nyman U, van Westen D, Almen T. Determining 'true' glomerular filtration rate in healthy adults using infusion of inulin and comparing it with values obtained using other clearance techniques or prediction equations. *Scand J Urol Nephrol* 2008;**42**(3):278–85.
52. Brandstrom E, Grzegorczyk A, Jacobsson L, Friberg P, Lindahl A, Aurell M. GFR measurement with iohexol and 51Cr-EDTA. A comparison of the two favoured GFR markers in Europe. *Nephrol Dial Transplant* 1998;**13**(5):1176–82.
53. Pucci L, Bandinelli S, Penno G, Nannipieri M, Rizzo L, Navalesi R. Iohexol plasma clearance in determining glomerular filtration rate in diabetic patients. *Ren Fail* 1998;**20**(2):277–84.
54. Delanaye P, Ebert N, Melsom T, Gaspari F, Mariat C, Cavalier E, et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 1: how to measure glomerular filtration rate with iohexol? *Clin Kidney J* 2016;**9**: 682–99.
55. Delanaye P, Melsom T, Ebert N, Back SE, Mariat C, Cavalier E, et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 2: why to measure glomerular filtration rate with iohexol? *Clin Kidney J* 2016;**9**: 700–4.
56. Luis-Lima S, Gaspari F, Negrin-Mena N, Carrara F, Diaz-Martin L, Jimenez-Sosa A, Gonzalez-Rinne F, Torres A, Porrini E. Iohexol plasma clearance simplified by dried blood spot testing. *Nephrol Dial Transplant* 2018;**33**(9):1597–603.
57. Qi Z, Whitt I, Mehta A, Jin J, Zhao M, Harris RC, et al. Serial determination of glomerular filtration rate in conscious mice using FITC-inulin clearance. *Am J Physiol Renal Physiol* 2004;**286**: F590–596.
58. Schock-Kusch D, Sadick M, Henninger N, Kraenzlin B, Claus G, Kloetzer HM, et al. Transcutaneous measurement of glomerular filtration rate using FITC-sinistrin in rats. *Nephrol Dial Transplant* 2009;**24**:2997–3001.
59. Schreiber A, Shulhevich Y, Geraci S, Hesser J, Stsepankou D, Neudecker S, et al. Transcutaneous measurement of renal function in conscious mice. *Am J Physiol Renal Physiol* 2012;**303**: F783–788.
60. Rizk DV, Meier D, Sandoval RM, Chacana T, Reilly ES, Seegmiller JC, et al. A novel method for rapid bedside measurement of GFR. *J Am Soc Nephrol* 2018;**29**:1609–13.
61. Rule AD, Bergstralh EJ, Slezak JM, Bergert J, Larson TS. Glomerular filtration rate estimated by cystatin C among different clinical presentations. *Kidney Int* 2006;**69**(2):399–405.
62. Frennby B, Sterner G. Contrast media as markers of GFR. *Eur Radiol* 2002;**12**(2):475–84.
63. Skluzacek PA, Szewc RG, Nolan III CR, Riley DJ, Lee S, Pergola PE. Prediction of GFR in liver transplant candidates. *Am J Kidney Dis* 2003;**42**(6):1169–76.
64. Agarwal R, Bills JE, Yigazu PM, Abraham T, Gizaw AB, Light RP, et al. Assessment of iothalamate plasma clearance: duration of study affects quality of GFR. *Clin J Am Soc Nephrol* 2009;**4**(1):77–85.
65. Stolz A, Hoizey G, Toupance O, Lavaud S, Vitry F, Chanard J, et al. Evaluation of sample bias for measuring plasma iohexol clearance in kidney transplantation. *Transplantation* 2010;**89**(4):440–5.
66. Delanaye P, Flamant M, Dubourg L, Vidal-Petiot E, Lemoine S, Cavalier E, et al. Single- versus multiple-sample method to measure glomerular filtration rate. *Nephrol Dial Transplant* 2018; **33**(10):1778–85.
67. Hsu CY, Propert K, Xie D, Hamm L, He J, Miller E, et al. Measured GFR does not outperform estimated GFR in predicting CKD-related complications. *J Am Soc Nephrol* 2011;**22**(10):1931–7.
68. Barri YM, Parker III T, Daoud Y, Glassock RJ. Definition of chronic kidney disease after uninephrectomy in living donors: what are the implications? *Transplantation* 2010;**90**(5):575–80.
69. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, et al. for the National Kidney Disease Education Program Laboratory Working Group Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem* 2006;**52**(1):5–18.
70. Pieroni L, Delanaye P, Boutten A, Bargnoux AS, Rozet E, Delatour V, et al. A multicentric evaluation of IDMS-traceable creatinine enzymatic assays. *Clin Chim Acta* 2011;**412**(23–24): 2070–5.
71. Cobbaert CM, Baadenhuijsen H, Weykamp CW. Prime time for enzymatic creatinine methods in pediatrics. *Clin Chem* 2009; **55**(3):549–58.
72. Boutten A, Bargnoux AS, Carlier MC, Delanaye P, Rozet E, Delatour V, et al. Enzymatic but not compensated Jaffe methods reach the desirable specifications of NKDEP at normal levels of creatinine. Results of the French multicentric evaluation. *Clin Chim Acta* 2013;**419**:132–5.
73. Lee ES, Collier CP, White CA. Creatinine assay attainment of analytical performance goals following implementation of IDMS standardization: further improvements required. *Can J Kidney Health Dis* 2017;**4**. 2054358117693353.
74. Greenberg N, Roberts WL, Bachmann LM, Wright EC, Dalton RN, Zakowski JJ, et al. Specificity characteristics of 7 commercial creatinine measurement procedures by enzymatic and Jaffe method principles. *Clin Chem* 2012;**58**:391–401.
75. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. *Clin Chem* 1992; **38**(10):1933–53.
76. Shemesh O, Golbetz H, Kriss JP, Myers BD. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int* 1985;**28**(5):830–8.

77. Heymsfield SB, Arteaga C, McManus C, Smith J, Moffitt S. Measurement of muscle mass in humans: validity of the 24-hour urinary creatinine method. *Am J Clin Nutr* 1983;**37**(3):478–94.
78. Rule AD, Bailey KR, Schwartz GL, Khosla S, Lieske JC, Melton III LJ. For estimating creatinine clearance measuring muscle mass gives better results than those based on demographics. *Kidney Int* 2009;**75**(10):1071–8.
79. Mitch WE, Walser M. A proposed mechanism for reduced creatinine excretion in severe chronic renal failure. *Nephron* 1978;**21**(5): 248–54.
80. Mayersohn M, Conrad KA, Achari R. The influence of a cooked meat meal on creatinine plasma concentration and creatinine clearance. *Br J Clin Pharmacol* 1983;**15**(2):227–30.
81. Preiss DJ, Godber IM, Lamb EJ, Dalton RN, Gunn IR. The influence of a cooked-meat meal on estimated glomerular filtration rate. *Ann Clin Biochem* 2007;**44**(Pt 1):35–42.
82. Delanaye P, Cohen EP. Formula-based estimates of the GFR: equations variable and uncertain. *Nephron Clin Pract* 2008;**110**(1): c48–53.
83. van Acker BA, Koomen GC, Koopman MG, de Waart DR, Arisz L. Creatinine clearance during cimetidine administration for measurement of glomerular filtration rate. *Lancet* 1992;**340**(8831): 1326–9.
84. Morgan DB, Dillon S, Payne RB. The assessment of glomerular function: creatinine clearance or plasma creatinine? *Postgrad Med* 1978;**54**(631):302–10.
85. Toto RD, Kirk KA, Coresh J, Jones C, Appel L, Wright J, et al. Evaluation of serum creatinine for estimating glomerular filtration rate in African Americans with hypertensive nephrosclerosis: results from the African-American Study of Kidney Disease and Hypertension (AASK) Pilot Study. *J Am Soc Nephrol* 1997; **8**(2):279–87.
86. Abrahamson M. Human cysteine proteinase inhibitors. Isolation, physiological importance, inhibitory mechanism, gene structure and relation to hereditary cerebral hemorrhage. *Scand J Clin Lab Invest Suppl* 1988;**191**:21–31.
87. Abrahamson M, Olafsson I, Palsdottir A, Ulvsback M, Lundwall A, Jensson O, et al. Structure and expression of the human cystatin C gene. *Biochem J* 1990;**268**(2):287–94.
88. Tenstad O, Roald AB, Grubb A, Aukland K. Renal handling of radiolabelled human cystatin C in the rat. *Scand J Clin Lab Invest* 1996;**56**(5):409–14.
89. Stevens LA, Schmid CH, Greene T, Li L, Beck GJ, Joffe MM, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int* 2009;**75**(6):652–60.
90. Macdonald J, Marcora S, Jibani M, Roberts G, Kumwenda M, Glover R, et al. GFR estimation using cystatin C is not independent of body composition. *Am J Kidney Dis* 2006;**48**(5):712–9.
91. Vinge E, Lindergard B, Nilsson-Ehle P, Grubb A. Relationships among serum cystatin C, serum creatinine, lean tissue mass and glomerular filtration rate in healthy adults. *Scand J Clin Lab Invest* 1999;**59**(8):587–92.
92. Liu X, Foster MC, Tighiouart H, Anderson AH, Beck GJ, Contreras G, et al. Investigators, CS: non-GFR determinants of low-molecular-weight serum protein filtration markers in CKD. *Am J Kidney Dis* 2016;**68**:892–900.
93. Fricker M, Wiesli P, Brandle M, Schwegler B, Schmid C. Impact of thyroid dysfunction on serum cystatin C. *Kidney Int* 2003;**63**(5): 1944–7.
94. Naour N, Fellahi S, Renucci JF, Poitou C, Rouault C, Basdevant A, et al. Potential contribution of adipose tissue to elevated serum cystatin C in human obesity. *Obesity* 2009;**17**(12):2121–6.
95. Knight EL, Verhave JC, Spiegelman D, Hillege HL, de Zeeuw D, Curhan GC, et al. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. *Kidney Int* 2004;**65**(4):1416–21.
96. Gagneux-Brunon A, Mariat C, Delanaye P. Cystatin C in HIV-infected patients: promising but not yet ready for prime time. *Nephrol Dial Transplant* 2012;**27**(4):1305–13.
97. Risch L, Huber AR. Glucocorticoids and increased serum cystatin C concentrations. *Clin Chim Acta* 2002;**320**(1–2):133–4.
98. White CA, Akbari A, Doucette S, Fergusson D, Ramsay T, Hussain N, et al. Effect of clinical variables and immunosuppression on serum cystatin C and beta-trace protein in kidney transplant recipients. *Am J Kidney Dis* 2009;**54**:922–30.
99. Delanaye P, Pieroni L, Abshoff C, Lutteri L, Chapelle JP, Krzesinski JM, et al. Analytical study of three cystatin C assays and their impact on cystatin C-based GFR-prediction equations. *Clin Chim Acta* 2008;**398**(1–2):118–24.
100. Voskoboev NV, Larson TS, Rule AD, Lieske JC. Importance of cystatin C assay standardization. *Clin Chem* 2011;**57**(8):1209–11.
101. Larsson A, Hansson LO, Flodin M, Katz R, Shlipak MG. Calibration of the Siemens cystatin C immunoassay has changed over time. *Clin Chem* 2011;**57**(5):777–8.
102. White CA, Rule AD, Collier CP, Akbari A, Lieske JC, Lepage N, et al. The impact of interlaboratory differences in cystatin C assay measurement on glomerular filtration rate estimation. *Clin J Am Soc Nephrol* 2011;**6**:2150–6.
103. Grubb A, Blirup-Jensen S, Lindstrom V, Schmidt C, Althaus H, Zegers I. First certified reference material for cystatin C in human serum ERM-DA471/IFCC. *Clin Chem Lab Med* 2010;**48**(11): 1619–21.
104. Eckfeldt JH, Karger AB, Miller WG, Rynders GP, Inker LA. Performance in measurement of serum cystatin C by laboratories participating in the college of American Pathologists 2014 CYS Survey. *Arch Pathol Lab Med* 2015;**139**:888–93.
105. Astor BC, Shafi T, Hoogeveen RC, Matsushita K, Ballantyne CM, Inker LA, Coresh J. Novel markers of kidney function as predictors of ESRD, cardiovascular disease, and mortality in the general population. *Am J Kidney Dis* 2012;**59**:653–62.
106. Foster MC, Inker LA, Levey AS, Selvin E, Eckfeldt J, Juraschek SP, et al. Novel filtration markers as predictors of all-cause and cardiovascular mortality in US adults. *Am J Kidney Dis* 2013;**62**: 42–51.
107. Tangri N, Inker LA, Tighiouart H, Sorensen E, Menon V, Beck G, et al. Filtration markers may have prognostic value independent of glomerular filtration rate. *J Am Soc Nephrol* 2012;**23**(2):351–9.
108. Bhavsar NA, Appel LJ, Kusek JW, Contreras G, Bakris G, Coresh J, et al. Comparison of measured GFR, serum creatinine, cystatin C, and beta-trace protein to predict ESRD in African Americans with hypertensive CKD. *Am J Kidney Dis* 2011;**58**(6):886–93.
109. Clausen J. Proteins in normal cerebrospinal fluid not found in serum. *Proc Soc Exp Biol Med* 1961;**109**:91–5.
110. Hoffmann A, Nimtz M, Conradt HS. Molecular characterization of beta-trace protein in human serum and urine: a potential diagnostic marker for renal diseases. *Glycobiology* 1997;**7**(4): 499–506.
111. White CA, Ghazan-Shahi S, Adams MA. Beta-trace protein: a marker of GFR and other biological pathways. *Am J Kidney Dis* 2015;**65**:131–46.
112. White CA, Akbari A, Eckfeldt JH, Chakraborty D, McCudden C, Flemming JA, et al. Beta-trace protein assays: a comparison between nephelometric and ELISA methodologies. *Am J Kidney Dis* 2017;**69**:866–8.
113. Poge U, Gerhardt TM, Stoffel-Wagner B, Palmedo H, Klehr HU, Sauerbruch T, et al. Beta-trace protein is an alternative marker for glomerular filtration rate in renal transplantation patients. *Clin Chem* 2005;**51**(8):1531–3.
114. Kobata M, Shimizu A, Rinno H, Hamada C, Maeda K, Fukui M, et al. Beta-trace protein, a new marker of GFR, may predict the early prognostic stages of patients with type 2 diabetic nephropathy. *J Clin Lab Anal* 2004;**18**:237–9.

115. Astor BC, Levey AS, Stevens LA, Van Lente F, Selvin E, Coresh J. Method of glomerular filtration rate estimation affects prediction of mortality risk. *J Am Soc Nephrol* 2009;**20**:2214–22.
116. Priem F, Althaus H, Birnbaum M, Sinha P, Conradt HS, Jung K. Beta-trace protein in serum: a new marker of glomerular filtration rate in the creatinine-blind range. *Clin Chem* 1999;**45**(4): 567–8.
117. Grey HM, Kubo RT, Colon SM, Poulik MD, Cresswell P, Springer T, et al. The small subunit of HL-A antigens is beta 2-microglobulin. *J Exp Med* 1973;**138**:1608–12.
118. Bethea M, Forman DT. Beta 2-microglobulin: its significance and clinical usefulness. *Ann Clin Lab Sci* 1990;**20**:163–8.
119. Miyata T, Jadoul M, Kurokawa K, Van Ypersele de Strihou C. Beta-2 microglobulin in renal disease. *J Am Soc Nephrol* 1998;**9**(9): 1723–35.
120. Stanga Z, Nock S, Medina-Escobar P, Nydegger UE, Risch M, Risch L. Factors other than the glomerular filtration rate that determine the serum beta-2-microglobulin level. *PLoS One* 2013; **8**:e72073.
121. Fedele PL, Choy KW, Doery JC, Grigoriadis G, Shortt J, Lu ZX. Inter-laboratory discordance of beta-2 microglobulin results: impact on the validity of the international staging system for multiple myeloma. *Br J Haematol* 2014;**166**:951–3.
122. Shinkai S, Chaves PH, Fujiwara Y, Watanabe S, Shibata H, Yoshida H, et al. Beta2-microglobulin for risk stratification of total mortality in the elderly population: comparison with cystatin C and C-reactive protein. *Arch Intern Med* 2008;**168**(2):200–6.
123. Sekula P, Goek ON, Quaye L, Barrios C, Levey AS, Romisch-Margl W, et al. A metabolome-wide association study of kidney function and disease in the general population. *J Am Soc Nephrol* 2016;**27**:1175–88.
124. Coresh J, Inker LA, Sang Y, Chen J, Shafi T, Post WS, et al. Metabolomic profiling to improve glomerular filtration rate estimation: a proof-of-concept study. *Nephrol Dial Transplant* 2018. https://doi.org/10.1093/ndt/gfy094.
125. Rule AD, Glassock RJ. GFR estimating equations: getting closer to the truth? *Clin J Am Soc Nephrol* 2013;**8**(8):1414–20.
126. Glassock RJ, Rule AD. Optimally predicting mortality with kidney function markers is not the same as optimally determining how kidney function predicts mortality. *Nephrol Dial Transplant* 2017;**32**:585–7.
127. Murata K, Baumann NA, Saenger AK, Larson TS, Rule AD, Lieske JC. Relative performance of the MDRD and CKD-EPI equations for estimating glomerular filtration rate among patients with varied clinical presentations. *Clin J Am Soc Nephrol* 2011;**6**(8): 1963–72.
128. Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. *Ann Intern Med* 2004;**141**(12):929–37.
129. Denic A, Mathew J, Lerman LO, Lieske JC, Larson JJ, Alexander MP, et al. Single-nephron glomerular filtration rate in healthy adults. *N Engl J Med* 2017;**376**:2349–57.
130. Foster MC, Inker LA, Hsu CY, Eckfeldt JH, Levey AS, Pavkov ME, et al. CKD Biomarkers Consortium. Filtration markers as predictors of ESRD and mortality in Southwestern American Indians with type 2 diabetes. *Am J Kidney Dis* 2015;**66**:75–83.
131. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**(2 Suppl. 1):S1–266.
132. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;**130**(6): 461–70.
133. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro III AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**(9):604–12.
134. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;**16**(1):31–41.
135. Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P. Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. *J Am Soc Nephrol* 2005;**16**(3):763–73.
136. Park EJ, Wu K, Mi Z, Dong T, Lawrence JP, Ko CW, et al. A systematic comparison of cockcroft-gault and modification of diet in renal disease equations for classification of kidney dysfunction and dosage adjustment. *Ann Pharmacother* 2012; **46**(9):1174–87.
137. Nyman HA, Dowling TC, Hudson JQ, Peter WL, Joy MS, Nolin TD. Comparative evaluation of the Cockcroft-Gault Equation and the Modification of Diet in Renal Disease (MDRD) study equation for drug dosing: an opinion of the Nephrology Practice and Research Network of the American College of Clinical Pharmacy. *Pharmacotherapy* 2011;**31**(11): 1130–44.
138. Frazee EN, Rule AD, Herrmann SM, Kashani KB, Leung N, Virk A, et al. Serum cystatin C predicts vancomycin trough levels better than serum creatinine in hospitalized patients: a cohort study. *Crit Care* 2014;**18**:R110.
139. Frazee E, Rule AD, Lieske JC, Kashani KB, Barreto JN, Virk A, et al. Cystatin C-guided vancomycin dosing in critically ill patients: a quality improvement project. *Am J Kidney Dis* 2017;**69**: 658–66.
140. Pottel H, Delanaye P, Schaeffner E, Dubourg L, Eriksen BO, Melsom T, et al. Estimating glomerular filtration rate for the full age spectrum from serum creatinine and cystatin C. *Nephrol Dial Transplant* 2017;**32**:497–507.
141. Grubb A, Horio M, Hansson LO, Bjork J, Nyman U, Flodin M, et al. Generation of a new cystatin C-based estimating equation for glomerular filtration rate by use of 7 assays standardized to the international calibrator. *Clin Chem* 2014;**60**:974–86.
142. Foster MC, Inker LA, Levey AS, Selvin E, Eckfeldt J, Juraschek SP, et al. Novel filtration markers as predictors of all-cause and cardiovascular mortality in US adults. *Am J Kidney Dis* 2013; **62**(1):42–51.
143. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 2005; **352**(20):2049–60.
144. Peralta CA, Shlipak MG, Judd S, Cushman M, McClellan W, Zakai NA, et al. Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. *J Am Med Assoc* 2011;**305**(15):1545–52.
145. Lafarge JC, Naour N, Clement K, Guerre-Millo M. Cathepsins and cystatin C in atherosclerosis and obesity. *Biochimie* 2010;**92**(11): 1580–6.
146. Staun-Ram E, Miller A. Cathepsins (S and B) and their inhibitor Cystatin C in immune cells: modulation by interferon-beta and role played in cell migration. *J Neuroimmunol* 2011;**232**(1–2): 200–6.
147. Rule AD, Bailey KR, Lieske JC, Peyser PA, Turner ST. Estimating the glomerular filtration rate from serum creatinine is better than from cystatin C for evaluating risk factors associated with chronic kidney disease. *Kidney Int* 2013;**83**(6):1169–76.
148. Mathisen UD, Melsom T, Ingebretsen OC, Jenssen T, Njolstad I, Solbu MD, et al. Estimated GFR associates with cardiovascular risk factors independently of measured GFR. *J Am Soc Nephrol* 2011;**22**(5):927–37.

149. Poge U, Gerhardt T, Stoffel-Wagner B, Palmedo H, Klehr HU, Sauerbruch T, et al. Beta-trace protein-based equations for calculation of GFR in renal transplant recipients. *Am J Transplant* 2008;**8**(3):608–15.
150. White CA, Akbari A, Doucette S, Fergusson D, Hussain N, Dinh L, et al. A novel equation to estimate glomerular filtration rate using beta-trace protein. *Clin Chem* 2007;**53**(11): 1965–8.
151. Inker LA, Tighiouart H, Coresh J, Foster MC, Anderson AH, Beck GJ, et al. GFR estimation using beta-trace protein and beta2-microglobulin in CKD. *Am J Kidney Dis* 2016;**67**:40–8.
152. Filler G, Guerrero-Kanan R, Alvarez-Elias AC. Assessment of glomerular filtration rate in the neonate: is creatinine the best tool? *Curr Opin Pediatr* 2016;**28**:173–9.
153. Filler G, Alvarez-Elias AC, Westreich KD, Huang SS, Lindsay RM. Can the new CKD-EPI BTP-B2M formula be applied in children? *Pediatr Nephrol* 2016;**31**:2175–7.
154. Priem F, Althaus H, Jung K, Sinha P. Beta-trace protein is not better than cystatin C as an indicator of reduced glomerular filtration rate. *Clin Chem* 2001;**47**:2181.
155. Ebert N, Koep C, Schwarz K, Martus P, Mielke N, Bartel J, et al. Beta trace protein does not outperform creatinine and cystatin C in estimating glomerular filtration rate in older adults. *Sci Rep* 2017;**7**:12656.
156. Werner K, Pihlsgard M, Elmstahl S, Legrand H, Nyman U, Christensson A. Combining cystatin C and creatinine yields a reliable glomerular filtration rate estimation in older adults in contrast to beta-trace protein and beta2-microglobulin. *Nephron* 2017;**137**:29–37.
157. Selistre L, De Souza V, Cochat P, Antonello IC, Hadj-Aissa A, Ranchin B, et al. GFR estimation in adolescents and young adults. *J Am Soc Nephrol* 2012;**23**(6):989–96.
158. Delanaye P, Ebert N. Assessment of kidney function: estimating GFR in children. *Nat Rev Nephrol* 2012;**8**(9):503–4.
159. Delanghe JR. How to estimate GFR in children. *Nephrol Dial Transplant* 2009;**24**(3):714–6.
160. Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009;**20**(3):629–37.
161. Schwartz GJ, Schneider MF, Maier PS, Moxey-Mims M, Dharnidharka VR, Warady BA, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. *Kidney Int* 2012;**82**(4):445–53.
162. den Bakker E, Gemke R, Bokenkamp A. Endogenous markers for kidney function in children: a review. *Crit Rev Clin Lab Sci* 2018;**55**: 163–83.
163. Coresh J, Toto RD, Kirk KA, Whelton PK, Massry S, Jones C, et al. Creatinine clearance as a measure of GFR in screenees for the African-American study of kidney disease and hypertension pilot study. *Am J Kidney Dis* 1998;**32**(1):32–42.
164. Peralta CA, Lin F, Shlipak MG, Siscovick D, Lewis C, Jacobs Jr DR, et al. Race differences in prevalence of chronic kidney disease among young adults using creatinine-based glomerular filtration rate-estimating equations. *Nephrol Dial Transplant* 2010;**25**(12): 3934–9.
165. Delanaye P, Mariat C, Maillard N, Krzesinski JM, Cavalier E. Are the creatinine-based equations accurate to estimate glomerular filtration rate in African American populations? *Clin J Am Soc Nephrol* 2011;**6**(4):906–12.
166. van Deventer HE, Paiker JE, Katz IJ, George JA. A comparison of cystatin C- and creatinine-based prediction equations for the estimation of glomerular filtration rate in black South Africans. *Nephrol Dial Transplant* 2011;**26**(5):1553–8.
167. Maple-Brown LJ, Hughes JT, Lawton PD, Jones GR, Ellis AG, Drabsch K, et al. Accurate assessment of kidney function in indigenous Australians: the estimated GFR study. *Am J Kidney Dis* 2012;**60**(4):680–2.
168. Bukabau JB, Sumaili EK, Cavalier E, Pottel H, Kifakiou B, Nkodila A, et al. Performance of glomerular filtration rate estimation equations in Congolese healthy adults: the inopportunity of the ethnic correction. *PLoS One* 2018;**13**:e0193384.
169. Delanaye P, Cavalier E, Mariat C, Krzesinski JM, Rule AD. Estimating glomerular filtration rate in Asian subjects: where do we stand? *Kidney Int* 2011;**80**(5):439–40.
170. Stevens LA, Claybon MA, Schmid CH, Chen J, Horio M, Imai E, et al. Evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating the glomerular filtration rate in multiple ethnicities. *Kidney Int* 2011;**79**(5):555–62.
171. Teo BW, Xu H, Wang D, Li J, Sinha AK, Shuter B, et al. GFR estimating equations in a multiethnic Asian population. *Am J Kidney Dis* 2011;**58**(1):56–63.
172. Bjork J, Back SE, Ebert N, Evans M, Grubb A, Hansson M, et al. GFR estimation based on standardized creatinine and cystatin C: a European multicenter analysis in older adults. *Clin Chem Lab Med* 2018;**56**:422–35.
173. Koppe L, Klich A, Dubourg L, Ecochard R, Hadj-Aissa A. Compared performance of creatinine-based equation in the elderly. *J Nephrol* 2013;**26**(4):716–23.
174. Alshaer IM, Kilbride HS, Stevens PE, Eaglestone G, Knight S, Carter JL, et al. External validation of the Berlin equations for estimation of GFR in the elderly. *Am J Kidney Dis* 2014;**63**:862–5.
175. Fan L, Levey AS, Gudnason V, Eiriksdottir G, Andresdottir MB, Gudmundsdottir H, et al. Comparing GFR estimating equations using cystatin C and creatinine in elderly individuals. *J Am Soc Nephrol* 2015;**26**:1982–9.
176. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012;**367**(1):20–9.
177. Poggio ED, Nef PC, Wang X, Greene T, Van Lente F, Dennis VW, et al. Performance of the Cockcroft-Gault and modification of diet in renal disease equations in estimating GFR in ill hospitalized patients. *Am J Kidney Dis* 2005;**46**(2):242–52.
178. Segarra A, de la Torre J, Ramos N, Quiroz A, Garjau M, Torres I, et al. Assessing glomerular filtration rate in hospitalized patients: a comparison between CKD-EPI and four cystatin C-based equations. *Clin J Am Soc Nephrol* 2011;**6**(10):2411–20.
179. Verhave JC, Fesler P, Ribstein J, du Cailar G, Mimran A. Estimation of renal function in subjects with normal serum creatinine levels: influence of age and body mass index. *Am J Kidney Dis* 2005;**46**(2):233–41.
180. Delanaye P, Cavalier E, Radermecker RP, Paquot N, Depas G, Chapelle JP, et al. Cystatin C or creatinine for detection of stage 3 chronic kidney disease in anorexia nervosa. *Nephron Clin Pract* 2008;**110**(3):c158–63.
181. Gaspari F, Ruggenenti P, Porrini E, Motterlini N, Cannata A, Carrara F, et al. The GFR and GFR decline cannot be accurately estimated in type 2 diabetics. *Kidney Int* 2013;**84**(1):164–73.
182. Gera M, Slezak JM, Rule AD, Larson TS, Stegall MD, Cosio FG. Assessment of changes in kidney allograft function using creatinine-based estimates of glomerular filtration rate. *Am J Transplant* 2007;**7**(4):880–7.
183. Rule AD, Torres VE, Chapman AB, Grantham JJ, Guay-Woodford LM, Bae KT, et al. Comparison of methods for determining renal function decline in early autosomal dominant polycystic kidney disease: the consortium of radiologic imaging studies of polycystic kidney disease cohort. *J Am Soc Nephrol* 2006;**17**(3):854–62.
184. Xie D, Joffe MM, Brunelli SM, Beck G, Chertow GM, Fink JC, et al. A comparison of change in measured and estimated glomerular filtration rate in patients with nondiabetic kidney disease. *Clin J Am Soc Nephrol* 2008;**3**(5):1332–8.

QUESTIONS AND ANSWERS

Question 1

A young 30-year-old white man is proposed as a living kidney donor for his daughter being treated with peritoneal dialysis (urological malformation). He is 190 cm high and weighs 90 kg. He is healthy, athletic, and frequently goes to a fitness center. Blood pressure is normal and urine analyses are normal. S[Cr] measured with a standardized assay is 1.4 mg/dL. Estimated GFR with the MDRD and CKD-EPI equations is 60 and 67 mL/min/1.73 m^2, respectively.

Which one of the following is true?

A. Donation must be refused because estimated GFR of the subject is too low for kidney donation
B. GFR must be measured by a reference method before potential donation
C. Donation is possible because the subject does not suffer from CKD according to its GFR level (>60 mL/min/1.73 m^2)
D. Cystatin C measurement in this subject would have no added value compared to S[Cr]

Answer: B

Measuring GFR by a reference method is recommended prior to living kidney donation. This would be especially recommended in an active person with high muscular mass. The increased S[Cr] levels could be due to a higher muscular mass, leading to an inaccurate decrease in GFR by the creatinine-based equations. Therefore, Answer A is incorrect. However, Answer C is also incorrect because his estimated GFR values are clearly abnormal for his age. Because Cystatin C concentration is less dependent on muscle mass, its measurement could be of interest. Elevated cystatin C is reflective of both GFR and non-GFR pathology that may preclude donation. Answer D is incorrect.

Question 2

A kidney recipient patient is admitted for pulmonary infection. He is 65 years old and his estimated GFR by the MDRD study equation is 40 mL/min/1.73 m^2. Because *Pneumocystis jirovecii* is suspected, the patient is treated by co-trimoxazole (trimethoprim/sulfamethoxazole) with doses adjusted for GFR level. Two days after starting the therapy, the estimated GFR significantly decreases to 30 mL/min/1.73 m^2.

Which one of the following is true?

A. Creatinine clearance must be measured to assess the potential effect of the therapy on GFR
B. In the absence of urine abnormalities and creatinine stabilization, the increase in S[Cr] is explained by the inhibition of the creatinine tubular secretion by sulfamides
C. In the absence of urine abnormalities and creatinine stabilization, the increase in S[Cr] is explained by the inhibition of the creatinine tubular secretion by trimethoprim
D. The dosage of co-trimoxazole must be decreased
E. Co-trimoxazole is not nephrotoxic and full doses should be given

Answer: C

Co-trimoxazole is a recommended and widely used antibiotic for the prevention and treatment of *Pneumocystis jirovecii* pneumonia and urinary tract infections. Co-trimoxazole combined trimethoprim and sulfamethoxazol (Sfx). Sfx may cause an abrupt increase in S[Cr] due to tubulointerstitial toxicity in high or incorrectly adjusted doses. Answer E is thus incorrect.

By inhibiting creatinine secretion, trimethoprim can lead to an elevation in S[Cr] and a decrease in creatinine clearance. Answer A is thus incorrect. This increase in S[Cr] is independent of any changes in GFR (Answer D is incorrect). This creatinine "elevation" impacts GFR estimation and will lead to the erroneous perception of a more severely impaired kidney function than there actually is. Answer C is the correct one. Trimethoprim induces a reversible and rapid (2–6 h after intake) increase in S[Cr]. Answer B is incorrect.

Question 3

A 75-year-old woman suffers from breast cancer. Oncologists recommend therapy by cisplatin. Except for the neoplasia, the patient is in good health and not treated by any therapy. Her body surface area is 1.7 m^2. Because the narrow therapeutic window, glomerular filtration rate was measured by iohexol plasma clearance at 50 mL/min. Urine analysis does not reveal proteinuria and renal sonography is normal.

Which one of the following is true?

A. Iohexol is not a reference method and GFR should be measured by iothalamate
B. Measuring GFR was not needed as both the MDRD and CKD-EPI equations are accurate enough in this setting
C. The patient's GFR is less than expected with normal aging.
D. Because the patient's GFR level is normal for her age, cisplatin dose adjustment for GFR is not needed.

E. The cisplatin dose should be adjusted to GFR because the subject is at risk for acute kidney injury.

Answer: E

Iohexol plasma clearance is an adequate reference method to measure GFR in the absence of edema. Therefore, there is no reason to measure GFR by another method and Answer A is incorrect. Estimating GFR by creatinine-based equations lacks precision in the elderly. Both the MDRD and the CKD-EPI equations tend to overestimate GFR. Answer B is thus incorrect. In the absence of other evidence for kidney damage, there is no reason to consider this level of GFR in an elderly subject as abnormal. Answer C is incorrect. However, senescence with a physiological decrease in GFR values make older subjects more sensitive to acute kidney injury. The dosage of cisplatin must thus be adapted. Answer D is incorrect and the correct Answer is E.

Question 4

A 60-year-old obese man with hypertension is found to have an eGFR of 50 mL/min/1.73 m^2 by cystatin C-based equation but an eGFR of 75 by a S[Cr]—based equation.

Which item about cystatin C is correct?

A. Cystatin C concentration is not influenced by obesity
B. Standardization of cystatin C measurement is not available
C. Equation only based on standardized cystatin C has been proven to be more accurate than creatinine-based equations in estimating measured GFR
D. Urinary clearance of cystatin C is a helpful confirmatory test for determining GFR
E. All items are false

Answer: E

Cystatin C is a cysteine proteinase inhibitor that is produced by nucleated cells and coded by a housekeeping gene. Cystatin C is freely filtered by the glomerulus and then reabsorbed by the proximal tubules, where it is fully catabolized. In the absence of tubular pathology, the level of cystatin C in the urine is thus very low. Answer D is incorrect. An advantage of cystatin C over S[Cr] is lesser dependence on muscular mass. However, other non-GFR determinants for cystatin C influence cystatin C. Obesity is one of these determinants and Answer A is incorrect. Moreover, in the general CKD population, there is no proof that the cystatin C-based equation performs better than the creatinine-based equations. Only equations combining cystatin C and creatinine seem to have slightly better precision. Answer C is incorrect. Cystatin C can be measured by nephelometric or turbidimetric assays but standardization is now available. Answer B is incorrect. The answer is E.

Question 5

A laboratory is reviewing how to report estimated GFR in patients whenever a S[Cr] is obtained. They are considering switching to the CKD-EPI equation instead of the MDRD study equation.

Which item about the creatinine-based equations is false?

A. The CKD-EPI equation is recommended by the KDIGO guidelines
B. Using the S[Cr]—based CKD-EPI equation leads to a lower prevalence of CKD in the general population than the MDRD Study equation
C. The CKD-EPI equation is more accurate to estimate GFR than the MDRD study equation in all patient settings.
D. An IDMS-traceable creatinine is needed to use either the MDRD Study or CKD-EPI equations

Answer: B

The CKD-EPI equation proposed by the CKD-EPI consortium in 2009 is now recommended by the international guidelines. Answer A is correct. Indeed, using this equation, instead of the MDRD, will lead to lower prevalence of stage 3 CKD in the general population because the MDRD equation systematically underestimates GFR in normal GFR ranges. Answer B is thus correct. An IDMS-traceable creatinine is needed to use these two equations and Answer D is correct. However, the performance of the CKD-EPI equation is not better than the MDRD equation to estimate GFR in CKD patients and even in subjects with GFR "around" 60 mL/min/1.73 m^2. Moreover, in subjects with abnormal or unusual muscular mass, both equations are similarly inaccurate. Answer C is thus incorrect.

Question 6

Which item about measured GFR is correct?

A. Measuring GFR with inulin is a convenient, inexpensive test with low patient burden.
B. GFR-estimating equations assume measured GFR is the gold standard method for determining GFR.
C. Measuring GFR with ^{51}Cr-EDTA and iohexol will give exactly the same results
D. Calculation of measured GFR by urinary clearances is usually higher than plasma clearances
E. Measured GFR is constant at night

Answer: B

Urinary clearance of inulin is still considered as the historical and "gold standard" reference method to measure GFR. However, inulin is not readily available and costly. Moreover, inulin can only be used with a constant infusion rate and repeated urinary clearances. Answer A is incorrect. According to these practical limitations, other markers such as ^{51}Cr-EDTA or iohexol are used with plasma clearances methodology. Even if both markers are considered as reference methods, GFR results will not be exactly the same and usually, differences of 5–10 mL/min/1.73 m^2 can be expected. Answer C is incorrect. Whatever the marker used, plasma clearances are not equivalent to urinary clearance. Because all GFR markers have a part of minimal extrarenal clearance, the plasma clearances results will be slightly but systematically higher than urinary clearances. Answer D is incorrect. Like any biological and physiological variable, GFR has within-individual variability, including nocturnal variation. Answer E is incorrect. Despite these limitations, measuring GFR is still helpful in certain populations and is used as the reference method when creatinine- or cystatin C-based equations are developed. Answer B is correct.

CHAPTER

5

Clinical Assessment and Management of Chronic Kidney Disease Across Its Stages

Ashte' K. Collins[a], *Mark E. Rosenberg*[b], *Paul L. Kimmel*[a]

[a]Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States; [b]Division of Renal Diseases and Hypertension, University of Minnesota Medical School, Minneapolis, MN, United States

Abstract

Defining and staging chronic kidney disease (CKD) has been a major public health and clinical advance that has benefited patient care by primary care providers, as well as nephrologists and other specialists. Each stage of CKD confronts both the patient and provider with different problems and clinical issues, often predictable from the natural history of each CKD stage. Proper CKD management requires understanding the physical and biochemical abnormalities that one can expect to occur throughout the course of a person's kidney disease, which is usually progressive and irreversible. The classification and staging of CKD have advanced care and facilitated research. The major clinical manifestations of each CKD stage, and typical accompanying laboratory abnormalities, in addition to merely extent of change in glomerular filtration rate, dictate the stage-specific management of the CKD patient.

INTRODUCTION

The normal kidneys are the sentinels of body homeostasis. They preserve the "internal milieu" as a stable environment. Functions of the normal kidney include balancing ever-changing dietary intake of a plethora of substances with their excretion and controlling the internal and external distribution of water, sodium, potassium, and trace elements. Normal kidneys maintain acid–base balance and are involved in carbohydrate metabolism, the metabolism of exogenous substances, including licit and illicit drugs, as well as toxic agents. In addition, the kidneys are critical in maintaining bone mineral health, in part by the regulation of calcium, phosphate, and magnesium balance, and producing and responding to control hormones, cytokines, and growth factors involved in mineral metabolism. The kidneys regulate volume status and are involved in the maintenance of normal blood pressure, in part by producing and responding to vasoactive hormones and regulating the excretion of sodium and water.

Over the last century, clinicians and renal physiologists have struggled to determine an overarching, clinically useful measure of renal function. Consensus since the days of Homer Smith has settled on the glomerular filtration rate (GFR). Acute and chronic changes in the level of GFR, depending on their extent and temporal sequence, are often predictably associated with characteristic impairments of the multitude of tasks the kidney accomplishes. Many systemic illnesses involve the kidneys, leading to functional changes which may have dire consequences. When GFR is diminished, disruption in a host of normal physiologic functions occurs, sometimes affecting the function of distant organs or modifying the function of seemingly disparate processes. The care of patients with severe decrements in GFR may involve many health professionals with specific areas of expertise, in addition to primary care physicians.

The course of chronic kidney disease (CKD) is often characterized by inexorable progression, from asymptomatic, clinically inapparent disease or "benign" biochemical abnormalities to uremia with potentially life-threatening neurologic disorders, dysregulated potassium, calcium, phosphate, and acid–base metabolism, as well as abnormal control of blood pressure and plasma volume. Although many CKD patients do not experience progressive loss of GFR, or lose GFR relatively slowly, the pace of the progression of CKD may often be influenced by judicious management of blood

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00005-X

pressure, dietary interventions, use of RAAS inhibitors, as tolerated, as well as identification and treatment of specific reversible causes of acute kidney injury (AKI). In the recent past, the scope of chronic, progressive renal disease was often categorized into four stages: loss of renal reserve, renal insufficiency, chronic renal failure, and end-stage renal disease (ESRD). This approach has been superseded by the CKD classification, a paradigm shift in public health and delivery of patient care by primary care providers, as well as nephrologists and other specialists. Nevertheless, each stage of CKD confronts both the patient and the physician, as well as other caregivers, with different problems and clinical issues, often predictable from the natural history of the underlying disorder.

OVERVIEW OF CKD

According to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline, CKD is defined as "abnormalities of kidney structure or function present for greater than 3 months with implications for health." Typical for any chronic disease, derangements in the normal functioning of the kidneys are responsible for the complications of CKD, which include clinical manifestations in a wide variety of other organ systems, including endocrine, cardiovascular, neurologic, gastrointestinal, musculoskeletal, and hematologic disorders. Proper CKD management requires an understanding of the physical and biochemical abnormalities that one can expect to occur throughout the course of a person's kidney disease, which is usually progressive and irreversible. This approach, previously guided by rough estimations of a person's kidney function as the patient progresses through the continuum of abnormal kidney function, is now more rigorously classified in the 2012 KDIGO guidelines (Figure 5.1).

Several goals are accomplished by this updated classification system, particularly regarding the relationship between certain kidney abnormalities and CKD outcomes. The current system expands on the actual risk of adverse outcomes stratified by GFR category. This classification provides a guide to assist primary care clinicians with timing and need for nephrologist referral by identifying high-risk patients. Second, the newest classification system not only stratifies CKD severity by GFR but also subclassifies CKD stage 3 into two groups, 3a (GFR 45–59 mL/min/1.73 m^2) and 3b (GFR 30–44 mL/min/1.73 m^2). This subclassification helps clinicians identify patients who are more likely to have biochemical and hematological abnormalities such as secondary hyperparathyroidism and anemia, which are more frequently encountered in CKD stage 3b. Furthermore, the new classification system indicates that not all CKD is equivalent. There are many more

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73 m^2) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD);
Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

FIGURE 5.1 Prognosis of chronic kidney disease (CKD) by glomerular filtration rate (GFR) and albuminuria category. *From Reference 13 with permission from National Kidney Foundation, Inc.*

patients with lower-stage CKD than the previous broader classification system identified, and the number of people with advanced CKD stages is much smaller. The fact that CKD stage 3 encompasses the fastest growing cohort of CKD patients in the US underscores the importance of classifying this group precisely. Third, the new system delineates the prognosis of CKD (see Figure 5.1) with respect to not only GFR categories but also albuminuria. For several years, albuminuria has been recognized as an independent risk factor for cardiovascular disease (CVD), CKD progression, AKI, and mortality, but it was not included in the previous KDIGO or Kidney Disease Outcomes Quality Initiative classifications. The inclusion of urinary albumin excretion as a factor in staging acknowledges its place as a risk factor for CVD as well as CKD progression and permits a more comprehensive prediction of CKD outcomes. Fourth, and critically, the new classification system calls for the inclusion of the cause of CKD, with emphasis on the presence of systemic disease and the specific anatomical abnormality present.

Estimating GFR

As the GFR categories in the new CKD classification system have become more complex, so have the methods for estimating GFR. Creatinine clearance was previously used as the primary clinical measure of GFR, the pre-eminent indicator of kidney dysfunction. Creatinine is a practical choice for estimating GFR because as a normal product of muscle metabolism, creatinine is produced in a relatively constant amount every day, is filtered as freely by the glomeruli as plasma water, and little creatinine is secreted or reabsorbed over the course of renal tubular transport. Because the vast majority of the constant daily production of creatinine is excreted every day in the urine, the serum creatinine concentration (S[Cr]) rises as the GFR falls. With every 50% decline in GFR, the corresponding S[Cr] should double, all other variables being unchanged. Were creatinine such an ideal indicator, it would be much easier to estimate GFR, but unfortunately S[Cr] is an imperfect filtration marker. Creatinine is secreted as well as filtered by the kidneys, and its production rate depends on patients' diet and muscle mass. The magnitude of creatinine production and its urinary excretion decrease with increasing age or muscle wasting, the latter often encountered in patients with advanced renal disease or systemic illnesses. The most serious error which stems from only following the level of S[Cr] as a marker of CKD is to grossly overestimate renal function in people with low weight or muscle mass, typically elderly women. Trimethoprim and cimetidine block maximal creatinine secretion by the renal tubules, leading to a decrease in creatinine clearance and a resultant increase in S[Cr], without affecting GFR.[1,2]

Several GFR estimation equations have been developed and validated to estimate GFR from S[Cr]. The Modification of Diet in Renal Disease (MDRD) equation has been in use since the early 2000s, replacing the Cockcroft-Gault equation on the strength of its broad applicability to the general population, as it adjusts for age, gender, and race. Despite its widespread use, the MDRD equation has certain deficiencies that limit its utility. The equation was developed in a population of patients exclusively with CKD. Therefore, its use in general populations presents inherent limitations. Although the MDRD equation is relatively accurate at lower GFRs, it tends to underestimate GFRs over 60 mL/min/1.73 m^2, especially in people without kidney disease. Due to this lack of accuracy, use of the MDRD estimating equation tends to overdiagnose stage 3 CKD. As the MDRD equation is S[Cr] based, it also loses accuracy in patients at the extremes of age and weight, as well as in malnourished patients.

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study equation was published in 2009. There have been several iterations of this equation, using either S[Cr], serum cystatin C concentration (S[Cys]), or both measures. Similar to the MDRD equation, the CKD-EPI equation also takes into account age, gender, and race, but the S[Cys]-based equations have the advantage of not being influenced by muscle mass, whereas the S[Cr]-based MDRD and CKD-EPI equations are. Cystatin C is a marker of GFR due to several properties. Cystatin C is produced by all nucleated cells, is freely filtered by the glomeruli, and undergoes tubular reabsorption with negligible urinary excretion. Diabetes mellitus, obesity, and inflammation are associated with elevated levels of S[Cys]. When the CKD-EPI and MDRD equations are compared, the CKD-EPI equation is more accurate than MDRD at GFRs greater than 60 mL/min/1.73 m^2, but the CKD-EPI equation is less likely than the MDRD equation to misclassify a patient with stage 3 CKD. When S[Cr] and S[Cys] are combined, the CKD-EPI equation becomes even more accurate, particularly in patients with measured creatinine clearances greater than 45 mL/min/1.73 m^2, those with decreased muscle mass, and those at extremes of age.[3–6]

Being able to estimate GFR accurately is important for identifying patients at high risk for CKD progression and complications, especially as most patients with CKD are asymptomatic. As a result, several organizations have proposed that CKD screening be done in high-risk populations, such as patients with diabetes and hypertension,[7,8] despite the fact that the American College of Physicians and the United States Preventive Services Task Force recommended against screening for CKD.[9–11] Although there are no RCTs demonstrating

a benefit from CKD screening, the slowly progressive nature of CKD suggests that a trial of screening would take several years and an enormous number of participants to demonstrate a benefit. Furthermore, the presence of biochemical, endocrine, and hematologic abnormalities early in the course of disease underscores the need for screening to identify and treat these early complications. In the early course of CKD (stages 1 and 2), elevations in S[Cr] and blood urea nitrogen can be detected, as well as the presence of albuminuria. In CKD stage 3 (GFR 30–59 mL/min/1.73 m^2), 1,25-dihydroxycholecalciferol (calcitriol) deficiency often becomes apparent, as do elevations in circulating parathyroid hormone (PTH) levels and blood pressure. Erythropoietin deficiency tends to occur in CKD stage 3b, manifesting as normocytic anemia.[1,12–14]

In CKD stage 4 (GFR 15–29 mL/min/1.73 m^2), these abnormalities become more pronounced, and there is also a markedly elevated risk of cardiovascular events, hospitalizations, and death. Metabolic acidosis often presents in CKD stage 4 due to retention of nitrogenous wastes, secondary to deficits in renal tubular proton secretion, and nutritional deficiencies become more prevalent as well.[13–15] Patients often have hyperphosphatemia and hypocalcemia, because GFR, renal tubular responses, and hormonal action are not capable of maintaining homeostasis. Controlling blood pressure becomes more challenging at this stage due to retention of sodium and water in the setting of low GFR, often requiring the administration of potent loop diuretics to achieve blood pressure goals.[14,16] There is recent evidence supporting the continued use of thiazide diuretics to establish volume homeostasis and control blood pressure in advanced CKD, though randomized controlled trials are needed.[16]

The vast majority of patients with CKD do not present with uremia, which is due to the retention of metabolic products, putative uremic toxins, fluid, acids, and electrolytes in the setting of CKD stage 5 (GFR <15 mL/min/1.73 m^2). The onset of uremia is variable across this level of GFR, and symptoms may differ among and between patients, even at the lowest levels of renal function. Uremic patients present with multiorgan dysfunction, manifesting as nausea, vomiting, weight loss, pruritus, complaints consistent with serositis such as pleuritic chest pain, and malaise, sleep disorders, mental lassitude, and inability to concentrate. On physical examination, classic neurologic signs can include asterixis, clonus, and neurocognitive defects. Volume overload or signs of pericardial disease may be present. Potassium metabolism is usually adequately compensated until the late CKD stages, but diabetic patients are more likely to develop hyperkalemia in CKD stage 3.[17–19] Treatment of uremia as well as refractory volume, electrolyte, and/or acid–base disorders usually calls for the initiation of RRT either using one of the several forms of dialysis or ideally renal transplantation (Table 5.1).

TABLE 5.1 Indications for Initiating End-Stage Renal Disease Therapy

Uremic symptoms
Hyperkalemia resistant to medical therapy
Metabolic acidosis resistant to medical therapy
Congestive heart failure
Uncontrollable hypertension
Pericarditis
Neuropathy
Encephalopathy
Uremic coagulopathy

Modified and used with permission of the editor and publisher, Primer on kidney diseases. 5th ed. San Diego: Academic Press; 2009.

Diagnostic Considerations

Identifying the cause of CKD has been included in the most recent KDIGO guideline. Ascertaining the cause of CKD with respect to the presence or absence of diabetes, hypertension, autoimmune disease, and human immunodeficiency virus infection as well as whether the abnormality is glomerular, tubulointerstitial, vascular, cystic or congenital is important because the locus of the abnormality often has prognostic and treatment implications. Detection of the nephrotic syndrome (conservatively based on the finding of urinary protein excretion greater than 3 g/24 hours) connotes the presence of an inflammatory or noninflammatory glomerular disease and leads to consideration of diseases such as diabetes mellitus (the most common cause of ESRD in the US), and less commonly systemic lupus erythematosus, dysproteinemias, viral infections, and rarely malignancies or drug-induced illnesses. Some patients with nephrotic syndrome have idiopathic kidney diseases, such as membranous nephropathy, focal segmental glomerulosclerosis, and minimal change disease.

The presence of dysmorphic red blood cells or red blood cell casts, hypertension, edema, subnephrotic proteinuria, and decreased GFR suggests the presence of an inflammatory glomerulonephritis, such as IgA nephropathy, lupus nephritis, membranoproliferative glomerulonephritis, Goodpasture's disease, vasculitis, postinfectious glomerulonephritis, cryoglobulinemia, fibrillary glomerulonephritis, or immunotactoid glomerulonephritis. Alternatively, patients with CKD with urinary protein excretion rates less than 3 g/24 hours often have hypertensive nephrosclerosis (the second most

common cause of ESRD in the US), renal vascular disease, chronic interstitial nephritis, or analgesic nephropathy. The presence or absence of chronic systemic hypertension and the findings on urinalysis add accuracy to these rough diagnostic guidelines. In many patients, a percutaneous kidney biopsy may be needed to determine the diagnosis.

Kidney ultrasonography is an important early step in the diagnosis of CKD, as it can rapidly detect increased renal cortical echogenicity, which often suggests the presence of interstitial fibrosis. Ultrasonography is noninvasive and relatively inexpensive and can also characterize kidney size, hydronephrosis, cysts, masses, stones, and vascular abnormalities in both native and transplanted kidneys.[20–22]

Treatment of CKD

While prevention of CKD is a primary, if difficult, goal to achieve, nephrologists are usually concerned with the care of patients who already have CKD. One can divide the management of CKD into two major areas: prevention of CKD progression and treatment of complications of CKD (Tables 5.2 and 5.3).

The first guiding principle in slowing the progression of CKD is exemplified by the Latin phrase *primum non nocere*, or "first, do no harm." The avoidance of treatments, medications, and procedures known to worsen renal function is paramount. Aminoglycoside antibiotics, nonsteroidal antiinflammatory drugs, and other nephrotoxic medications should be avoided in patients with CKD, especially because preexisting CKD is known to be a major risk factor for AKI. Furthermore, iodinated radiocontrast administration can also cause acute deterioration of renal function, sometimes requiring dialysis either temporarily or permanently. When the above interventions are deemed necessary, attenuation of the anticipated renal injury can be accomplished by early recognition of the risk of renal injury, volume expansion with isotonic saline or bicarbonate solutions, and perhaps use of low-osmolar contrast, and *N*-acetylcysteine administration, although the field is currently marked by controversy.[23–25] A recent landmark study, however, did not demonstrate differences between outcomes in patients undergoing procedures associated with administration of intravenous contrast treated with either bicarbonate or acetylcysteine.[26]

The second important principle in slowing the progression of CKD is the prompt recognition and treatment of reversible causes of AKI. AKI is a well-recognized risk factor for CKD progression, imparting an eight- to ninefold risk for subsequent CKD. The degree of renal injury during an AKI episode can be used to predict the likelihood of a person developing advanced CKD.[13,27,28] Furthermore, delayed recovery of renal function after an AKI episode is a strong predictor of incident CKD, even in patients with mild AKI.[29]

Additional factors may reversibly decrease renal function in patients with CKD (Table 5.4). CKD patients are particularly prone to AKI from volume depletion as they have diminished capacity to adapt to changes in renal blood flow from volume depletion. Specifically, patients with CKD have GFR-dependent changes in tubular responsiveness to volume stressors, providing a narrower range of concentrating and diluting capacity and sodium handling than normal subjects.[30,31] In times of stress or illness, diminished ability to concentrate

TABLE 5.2 Complications of Chronic Kidney Disease

Fluid, electrolyte, and acid–base complications
Volume overload
Volume depletion
Hyponatremia
Hypernatremia
Hyperkalemia
Hypokalemia
Hypocalcemia
Hyperphosphatemia
Hypermagnesemia
Metabolic acidosis
Metabolic alkalosis

TABLE 5.3 Organ-System Function and Metabolic Disorders Associated with Renal Dysfunction

Hypertension
Renal osteodystrophy
Anemia of renal disease
Disordered lipid metabolism
Uremic coagulopathy
Uremic pericarditis
Gastrointestinal disorders
Uremic neuropathy and encephalopathy
Uremic sleep disorders
Sexual dysfunction
Psychological disorders
Immune disorders
Dermatologic complications

Tables 5.2 and 5.3 modified and used with permission of the editor and publisher, Primer on kidney diseases. 5th ed. San Diego: Academic Press; 2009.

TABLE 5.4 Factors Which Can Decrease Marginal Renal Function

Volume depletion
Infection
Intravenous radiographic contrast
Nephrotoxic agents and drugs
Nonsteroidal antiinflammatory drugs
Uncontrolled hypertension
Hypotension
Angiotensin-converting enzyme inhibitor and angiotensin receptor blocker
Renal vascular disease
Urinary obstruction

Modified and used with permission from K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 Suppl. 1):S1–266.

urine may lead to excess fluid losses. Patients with congestive heart failure and renal disease may have diminution of renal blood flow as cardiac function worsens. Local renal arteriolar prostaglandin production becomes important in maintaining GFR in the face of falling cardiac output, which is opposed by nonsteroidal antiinflammatory drug administration. Therapy directed at improving cardiac hemodynamics may in turn substantially improve renal function. Renal function in patients with nephrotic syndrome and cirrhosis is also more dependent on renal prostaglandin production, so optimizing the volume status in these patients is crucial to the maintenance of renal hemodynamics.[13,20]

Urinary tract obstruction (UTO) is an important cause of decline in GFR. Bilateral or unilateral UTO in CKD patients can often cause rapid diminution of renal function due to intense renal vasoconstriction, leading to a subsequent fall in GFR. UTO can sometimes be suggested by findings in the history (such as a history of prostatic disease or difficulty beginning the stream or by symptoms suggestive of gynecologic malignancy) or physical examination (such as identification of a suprapubic mass or dullness). UTO is usually associated with hydronephrosis on ultrasound or computed tomography (CT), but obstruction from renal lymphoma or retroperitoneal fibrosis may not present with hydronephrosis.[21,22,32]

Renal arterial disease can accelerate the progression of CKD. This diagnosis should be considered in patients with atherosclerotic vascular disease, suddenly worsening hypertension (especially when it was previously well controlled), abrupt decline of renal function after initiation of therapy with RAAS inhibitors, asymmetric kidney size, and/or flash pulmonary edema with normal left ventricular function. CT and magnetic resonance imaging studies are helpful in confirming the presence of renovascular disease. Statin therapy, RAAS blockade, antiplatelet therapy, and possibly renal artery stenting are the cornerstones of treating renal arterial disease.[33,34] Of note, in patients with renal vascular disease and either difficult to control systolic hypertension or CKD, there was no benefit of renal artery stenting combined with medical therapy compared with medical therapy alone on a combined cardiovascular and renal endpoint. This finding is consistent with other studies that failed to show a benefit of renal artery stenting on kidney function.[35–38]

SPECIFIC TREATMENT RECOMMENDATIONS

Adjustment of Drug Dosages

The treatment of CKD requires an understanding of the complex interplay between the etiology of the patient's CKD, severity of disease, comorbid conditions, CKD complications, and CVD risk management.[39] Prompt recognition and management of each of these issues is necessary to develop an individualized clinical action plan for CKD management (Table 5.5). Part of the clinical action plan should involve adjustments in drug prescription, especially because compromised kidney function can drastically alter the pharmacokinetics of many medications. Many CKD patients require individualized decreases in certain medication doses or extension of the administration intervals. Therapeutic drug monitoring may be required to assess for efficacy and toxicity. The increased bioavailability and diminished metabolism or clearance of certain medications in the setting of CKD are associated with increased mortality in CKD patients, and some medications are contraindicated in more advanced stages of CKD.[40,41]

Management of Hypertension

Regardless of the cause of CKD, strict blood pressure control has been thought to slow the progression of CKD.[39] CKD patients with poorly controlled blood pressure (systolic blood pressure greater than 150 mm Hg) are almost 10 times more likely to progress to ESRD than those with systolic blood pressure less than 130 mm Hg.[42] Decreased renal blood flow associated with vasoconstriction, renal cellular ischemia, or shear stress in the setting of hypertension as well as activation of hormones, growth factors, and cytokines may be important mediators of renal pathogenic processes, including renal fibrosis.[43] In previous reports of the Joint

TABLE 5.5 Stages of Chronic Kidney Disease: A Clinical Action Plan

Stage	Description	Glomerular Filtration Rate (GFR) (mL/min/1.73 m^2)	Action*
1	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment, treatment of comorbid conditions, slowing progression, CVD risk reduction
2	Kidney damage with mild ↓ GFR	60–89	Estimating and treating progression
3	Moderate ↓ GFR	30–59	Evaluating and treating complications
4	Severe ↓ GFR	15–29	Preparation for kidney replacement therapy
5	Kidney failure	<15 (or dialysis)	Replacement (if uremia present)

Chronic kidney disease is defined as either kidney damage or GFR<60 mL/min/1.73 m^2 for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. Abbreviations: *CVD*, cardiovascular disease.
** Includes action from preceding stages.*
Reprinted from K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 Suppl. 1):S1–266.

National Committee (JNC) guidelines for the management of hypertension in adults, the target blood pressure for all patients with CKD was less than 130/80 mm Hg.[44] However, this recommendation was based on a minimal evidence base largely composed of trials with inconclusive results.[45]

Recent evidence has served to provide a more specific framework which clinicians can use to treat hypertension in CKD patients. The African-American Study of Kidney Disease and Hypertension (AASK) RCT clearly demonstrated that in the subset of patients with higher levels of proteinuria (urine protein:creatinine ratio >0.22), achieving a blood pressure less than 130/80 mm Hg was associated with decreased risk of CKD progression.[46,47] However, in the MDRD, AASK, and REIN-2 trials, achieving a blood pressure target of less than 130/80 mm Hg did not slow CKD progression compared with a target of less than 140/90 mm Hg when all study patients with varying levels of proteinuria were analyzed together.[45] Based on these trial data, the JNC 8 guidelines released in 2013 recommend a target blood pressure of less than 140/90 mm Hg for all patients with CKD.[48] It is noteworthy that the benefits of blood pressure lowering to less than 130/80 mm Hg in patients with proteinuria were obtained by *post hoc* analysis of a subgroup.[48] These blood pressure treatment recommendations are consistent with those recommended by the KDIGO Blood Pressure Work Group.[49]

The SPRINT trial investigators randomized over 9000 nondiabetic patients over age 50 with increased CVD risk to an intensive systolic blood pressure target of less than 120 mm Hg vs. a standard target of less than 140 mm Hg. This randomized, controlled, open-label trial allowed for the use of any antihypertensive agent. Although the intensive treatment arm only achieved a mean systolic blood pressure of 121.4 mm Hg (vs. 136.2 mm Hg in the standard treatment group), there was a 25% lower risk of reaching the primary outcome in the intensive treatment group, leading to an early termination of the study after less than 4 years of intervention.[50] Over 2600 patients had CKD, which did not influence the primary outcome of myocardial infarction, stroke, heart failure, or death from cardiovascular causes. The prespecified kidney outcome was a composite of ≥50% decrease in estimated GFR (eGFR) from baseline or ESRD. While the number of events was low, there was no difference in the kidney outcome between the intensive and standard groups (HR 0.90, 95% CI 0.44–1.83).[51] This and other observations led to the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines updating their definition of hypertension to a blood pressure greater than 130/80 mm Hg, irrespective of CKD.[52] While the appropriate blood pressure goal to reduce progression of CKD is unknown, a target blood pressure of ≤130/80 mm Hg is reasonable given the benefits with regard to CVD risk reduction.[53] Of note there was a higher incidence of AKI, eGFR decline ≥30%, hypokalemia, hyponatremia, and hypotension in the intensive treated group in SPRINT.

Antihypertensive therapeutic regimens in CKD patients should include an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), unless there are specific contraindications to their use. These medications have been shown in multiple trials to slow the progression of CKD and reduce urinary protein excretion, and they are now recommended in all CKD patients regardless of race or diabetes status.[48,49,54–56] The antiproteinuric benefits of ACEIs and ARBs are independent of their effects on systemic blood pressure.[46,47,54–56]

It has been postulated that combining ACEIs and ARBs in patients with CKD, particularly proteinuric CKD, may confer added renal protection and reduce cardiovascular events. Much of the enthusiasm for dual therapy was initially generated by the COOPERATE study, which was subsequently retracted.[57] In the Ongoing Telmisartan Alone and in Combination with

Ramipril Global Endpoint Trial (ONTARGET), patients with established atherosclerotic vascular disease or diabetes with end-organ damage were randomized to receive the ACEI ramipril, ARB telmisartan, or both drugs.[58] Combination therapy was associated with a higher occurrence of the composite primary renal outcome of dialysis, doubling of S[Cr] and death.

In another study, when the direct renin inhibitor aliskiren was combined with an ACEI or ARB in patients with type 2 diabetes mellitus with CKD and/or CVD, there was no cardiovascular or renal benefit observed compared with patients on monotherapy.[59] There was a higher incidence of hypotension and hyperkalemia in the combination therapy group. Fried and colleagues evaluated the effect of combination ACEI/ARB therapy in a study of Veterans with diabetic nephropathy, but they found no cardiovascular or renal benefit of the combination compared with monotherapy with losartan.[60] However, an increased risk of hyperkalemia and AKI was seen in the combination therapy group, further supporting the notion that ACEI/ARB combination therapy cannot be recommended for CKD patients.[48,52,60]

Diuretics are useful antihypertensives in CKD patients, particularly in those with volume overload. They are still recommended as first-line agents in patients with hypertension in general, but their efficacy in stage 4 CKD may be limited. There are observational data supporting their efficacy in advanced stages of CKD, as thiazide diuretics cause negative sodium balance and weight loss in stage 4 CKD.[16] However, loop diuretics are still the recommended diuretics in those patients with advanced CKD, as they can produce a dose-dependent diuresis in patients with late stages of CKD.[52,61,62]

Calcium channel blockers (CCBs) are commonly used for the treatment of hypertension, and their utility in reducing proteinuria is currently an area of great research interest. In particular, the use of nondihydropyridine CCBs, such as diltiazem, is associated with a reduction in urinary protein excretion in patients with renal disease.[63] On the other hand, there are only limited data to specifically recommend dihydropyridine CCBs as first line or monotherapy in CKD patients.[48] Combination therapy, using a CCB (amlodipine) with an ACEI (benazepril) was compared with combination therapy using benazepril with hydrochlorothiazide in the ACCOMPLISH trial. The trial was stopped early due to a significant cardiovascular benefit observed in the ACEI/CCB group compared with the ACEI/hydrochlorothiazide group.[64] Furthermore, in the renal outcomes follow-up study, patients in the benazepril/hydrochlorothiazide group had faster CKD progression and a higher incidence of ESRD.[65]

Cardiovascular Disease

CKD is independently associated with CVD and increased cardiovascular mortality. Stage 4 CKD patients are more than four times more likely to experience coronary heart disease than those with preserved renal function.[66,67] In this population-based study, the risk of CVD in patients with stages 1 and 2 CKD was actually higher than in patients with stage 3 CKD, likely related to albuminuria.[66] There is clear and consistent evidence linking albuminuria to heightened CVD risk, thus leading to the inclusion of albuminuria in the new KDIGO guidelines.[68–71] Furthermore, reduction of albuminuria in CKD patients has been associated with decreased CVD risk.[72] CKD patients often have many of the traditional risk factors for CVD, but they also have nontraditional risk factors such as inflammation, anemia, oxidative stress, endothelial dysfunction, increased sympathetic activity, abnormal calcium/phosphate metabolism, and hyperhomocysteinemia, all of which may enhance overall CVD risk.[67,73] Optimization of volume status, blood pressure control, and treatment of the nontraditional CVD risk factors may decrease the overall CVD burden in CKD patients.

Statins have been widely used to decrease CVD risk in CKD patients. In two meta-analyses, statins decreased all-cause and cardiovascular mortality and CVD events in nondialysis CKD patients, but this benefit was not evident in patients treated with dialysis.[74–77] In the SHARP trial, 6247 patients not on dialysis were randomized to simvastatin plus ezetimibe vs. placebo. After a median follow-up of 4.9 years, there was a significant reduction in major atherosclerotic events, although no effect was seen on the progression of CKD.[78] Based on this study, the KDIGO clinical practice guideline recommends statin therapy and LDL lowering to reduce risk of CVD in patients with CKD.[79]

Other Treatments

Dietary Protein Restriction

Dietary protein restriction has long been employed and recommended to slow the progression of CKD, but the evidence base remains controversial.[13] There have been several systematic reviews and meta-analyses to evaluate the effects of dietary protein restriction, with some of the earlier trials showing benefit in slowing CKD progression.[80,81] These results conflict with findings from the MDRD study, however. The MDRD study, now more than two decades ago, compared normal- to low-protein diets (1.3–0.58 g/kg/day) in patients with moderate CKD (eGFR 25–55 mL/min/1.73 m^2), and low-protein to very low-protein diets (0.58–0.28 g/kg/day) in patients with advanced CKD (eGFR

13–24 mL/min/1.73 m^2), finding no benefit in slowing CKD progression in either group.[82] Moreover, a long-term follow-up of this study concluded that the very low-protein diet patients were almost twice as likely to die during the follow-up period, perhaps related to protein malnutrition once patients reach ESRD. Measures of nutrition should be closely monitored in CKD patients on protein-restricted diets.[83] High-protein intake, greater than 1.3 g/kg/day, has been associated with increased incidence of cardiovascular events in CKD patients, and should be avoided.[84] A systematic review demonstrated that most dietary interventions have uncertain effects on cardiovascular events, CKD progression, and mortality in CKD patients, though increased fruit and vegetable intake, polyphenol enriched diets, and Mediterranean diets may improve blood pressure and LDL cholesterol.[85]

Sodium-Glucose Cotransporter 2 Inhibitors

An emerging area is the investigation of whether some glucose-lowering drugs have beneficial effects on diabetic nephropathy and cardiovascular outcomes above and beyond their effects on glucose control.

These drugs inhibit sodium and glucose transport in the S1 segment of the proximal tubule and consequently increase glucose and sodium excretion. In addition to effects on glycemic control, sodium-glucose cotransporter 2 (SGLT2) inhibitors lower BP, weight, and albuminuria and are associated with a decline in GFR.[86] In the first of these studies, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME trial), the effects of empagliflozin was examined in 7020 adults with type 2 diabetes mellitus and established CVD with an eGFR of at least 30 mL/min/1.73 m^2.[87] Empagliflozin treatment over a median follow-up of 3.1 years reduced the risk of cardiovascular events defined as a composite of first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The risk of the prespecified renal outcome of incident or worsening nephropathy (progression to macroalbuminuria, doubling of S[Cr] accompanied by an eGFR $\leq$45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease) and incident albumuniuria was also reduced by empagliflozin.[88] Interestingly, treatment with empagliflozin was associated with a decrease in eGFR that was reversible after stopping the study drug.

In the CANVAS Program, the SGLT2 inhibitor canagliflozin was studied in 10,142 type 2 diabetic subjects at high risk for CVD. Canagliflozin decreased the primary cardiovascular endpoint of death from cardiovascular cause, nonfatal myocardial infarction, or nonfatal stroke.[89] The renal outcomes were not statistically significant based on the "prespecified hypothesis testing sequence," with a possible benefit in progression of albuminuria and the composite of sustained 40% reduction in eGFR, the need for renal replacement therapy, or death from renal causes. There was an unexplained increased risk for amputation in the canagliflozin group. The use of SGLT2 inhibitors is not recommended when the eGFR is <30 mL/min/1.73 m^2.

These results demonstrating renal protective effects of SGLT2 inhibitors are promising but before they are widely used as renal protective agents studies are needed examining long-term kidney outcomes. In this regard, the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation trial (CREDENCE; ClinicalTrials.gov number NCT02065791) provides important information about renal outcomes.[86] This is a trial in 4400 patients with type 2 diabetes and urinary albumin:creatinine ratio (UACR) > 300 to 5000 mg/g and eGFR of 30 to < 90 mL/min/1.73 m^2 adding canagliflozin to standard care consisting of maximum labeled or tolerated dose of ACEI or ARB. The primary endpoint was a composite of time to dialysis or kidney transplantation, doubling of S[Cr], and renal or CV death. The relative risk of the primary outcome was 30% lower in the canaglifozin group than in the placebo group. The canaglifozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke. There were no differences in the rates of amputation or fracture. This exciting study provides strong data for a renal protective effect of canaglifozin.

The potential mechanism of the beneficial effects of SGLT2 inhibitors may be through decreasing hyperfiltration. By reducing proximal reabsorption of sodium, distal sodium delivery is increased activating tubular glomerular feedback leading to afferent arteriolar vasoconstriction and a reduction in hyperfiltration. This is a class effect and is reversible after stopping the drug. If true, then these drugs may also be effective in nondiabetic kidney disease, a hypothesis that is being tested in the Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With CKD (DAPA CKD) in which half the patients are diabetic and half are nondiabetic. The primary outcome is a composite of $\geq$50% sustained decline in eGFR, ESRD, or CV or kidney death (ClinicalTrials.gov NCT03036150).[86]

Targeting Uric Acid

Recent studies have examined the relationship between elevated uric acid levels and both renal and CVD events. It has been suggested that hyperuricemia is independently associated with increased incidence of CVD events, and that this association is strengthened in advanced CKD.[90–93] However, in light of recent studies suggesting only a marginal benefit in left ventricular mass index and endothelial function when

hyperuricemia is treated with allopurinol, there is insufficient evidence to either support or refute the use of uric acid lowering agents in CKD patients with hyperuricemia.[13,90–94]

Metabolic acidosis is an important complication and potential target of therapy in CKD patients. Metabolic acidosis initially ensues from impaired ammoniagenesis and diminished renal hydrogen ion excretion in the setting of low GFR, then progresses to retention of metabolic wastes as CKD progresses.[95,96] Metabolic acidosis can lead to myocardial depression, arrhythmias, insulin resistance, hyperventilation, muscle weakness, inflammation, and bone disease. Treatment of metabolic acidosis with oral alkali has been prospectively shown to slow progression of CKD.[97,98] KDIGO recommendations endorse treatment of metabolic acidosis with bicarbonate in CKD patients when serum bicarbonate concentration is less than 22 mmol/L.[13] However, an analysis of 3586 patients in the Chronic Renal Insufficiency Cohort demonstrated a higher risk of heart failure events and mortality when the serum bicarbonate is maintained above 26 mmol/L.[99]

Vitamin D

Vitamin D metabolism becomes impaired in CKD, primarily due to decreased conversion of 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3 by the kidneys.[100,101] It has been proposed that vitamin D supplementation can inhibit the RAAS and attenuate podocyte injury, and vitamin D supplementation has been associated with reduction in proteinuria.[102] De Zeeuw and colleagues showed in the VITAL study that high-dose paracalcitol supplementation was associated with a significant decline in proteinuria in patients with type 2 diabetes with CKD compared to placebo, but there was no significant slowing of CKD progression.[103] As more information is developed regarding circulating fibroblast growth factor-23 (FGF-23) and phosphate levels, and their interrelationships with CKD progression and mortality, the role of vitamin D supplementation in preserving residual renal function will become clearer.[104]

Serum Phosphate

As CKD progresses, deranged phosphate metabolism becomes apparent, even before serum phosphate (S[P]) levels begin to rise. Although overt hyperphosphatemia usually presents at or after CKD stage 3a, decreased tubular phosphate reabsorption as a result of increased levels of PTH and FGF-23 occurs as early as CKD stage 2.[12,105–107] These metabolic complications, in particular hyperphosphatemia, have been shown in multiple studies to be independently associated with higher mortality in CKD patients.[108,109] Furthermore, hyperphosphatemia in CKD is associated with increased risk of cardiovascular events, vascular and valvular calcification, fractures, and progression of CKD to ESRD.[110,111] Phosphate restriction to maintain S[P] levels within the normal range has been recommended for many years, most recently by KDIGO.[13,112,113] The beneficial effects of lowering S[P] on surrogate biochemical outcomes such as PTH levels, calcium × phosphate product, and FGF-23 levels have supported the use of phosphate binders in CKD patients.[113–116] Phosphate binders are widely employed in stages 3–5 CKD patients based on the premise that control of surrogate outcomes will lead to improved hard outcomes in this high-risk population. Unfortunately, when cardiovascular events and mortality are considered, there is insufficient evidence to support the use of either calcium-containing or non-calcium-containing phosphate binders in CKD patients, although it is clear that phosphate lowering is the first and most important step in controlling secondary hyperparathyroidism.[116–120]

Anemia

Anemia is a frequent complication of CKD and can be detected with 90% sensitivity at a measured GFR of 44 mL/min/1.73 m^2. The prevalence of anemia increases with advancing stages of CKD and is independently associated with increased risk of hospitalizations, mortality, and CKD progression.[121–124] Based on these observations, the most recent KDIGO guidelines recommend that hemoglobin concentrations be measured with increasing frequency with increasing severity of CKD. Furthermore, iron supplementation should be employed in anemic CKD patients with iron deficiency prior to prescribing erythropoiesis-stimulating agents (ESAs).[125] It was previously assumed that ESA therapy would not only correct the anemia but also slow the progression of CKD. However, the TREAT trial demonstrated no difference in CKD progression between patients randomized to darbepoetin or placebo with a target hemoglobin level of 13 g/dL.[126] The CREATE and CHOIR trials both demonstrated that treatment of anemia with ESAs to a target hemoglobin greater than 13–13.5 g/dL was associated with more rapid progression to ESRD than those with lower target hemoglobin levels.[127,128] Based on these trial data, KDIGO guidelines recommend that ESAs not be used to treat anemic CKD patients to a target hemoglobin above 11.5 g/dL.[125]

DELIVERY OF CKD CARE

The way we deliver care to CKD patients may also affect health outcomes. For example, multidisciplinary CKD programs (CKD clinics) are associated with better patient adherence to CKD guidelines, a higher incidence of fistula use at initiation of dialysis, and more outpatient dialysis starts (vs. emergency inpatient starts).[129] Also, early referral to a nephrologist is associated with improved outcomes once patients initiate dialysis. KDIGO recommends referral to a nephrologist when eGFR is less than 30 mL/min/1.73 m^2 and/or UACR is greater than 300 mg/g, with earlier referral recommended in specific cases.[13] Early referral has been associated with a number of beneficial effects including decreased mortality, reduced hospitalization days, and improvement in the appropriate use of fistulas and grafts as opposed to catheters at initiation of dialysis.

CONCLUSION

Defining and staging CKD has allowed the provider to take a systematic approach to CKD management. Each stage of CKD confronts both the patient and provider with different problems and clinical issues, often predictable from the natural history of each CKD stage. Proper CKD management requires an understanding of the physical and biochemical abnormalities that occur throughout the course of a patient's kidney disease, which is usually progressive and irreversible. The classification and staging of CKD has had a great effect on clinical care over the last decade. Major manifestations of biochemical abnormalities are predictable at each CKD stage. Stage-specific management of CKD is directed at avoiding additional kidney injury, adjusting and monitoring medications, slowing CKD progression, and managing the complications that arise at each stage.

Therapies to slow progression include blood pressure control with a target blood pressure less than 130/80 mm Hg. Preferential use of ACEI and ARBs, but not both together, should be a cornerstone of hypertension management in CKD patients. Reducing risk factors for CVD is an important component of management of the CKD patient, given the almost universal presence of this devastating complication. Guidelines are available for proper management of anemia and hyperphosphatemia. Other therapies for managing CKD are important at each stage, but evidence-based recommendations to change outcomes in CKD patients are largely lacking. Well-designed RCTs addressing such issues in patients with CKD are urgently needed to guide therapy for many of the complications of CKD. The care of the CKD patient must be individualized at present, as RCTs in this population have yielded variable success.

References

1. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P. Prevalence of chronic kidney disease in the United States. *J Am Med Assoc* 2007;**298**(17):2038–47.
2. Coresh J, Toto RD, Kirk KA, Whelton PK, Massry S, Jones C. Creatinine clearance as a measure of GFR in screens for the African-American Study of Kidney Disease and Hypertension pilot study. *Am J Kidney Dis* 1998;**32**(1):32–42.
3. Matsushita K, Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH, Chronic Kidney Disease Prognosis Consortium. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *J Am Med Assoc* 2012;**307**(18):1941–51.
4. Earley A, Miskulin D, Lamb EJ, Levey AS, Uhlig K. Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. *Ann Intern Med* 2012; **156**(11):785–95.
5. Stevens LA, Schmid CH, Greene T, Li L, Beck GJ, Joffe MM. Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int* 2009;**75**(6):652–60.
6. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T. CKD-EPI Investigators: estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012; **367**(1):20–9.
7. de Boer IH, Olan GA, Patel UD, American Society of Nephrology Chronic Kidney Disease Advisory Group. Screening for chronic kidney disease. *Ann Intern Med* 2013;**158**(5 Pt 1):362–3.
8. KDOQI. KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. *Am J Kidney Dis* 2007;**49**(2 Suppl. 2):S12–154.
9. Qaseem A, Hopkins RH, Sweet DE, Starkey M, Shekelle P. Screening, monitoring, and treatment of stage 1 to 3 chronic kidney disease: a clinical practice guideline from the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med* 2013;**159**(12):835–47.
10. Moyer VA, U.S. Preventive Services Task Force. Screening for chronic kidney disease: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2012;**157**(8):567–70.
11. Fink HA, Ishani A, Taylor BC, Greer NL, MacDonald R, Rossini D. Screening for, monitoring, and treatment of chronic kidney disease stages 1 to 3: a systematic review for the U.S. Preventive Services Task Force and for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2012;**156**(8):570–81.
12. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int* 2007;**1**(1): 31–8.
13. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:1–150.
14. Drawz PE, Babineau DC, Rahman M. Metabolic complications in elderly adults with chronic kidney disease. *J Am Geriatr Soc* 2012; **60**(2):310–5.

15. United States Renal Data System. *USRDS annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2017.
16. Sinha AD, Agarwal R. Thiazide diuretics in chronic kidney disease. *Curr Hypertens Rep* 2015;**17**(3):13.
17. Einhorn LM, Zhan M, Hsu VD, Walker LD, Moen MF, Seliger SL. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med* 2009;**169**(12):1156–62.
18. Weinberg JM, Appel LJ, Bakris G, Gassman JJ, Greene T, Kendrick CA. Risk of hyperkalemia in nondiabetic patients with chronic kidney disease receiving antihypertensive therapy. *Arch Intern Med* 2009;**169**(17):1587–94.
19. Loutradis C, Tolika P, Skodra A, Avdelidou A, Sarafidis PA. Prevalence of hyperkalemia in diabetic and non-diabetic patients with chronic kidney disease: a nested case-control study. *Am J Nephrol* 2015;**42**(5):351–60.
20. Orth SR, Ritz E. The nephrotic syndrome. *N Engl J Med* 1998; **338**(17):1202–11.
21. Gosmanova EO, Wu S, O'Neill WC. Application of ultrasound in nephrology practice. *Adv Chron Kidney Dis* 2009;**16**(5): 396–404.
22. Khati NJ, Hill MC, Kimmel PL. The role of ultrasound in renal insufficiency: the essentials. *Ultrasound Q* 2005;**21**(4):227–44.
23. Barrett BJ, Parfrey PS. Clinical practice. Preventing nephropathy induced by contrast medium. *N Engl J Med* 2006;**354**(4): 379–86.
24. Weisbord SD, Gallagher M, Kaufman J, Cass A, Parikh CR, Chertow GM. Prevention of contrast-induced AKI: a review of published trials and the design of the prevention of serious adverse events following angiography (PRESERVE) trial. *Clin J Am Soc Nephrol* 2013;**8**(9):1618–31.
25. Kang X, Hu DY, Li CB, Ai ZS, Peng A. N-acetylcysteine for the prevention of contrast-induced nephropathy in patients with pre-existing renal insufficiency or diabetes: a systematic review and meta-analysis. *Ren Fail* 2015;**37**(10):297–303.
26. Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin SS, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. *N Engl J Med* 2018;**378**:603–14.
27. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int* 2012;**81**(5):442–8.
28. Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. *Kidney Int* 2011;**79**(12):1361–9.
29. Heung M, Steffick DE, Zivin K, Gillespie BW, Banerjee T, Hsu CY, Powe NR, Pavkov ME, Williams DE, Saran R, Shahinan VB, Centers for Disease Control and Prevention CKD Surveillance Team. Acute kidney injury recovery pattern and subsequent risk of CKD: an analysis of Veterans Health Administration data. *Am J Kidney Dis* 2016;**67**(5):742–52.
30. Esposito C, Dal Canton A. Functional changes in the aging kidney. *J Nephrol* 2010;**23**(Suppl. 15):S41–5.
31. Gottschalk CW. Function of the chronically diseased kidney. The adaptive nephron. *Circ Res* 1971;**5**(Suppl. 2):1–13.
32. Klahr S. Effects of obstruction on renal functions. *Pediatr Nephrol* 1988;**2**(1):34–42.
33. Conlon PJ, O'Riordan E, Kalra PA. New insights into the epidemiologic and clinical manifestations of atherosclerotic renovascular disease. *Am J Kidney Dis* 2000;**35**(4):573–87.
34. Textor SC, Misra S, Oderich GS. Percutaneous revascularization for ischemic nephropathy: the past, present, and future. *Kidney Int* 2013;**83**(1):28–40.
35. Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM. CORAL Investigators. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med* 2014; **370**(1):13–22.
36. ASTRAL Investigators, Wheatley K, Ives N, Gray R, Kalra PA, Moss JG. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med* 2009;**361**(20):1953–62.
37. Bax L, Woittiez AJ, Kouwenberg HJ, Mali WP, Buskens E, Beek FJ. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. *Ann Intern Med* 2009;**150**(12):840–8.
38. Raman G, Adam GP, Halladay CW, Langberg VN, Azodo IA, Balk EM. Comparative effectiveness of management strategies for renal artery stenosis: an updated systematic review. *Ann Intern Med* 2016;**165**(9):635–49.
39. Eknoyan G, Levin NW. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**(2 Suppl. 1):S1–266.
40. Breton G, Froissart M, Janus N, Launay-Vacher V, Berr C, Tzourio C. Inappropriate drug use and mortality in community dwelling elderly with impaired kidney function—the Three-City population-based study. *Nephrol Dial Transplant* 2011;**26**(9): 2852–9.
41. Lea-Henry TN, Carland JE, Stocker SL, Sevastos J, Roberts DM. Clinical pharmacokinetics in kidney disease: fundamental principles. *Clin J Am Soc Nephrol* 2018;**13**(7):1085–95.
42. Agarwal R. Blood pressure components and the risk for end-stage renal disease and death in chronic kidney disease. *Clin J Am Soc Nephrol* 2009;**4**(4):830–7.
43. Grabias BM, Konstantopoulos K. The physical basis of renal fibrosis: effects of altered hydrodynamic forces on kidney homeostasis. *Am J Physiol Renal Physiol* 2014;**306**(5):F473–85.
44. Chobanian AV. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *J Am Med Assoc* 2003;**289**(19):2560.
45. Upadhyay A. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. *Ann Intern Med* 2011;**154**(8):541–8.
46. Wright JT, Bakris G, Greene T, African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *J Am Med Assoc* 2002;**288**(19):2421–31.
47. Appel LJ. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010;**363**(10):918–29.
48. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J. Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the eighth Joint National Committee (JNC 8). *J Am Med Assoc* 2014;**311**(5):507–20.
49. Kidney Disease: Improving Global Outcomes (KDIGO), Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2012;**2**:337–414.
50. SPRINT Research Group, Wright Jr TJ, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff Jr DC, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**(22):2103–16.
51. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol* 2017;**28**(9):2812–23.

52. Whelton PK, Carey RM, Aronow WS, Casey Jr DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith Jr SC, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams Sr KA, Williamson JD, Wright Jr JT. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;**71**(19):e127–248.
53. Chang AR, Loser M, Malhotra R, Appel LJ. Blood pressure goals in patients with chronic kidney disease: a review of evidence and guidelines. *Clin J Am Soc Nephrol* 2019;**14**:161–9.
54. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD, The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;**329**(20):1456–62.
55. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**(12):851–60.
56. Brenner BM, Cooper ME, de Zeeuw D, RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**(12):861–9.
57. Retraction. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *Lancet* 2009;**374**(9697):1226.
58. Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008;**372**(9638):547–53.
59. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012;**367**(23):2204–13.
60. Fried LF, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth W. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;**369**(20):1892–903.
61. ALLHAT Officers, Coordinators for the ALLHAT Collaborative Research Group. The antihypertensive and lipid-lowering treatment to prevent heart attack trial: major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. *J Am Med Assoc* 2002;**288**(23):2981–97.
62. Rahman M, Ford CE, Cutler JA, Davis BR, Piller LB, Whelton PK. Long-term renal and cardiovascular outcomes in Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Atrial (ALLHAT) participants by baseline estimated GFR. *Clin J Am Soc Nephrol* 2012;**7**(6):989–1002.
63. Smith AC, Toto R, Bakris GL. Differential effects of calcium channel blockers on size selectivity of proteinuria in diabetic glomerulopathy. *Kidney Int* 1998;**54**(3):889–96.
64. Bakris GL, Sarafidis PA, Weir MR, Dahlof B, Pitt B, Jamerson K. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomized controlled trial. *Lancet* 2010;**375**(9721):1173–81.
65. Weir MR, Bakris GL, Weber MA, Dahlof B, Devereux RB, Kjeldsen SE. Renal outcomes in hypertensive black patients at high cardiovascular risk. *Kidney Int* 2012;**81**(6):568–76.
66. Di Angelantonio E, Chowdhury R, Sarwar N, Aspelund T, Danesh J, Gudnason V. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. *BMJ* 2010;**341**:c4986.
67. Dikow R, Zeier M, Ritz E. Pathophysiology of cardiovascular disease and renal failure. *Cardiol Clin* 2005;**23**(3):311–7.
68. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ. Chronic kidney disease prognosis consortium. associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012;**380**(9854):1662–73.
69. Bello AK, Hemmelgarn B, Lloyd A, James MT, Manns BJ, Klarenbach S. Alberta Kidney Disease Network: associations among estimated glomerular filtration rate, proteinuria, and adverse cardiovascular outcomes. *Clin J Am Soc Nephrol* 2011;**6**(6):1418–26.
70. Clase CM, Gao P, Tobe SW, McQueen MJ, Grosshennig A, Teo KK. ONTARGET (ONgoing telmisartan alone and in combination with ramipril global endpoint trial) and TRANSCEND (telmisartan randomized assessment study in angiotensin-converting-enzyme-inhibitor intolerant subjects with cardiovascular disease): estimated glomerular filtration rate and albuminuria as predictors of outcomes in patients with high cardiovascular risk: a cohort study. *Ann Intern Med* 2011;**154**(1):310–8.
71. Waheed S, Matsushita K, Sang Y, Hoogeveen R, Ballantyne C, Coresh J. Combined association of albuminuria and cystatin C-based estimated GFR with mortality, coronary heart disease, and heart failure outcomes: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis* 2012;**60**(2):207–16.
72. Schmieder RE, Mann JF, Schumacher H, Gao P, Mancia G, Weber MA. ONTARGET Investigators: changes in albuminuria predict mortality and morbidity in patients with vascular disease. *J Am Soc Nephrol* 2011;**22**(7):1353–64.
73. Sarnak MJ, Levey AS, Schoowerth AC, Coresh J, Culleton B, Hamm LL. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003;**108**(17):2154–69.
74. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2012;**157**(4):263–75.
75. Upadhyay A, Earley A, Lamont JL, Haynes S, Wanner C, Balk EM. Lipid-lowering therapy in persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2012;**157**(4):251–62.
76. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;**353**(3):238–48.
77. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;**360**(14):1395–407.
78. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**(9784):2181–92.
79. Wanner C, Tonelli M, Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO Clinical Practice Guideline for Lipid Management in

CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int* 2014;**85**(6):1303–9.
80. Kasiske BL, Lakatua JD, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am J Kidney Dis* 1998;**31**(6):954–61.
81. Robertson L, Waugh N, Robertson A. Protein restriction for diabetic renal disease. *Cochrane Database Syst Rev* 2009:CD002181.
82. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW. The effects of dietary protein restriction and blood pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 1994;**330**(13): 877–84.
83. Menon V, Kopple JD, Wang X, Beck GJ, Collins AJ, Kusek JW. Effect of a very low-protein diet on outcomes: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) study. *Am J Kidney Dis* 2009;**53**(2):208–17.
84. Halbesma N, Bakker SJL, Jansen DF, Stolk RP, De Zeeuw D, De Jong PE. High protein intake associates with cardiovascular events but not with loss of renal function. *J Am Soc Nephrol* 2009;**20**(8):1797–804.
85. Palmer SC, Maggo JK, Campbell KL, Craig JC, Johnson DW, Sutanto B, Ruospo M, Tong A, Strippoli GF. Dietary interventions for adults with chronic kidney disease. *Cochrane Database Syst Rev* 2017;**23**(4):CD011998.
86. Perkovic V, Jardine MJ, Neal B, et al. CREDENCE Trial Investigators. Canagliflozin and renal outcomes in Type 2 diabetes and nephropathy. *N Engl J Med* 2019;**13**(2):318–20.
87. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**(22):2117–28.
88. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;**375**(4):323–34.
89. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**(7):644–57.
90. Neri L, Rocca Rey LA, Lentine KL, Hinyard LJ, Pinsky B, Xiao H. Joint association of hyperuricemia and reduced GFR on cardiovascular morbidity: a historical cohort study based on laboratory and claims data from a national insurance provider. *Am J Kidney Dis* 2011;**58**(3):398–408.
91. Liu WC, Hung CC, Chen SC, Yeh SM, Lin MY, Chiu YW. Association of hyperuricemia with renal outcomes, cardiovascular disease, and mortality. *Clin J Am Soc Nephrol* 2012;**7**(4):541–8.
92. Kanbay M, Huddam B, Azak A, Solak Y, Kadioglu GK, Kirbas I. A randomized study of allopurinol on endothelial function and estimated glomerular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. *Clin J Am Soc Nephrol* 2011;**6**(8):1887–94.
93. Kao MP, Ang DS, Gandy SJ, Nadir MA, Houston JG, Lang CC. Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease. *J Am Soc Nephrol* 2011; **22**(7):1382–9.
94. Sampson AL, Singer RF, Walters GD. Uric acid lowering therapies for preventing or delaying the progression of chronic kidney disease. *Cochrane Database Syst Rev* 2017;**30**(10):CD009460.
95. MacClean AJ, Hayslett JP. Adaptive change in ammonia excretion in renal insufficiency. *Kidney Int* 1980;**17**(5):595–606.
96. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD. *Nephrol Dial Transplant* 2009;**24**(4): 1232–7.
97. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol* 2009;**20**(9):2075–84.
98. Phisitkul S, Khanna A, Simoni J, Broglio K, Sheather S, Rajab MH. Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR. *Kidney Int* 2010;**77**(7):617–23.
99. Dobre M, Yang W, Pan Q, Appel L, Bellovich K, Chen J, Feldman H, Fischer MJ, Ham LL, Hostetter T, Jaar BG, Kallem RR, Rosas SE, Scialla JJ, Wolf M, Rahman M, CRIC Study Investigators. Persistent high serum bicarbonate and the risk of heart failure in patients with chronic kidney disease (CKD): a report from the Chronic Renal Insufficiency Cohort (CRIC) study. *J Am Heart Assoc* 2015;**20**(4):e001599.
100. Andress DL. Vitamin D in chronic kidney disease: a systemic role for selective vitamin D receptor activation. *Kidney Int* 2006;**69**(1): 33–43.
101. Sterling KA, Eftekhari P, Girndt M, Kimmel PL, Raj DS. The immunoregulatory function of vitamin D: implications in chronic kidney disease. *Nat Rev Nephrol* 2012;**8**(7):403–12.
102. Agarwal R, Acharya M, Tian J, Hippensteel RL, Melnick JZ, Qiu P. Antiproteinuric effect of oral paricalcitol in chronic kidney disease. *Kidney Int* 2005;**68**(6):2823–8.
103. de Zeeuw D, Agarwal R, Amdahl M, Audhya P, Coyne D, Garimella T. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. *Lancet* 2010; **376**(9752):1543–51.
104. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, Chronic Renal Insufficiency Cohort (CRIC) Study Group. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. *J Am Med Assoc* 2011;**305**(23):2432–9.
105. Block GA, Ix JH, Ketteler M, Martin KJ, Thadhani RI, Tonelli M. Phosphate homeostasis in CKD: report of a scientific symposium sponsored by the National Kidney Foundation. *Am J Kidney Dis* 2013;**62**(3):457–73.
106. Inker LA, Coresh J, Levey AS, Tonelli M, Muntner P. Estimated GFR, albuminuria, and complications of chronic kidney disease. *J Am Soc Nephrol* 2011;**22**(12):2322–31.
107. Moranne O, Froissart M, Rossert J, Gauci C, Boffa JJ, Haymann JP. Timing of onset of CKD-related metabolic complications. *J Am Soc Nephrol* 2009;**20**(1):164–71.
108. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998;**31**(4):607–17.
109. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 2004;**15**(8):2208–18.
110. Zoccali C, Ruggenenti P, Perna A, Leonardis D, Tripepi R, Tripepi G. Phosphate may promote CKD progression and attenuate renoprotective effect of ACE inhibition. *J Am Soc Nephrol* 2011;**22**(10):1923–30.
111. Adeney KL, Siscovick DS, Ix JH, Seliger SL, Shlipak MG, Jenny NS. Association of serum phosphate with vascular and valvular calcification in moderate CKD. *J Am Soc Nephrol* 2009; **20**(2):381–7.
112. Martin KJ, González EA. Prevention and control of phosphate retention/hyperphosphatemia in CKD-MBD: what is normal, when to start, and how to treat? *Clin J Am Soc Nephrol* 2011;**6**(2): 440–6.

113. Lynch KE, Lynch R, Curhan GC, Brunelli SM. Prescribed dietary phosphate restriction and survival among hemodialysis patients. *Clin J Am Soc Nephrol* 2011;**6**(3):620−9.
114. Isakova T, Gutiérrez OM, Smith K, Epstein M, Keating LK, Jüppner H. Pilot study of dietary phosphorus restriction and phosphorus binders to target fibroblast growth factor 23 in patients with chronic kidney disease. *Nephrol Dial Transplant* 2011;**26**(2):584−91.
115. Navaneethan SD, Palmer SC, Craig JC, Elder GJ, Strippoli GF. Benefits and harms of phosphate binders in CKD: a systematic review of randomized controlled trials. *Am J Kidney Dis* 2009;**54**(4): 619−37.
116. Navaneethan SD, Palmer SC, Vecchio M, Craig JC, Elder GJ, Strippoli GF. Phosphate binders for preventing and treating bone disease in chronic kidney disease patients. *Cochrane Database Syst Rev* 2011;**16**(2):CD006023.
117. Jamal SA, Fitchett D, Lok CE, Mendelssohn DC, Tsuyuki RT. The effects of calcium-based versus non-calcium-based phosphate binders on mortality among patients with chronic kidney disease: a meta-analysis. *Nephrol Dial Transplant* 2009;**24**(10):3168−674.
118. Block GA, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM. Effects of phosphate binders in moderate CKD. *J Am Soc Nephrol* 2012;**23**(8):1407−15.
119. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2009;**113**:S1−130.
120. Palmer SC, Gardner S, Tonelli M, Mavridis D, Johnson DW, Craig JC, French R, Ruospo M, Strippoli GF. Phosphate-binding agents in adults with CKD: a network meta-analysis of randomized trials. *Am J Kidney Dis* 2016;**68**(5):691−702.
121. Hsu CY, McCulloch CE, Curhan GC. Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: results from the third National Health and Nutrition Examination Survey. *J Am Soc Nephrol* 2002;**13**(2):504−10.
122. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the third National Health and Nutrition Examination Survey. (1988-1994). *Arch Intern Med* 2002;**162**(12):1401−8.
123. Newsome BB, Onufrak SJ, Warnock DG, McClellan WM. Exploration of anaemia as a progression factor in African Americans with cardiovascular disease. *Nephrol Dial Transplant* 2009;**24**(11): 3404−11.
124. Voormolen N, Grootendorst DC, Urlings TA, Boeschoten EW, Sijpkens YW, Huisman RM. Prevalence of anemia and its impact on mortality and hospitalization rate in predialysis patients. *Nephron Clin Pract* 2010;**115**(2):c133−41.
125. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2012;**2**:279−335.
126. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;**361**(21):2019−32.
127. Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006;**355**(20):2071−84.
128. Inrig JK, Barnhart HX, Reddan D, Patel UD, Sapp S, Califf RM. Effect of hemoglobin target on progression of kidney disease: a secondary analysis of the CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) trial. *Am J Kidney Dis* 2012; **60**(3):390−401.
129. Turner JM, Bauer C, Abramowitz MK, Melamed ML, Hostetter TH. Treatment of chronic kidney disease. *Kidney Int* 2012;**81**(4):351−62.
130. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 2007;**53**(4):766−72.

QUESTIONS AND ANSWERS

Question 1

Which ONE of the following is NOT TRUE regarding S[Cr] as a marker of kidney function?

A. S[Cr] level depends on diet and muscle mass
B. Creatinine production decreases with aging
C. S[Cr] underestimates renal function in people with low body weight
D. Creatinine secretion can be inhibited by drugs such as cimetidine

Answer: C

Answer C is incorrect as S[Cr] overestimates renal function in people with low body weight or with decreased muscle mass. The other statements about creatinine as a marker of kidney function are correct. The other drug that blocks creatinine secretion by renal tubules and therefore results in falsely elevated S[Cr] is trimethoprim.[1,2]

Question 2

Which ONE of the following is TRUE about the MDRD equation for estimating GFR?

A. It underestimates GFRs >60 mL/min/1.73 m^2
B. It leads to underestimation of the burden of stage 3 CKD
C. It is more accurate in older and malnourished patients
D. It should only be used in patients on a high-protein diet

Answer: A

Despite its widespread use, the MDRD equation has certain deficiencies that limit its utility. Although it is relatively accurate at lower GFRs, the MDRD equation tends to underestimate GFRs over 60 mL/min/1.73 m^2 especially in people without kidney disease. Therefore, **Answer A** is correct. Due to this lack of accuracy, use of the MDRD estimating equation tends to overdiagnose stage 3 CKD, making **Answer B** incorrect. Because the MDRD equation is S[Cr]-based, it also loses accuracy in patients at the extremes of age and weight, as well as in malnourished patients, making **Answer C** incorrect.[130] Although the equation was derived from patients enrolled in the MDRD study, the level of dietary protein intake has not been demonstrated to be a factor in the accuracy of the equation.

Question 3

A 55-year-old African-American woman has CKD secondary to diabetic nephropathy. Her GFR estimated by the CKD-EPI study equation using cystatin C is 38 mL/min/1.73 m^2.

Which ONE of the following is true regarding the use of cystatin as a marker of GFR in patients with CKD?

A. It can only be used in epidemiologic studies of CKD
B. It is less accurate than MDRD equation at GFRs greater than 60 mL/min/1.73 m^2
C. Cystatin C-based eGFR is a better predictor of death or ESRD compared to formulas that use creatinine
D. Estimating eGFR can be done with either S[Cr] or S[Cys] but not both

Answer: C

Cystatin C is a 120 amino acid protein that is synthesized and secreted at a nearly constant rate by almost all nucleated cells. It is freely filtered by the glomerulus and metabolized by the proximal tubule with negligible urinary excretion. Its advantage as a filtration marker is that it is not affected by muscle mass or chronic disease as is creatinine.

The use of cystatin C alone or in combination with S[Cr] improved the association between eGFR and the risks of death and ESRD in a meta-analysis of 11 general-population studies and 5 cohorts with CKD, making **Answer C** the correct answer.[118]

Answer A is incorrect as the CKD-EPI formulas were derived from large epidemiologic studies but can be used to estimate eGFR in individual patients.

Answer B is incorrect because any of the CKD-EPI equations are more accurate than the MDRD equation, which underestimates eGFR in those with levels >60 mL/min/1.73 m^2.

Answer D is incorrect as a CKD-EPI formula was developed and published in 2012 that uses both S[Cr] and cystatin C. This formula is more accurate than formulas using only one of these markers.[6]

Question 4

A 42-year-old African-American man with focal and segmental glomerulosclerosis has stage G3a CKD based on the 2012 staging system developed by KDIGO working group. His UACR is 750 mg/g placing him in the A3 albuminuria category.

Which ONE of the following is NOT TRUE regarding staging of his CKD?

A. Albuminuria is a risk factor for cardiovascular disease in CKD patients
B. Albuminuria is a risk factor for CKD progression
C. eGFR and albuminuria should be assessed at least annually in patients with CKD
D. Risk for CKD progression can be adequately assessed at the time of initial staging

Answer: D

Albuminuria is a risk factor for both CVD and CKD progression, therefore **Answers A and B** are true. KDIGO recommends GFR and albuminuria should be assessed at least annually in patients with CKD, and more frequently for those at higher risk of progression and/or where measurement will impact therapeutic decisions, therefore **Answer C** is true.[13] **Answer D** is not true and is the correct answer to this question. The confidence is assessing progression is increased with increasing number of S[Cr] measurements and duration of follow-up. It is important to realize that small fluctuations in GFR are common and not necessarily indicative of progression.

Question 5

A 58-year-old Hispanic woman with stage 3bA3 CKD secondary to diabetic nephropathy is seen in the outpatient clinic for management of CKD. Current S[Cr] is 3.7 mg/dL and eGFR using the abbreviated MDRD equation is 16 mL/min/1.73 m^2. A UACR is 3520 mg/g. Other medical problems include hypertension, currently treated with furosemide 40 mg orally twice daily and lisinopril 40 mg once daily. Her blood pressure is 155/95 mm Hg.

Which ONE of the following is true regarding management of her hypertension?

A. An ARB should be added to her antihypertensive regimen
B. Her blood pressure is adequately controlled on her current antihypertensive regimen
C. Hydrochlorothiazide should be added for better blood pressure control
D. Target BP is less than 130/80 mm Hg

Answer: D

Dual therapy with an ACEI and an ARB has not been effective in slowing progression of CKD and has been associated with significant complications such as hyperkalemia, hypotension, and AKI.[49–52] The current recommendations are not to use dual therapy, making **Answer A** incorrect. Although the exact target blood pressure in patients with CKD is unknown, most observational studies have demonstrated an association between level of blood pressure and clinical outcomes in CKD patients. Current clinical practice guidelines recommend BP <140/90 mm Hg, making **Answer B** incorrect. Hydrochlorothiazide is not the best agent to add, because in advanced CKD it is a relatively weak antihypertensive. Furthermore, in the ACCOMPLISH Study worse renal outcomes were seen in the ACEI/hydrochlorothiazide group compared with the ACEI/CCB group, therefore **Answer C** is incorrect.[57] Based on clinical practice guidelines, **Answer D** is the best choice.

Question 6

A 62-year-old man with known coronary artery disease and hypertension presented to the outpatient clinic for management of CKD secondary to membranous glomerulopathy. He has stable angina requiring 1 to 5 nitroglycerin tablets per week. His eGFR is 31 mL/min/1.73 m^2 and UACR is 920 mg/g (stage G3bA3 CKD). Other labs included a hemoglobin of 9.1 g/dL, transferrin saturation (TSAT) 21%, and ferritin 150 ng/mL.

Which ONE of the following is NOT TRUE regarding management of his anemia?

A. Hemoglobin concentration should be measured at least every three months in this patient
B. A trial of oral iron therapy should be initiated to try to correct the anemia
C. ESA therapy should be started targeting a hemoglobin concentration of 14 g/dL
D. ESA therapy should be started if there is no response to iron

Answer: C

Answer A is true. KDIGO clinical practice guidelines recommend measurement of hemoglobin concentration when clinically indicated and at least annually in patients with stage 3 CKD with anemia not being treated with an ESA.

Answer B is true. For CKD patients not treated with dialysis with anemia and not on iron or ESA therapy, KDIGO recommends a trial of oral iron therapy for 1–3 months if an increase in Hb concentration is desired, and TSAT is ≤30% and ferritin is ≤500 ng/mL. In this patient, an increase in hemoglobin is desired based on his stable but persistent angina. If oral iron is not effective, a trial of intravenous iron should be considered. Patients with CKD and anemia, if found to be iron deficient, need to have an evaluation for causes of blood loss.

When the hemoglobin concentration is less than 10 g/dL, the decision to initiate ESA therapy should be individualized. In this patient with angina, ESA therapy should be started to correct the anemia if there is no iron therapy. Therefore, **Answer D** is true. ESA should not be used to intentionally increase the hemoglobin concentration above 13 g/dL. In general, KDIGO recommends ESAs not be used to maintain Hb concentration above 11.5 g/dL in adult patients with CKD. Therefore, **Answer C** is not true and is the correct answer.[113]

CHAPTER

6

Epidemiology of Chronic Kidney Disease—Scope of the Problem

Mark Canney[a], *Peter Birks*[b], *Adeera Levin*[a]

[a]UBC Division of Nephrology and British Columbia Renal Agency, Vancouver, BC, Canada; [b]British Columbia Renal Agency, Vancouver, BC, Canada

Abstract

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function that are present for at least 3 months. In epidemiological studies, CKD is usually defined by a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 and/or a urinary albumin:creatinine ratio ≥30 mg/g (≥3 mg/mmol). In these studies, the prevalence of CKD often exceeds 10%, increases markedly with age, and varies by race. Major risk factors for CKD include hypertension, diabetes, and vascular disease. In developing countries, infection and glomerulonephritis are important contributors. Although end-stage renal disease (ESRD) is the most commonly recognized outcome, CKD confers an increased risk for all-cause mortality, cardiovascular events, acute kidney injury, infection, hospitalizations, and frailty. Although our knowledge and understanding of the epidemiology of CKD has improved substantially over the past decade, significant gaps remain, most notably in the developing world.

INTRODUCTION

The purpose of this chapter is to describe the scope of the problem of chronic kidney disease (CKD) using the best available data and literature. We begin with some background regarding the CKD paradigm, starting with the harmonized definition of CKD in 2002, data generated since that seminal publication, and the refinement of definitions and classification systems outlined in 2012. Most of the information about the epidemiology of CKD is predicated on these definitions. This chapter describes the profound and consistent relationship of CKD with adverse outcomes, highlighting the importance of CKD as a public health priority. Although knowledge gaps remain, particularly in capturing the burden of CKD in developing countries and in our understanding of individual risks associated with CKD in different circumstances, accruing data from multiple sources confirms the global impact of CKD on health.

BACKGROUND

In 2002, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) published a guideline on the definition, classification, and evaluation of CKD.[1,2] This represented a major paradigm shift for clinicians and researchers. The guideline recognized that patients with kidney disease were at risk of developing complications long before the need for renal replacement therapy and proposed that patients could be identified much earlier in the course of their disease using simple laboratory markers. Importantly, the classification system harmonized the nomenclature of kidney disease, thereby streamlining clinical care and facilitating collaborative research efforts. The publication has had a profound impact. It has stimulated discussion and debate, generated substantial research globally, and influenced public policy and laboratory practice.

It is of fundamental importance to recognize that the classification of CKD is built on risk of clinical outcomes. Multiple studies from different populations have consistently demonstrated higher risk of end-stage renal disease (ESRD), cardiovascular (CV), and all-cause mortality in individuals with a urine albumin:creatinine ratio (UACR) greater than 30 mg/g (3 mg/mmol) and/or estimated glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2, irrespective of the etiology or duration of kidney disease.[3] The international interest in understanding the epidemiology of CKD and improving the outcomes of people living with kidney

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00006-1

disease led to the revision and updating of the original NKF-KDOQI guideline by the international Kidney Disease: Improving Global Outcomes (KDIGO) group. The 2012 Clinical Practice Guideline on Evaluation and Management of CKD was informed by a decade of systematic research using common definitions, standardization of assays, and development of robust equations to estimate GFR.[4]

DEFINITION OF CKD

KDIGO defines CKD as abnormalities of kidney structure or function, present for at least 3 months, with implications for health. GFR has long been considered the best overall index of kidney function. The threshold to define CKD is a value less than 60 mL/min/1.73 m^2 body surface area. The categorization of GFR stage is described in Table 6.1. If GFR is ≥60 mL/min/1.73 m^2, CKD can be diagnosed by the presence of other markers of kidney damage including albuminuria, abnormal urinary sediment (such as hematuria or casts), renal tubular disorders, pathologic abnormalities such as tubulointerstitial diseases, and structural abnormalities detected by imaging (such as polycystic kidneys). The threshold of albuminuria to diagnose CKD is a UACR ≥30 mg/g (≥3 mg/mmol) (Table 6.2). KDIGO highlights the need to address three dimensions when describing CKD: cause, GFR category, and albuminuria category. Including cause of disease in the definition of CKD acknowledges potential differences in prognosis and therapy depending on the specific underlying etiology. The cross classification of GFR and albuminuria categories provides a color-coded stratification of risk for adverse outcomes (Figure 6.1). It is important to note that risk is high in the setting of significant albuminuria (>300 mg/g or >30 mg/mmol) even if GFR is preserved (>60 mL/min/1.73 m^2).

TABLE 6.1 GFR and ACR Categories in the KDIGO 2012 Classification GFR Categories

GFR Category	GFR (mL/min/1.73 m^2)	Descriptor
G1	≥90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Abbreviations: *ACR*, albumin:creatinine ratio; *CKD*, chronic kidney disease; *GFR*, glomerular filtration rate.
* *Relative to young adult level. In the absence of evidence of kidney damage, or structural abnormalities, neither GFR category G1 nor G2 fulfill the criteria for CKD.*

TABLE 6.2 ACR Categories

ACR Category	AER (mg/day)	ACR Equivalent (mg/mmol)	ACR Equivalent (mg/g)	Descriptor
A1	<30	<3	<30	Normal to mildly increased
A2	30–300	3–30	30–300	Moderately increased*
A3	>300	>30	>300	Severely increased**

Abbreviations: *ACR*, albumin:creatinine ratio; *AER*, albumin excretion rate; *CKD*, chronic kidney disease.
* *Relative to young adult level.*
** *Including nephrotic syndrome (albumin excretion usually >2200 mg/day [ACR >2220 mg/g; >220 mg/mmol]).*

The thresholds for GFR and albuminuria to classify the stage of CKD are based on large population studies examining prognosis. The CKD Prognosis Consortium (CKD-PC) was established in 2009 by KDIGO and sponsored by the US NKF.[5] CKD-PC is composed of investigators from around the world who share data from over 70 cohorts. Each participating study prepares a dataset with relevant variables according to a standardized coding framework. The data are sent to a coordinating center where they are pooled and meta-analyzed. CKD-PC investigators have consistently demonstrated that a GFR <60 mL/min/1.73 m^2 and an albumin:creatinine ratio (ACR) ≥30 mg/g (≥3 mg/mmol) are associated with increased risk of all-cause and CV mortality, CKD progression, and ESRD in the general population, high risk (for vascular disease), and kidney disease cohorts.[6–9]

Assessment of GFR

Although clearance of an exogenous filtration marker remains the gold standard for measuring GFR, the procedure is invasive, expensive, and time-consuming. A key factor in the rapid uptake of the CKD classification system was the availability of an equation to estimate GFR from an endogenous filtration marker such as creatinine. The first GFR estimating equation came from the Modification of Diet in Renal Disease (MDRD) study. The investigators used stepwise regression to generate a formula to predict measured GFR in 1628 participants from serum creatinine concentration (S[Cr]), demographic and clinical variables.[10] An updated, more parsimonious MDRD equation was published in 2006 which included just four variables: age, sex, race, and S[Cr] using a standardized assay.[11] The generalizability of the MDRD equation was hampered by the original study design. For example, included participants all had an underlying diagnosis of kidney disease, and the exclusion criteria included age >70 years and insulin-requiring diabetes mellitus.

Prognosis of CKD by GFR and Albuminuria Categories				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73m^2) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD);
Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
KDIGO 2012

FIGURE 6.1 KDIGO 2012. Prognosis of chronic kidney disease (CKD) by glomerular filtration rate (GFR) and albuminuria categories. *Reproduced with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Kidney Int Suppl 2013;3:1–150.*

An alternative GFR estimating equation was published in 2009 by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[12] The CKD-EPI equation was developed in a more diverse population than the MDRD cohort and included individuals with and without evidence of kidney disease. The equation was developed and internally validated in 8254 participants from 10 studies and externally validated in 3896 participants from 16 other studies. The CKD-EPI equation was shown to be as accurate as the four-variable MDRD equation at lower levels of GFR (<60 mL/min/1.73 m^2) and to demonstrate less bias than the MDRD formula at higher levels of GFR (≥60 mL/min/1.73 m^2). Where CKD-EPI has been modified for use in other racial and ethnic groups, and where validated country- or region-specific equations have been developed, those modified equations should provide valid estimates and can be used.[4] An important limitation of the CKD-EPI equation was the relatively small sample size for adults >70 years of age. This important gap has been addressed by the Berlin Initiative Study equations, which were specifically developed and validated in individuals over the age of 70.[13]

Despite the refinement of GFR estimating equations over time, they are still subject to the limitations of S[Cr] as a filtration marker, most notably large interindividual variability in creatinine generation due to differences in dietary protein intake and muscle mass.[14] The precision of GFR estimating equations remains limited at values of GFR >60 mL/min/1.73 m^2, suggesting that age, sex, and race do not account for all of the variation in non-GFR determinants of creatinine. The filtration marker that has gained most traction as an alternative to creatinine is cystatin C, a 13 kDa protein thought to be produced by all nucleated cells at a constant rate. Early studies demonstrated that cystatin C was a better predictor of measured GFR than creatinine.[15] An equation to estimate GFR from cystatin C was published by the CKD-EPI group in 2012.[16] While adjusting for non-GFR determinants of creatinine generation (age, sex, and race) significantly improved the correlation between S[Cr] and measured GFR, the same adjustments only minimally improved the correlation between cystatin C and measured GFR. For this reason, as well as higher cost and limited availability of assays, cystatin C struggled to enter clinical practice as a viable long-term alternative to S[Cr].[17] Where cystatin C has shown most promise is in risk stratification of CKD. A number of landmark studies have demonstrated that reclassification of estimated GFR (eGFR) stage using cystatin C can discriminate between high and low risk for important outcomes.[18,19] For this reason, cystatin C has entered KDIGO guidelines as a confirmatory test of CKD among individuals with GFR between 45 and 59 mL/min/1.73 m^2 without other evidence of kidney damage such as albuminuria. Cystatin C has strong associations with CV risk factors, independent of GFR, such as inflammation, smoking, and

obesity.[20–22] It is unclear if the improved risk discrimination of cystatin C relates entirely to its role as a marker of filtration or whether these non-GFR determinants of cystatin C also contribute to higher risk of adverse outcomes.

Assessment of ACR

To evaluate proteinuria, the measurement of urinary albumin, expressed as ACR, is recommended. By reporting the urinary albumin level in relation to urinary creatinine concentration, the ACR provides a standardized measure. Albumin is the most abundant protein excreted in the urine in most proteinuric kidney diseases (although urinary immunoglobulin loss characterizes monoclonal gammopathies affecting the kidney). ACR has greater sensitivity for detecting low-grade but clinically important albuminuria and is more precise at low but diagnostically important concentrations. Other measures of protein in the urine can be used, including total protein or qualitative measures (dipsticks), where circumstance does not permit use of the more expensive test of ACR.

PREVALENCE OF CKD

The standardized definitions of CKD have led to improved understanding of the burden of CKD in multiple populations. The remainder of this chapter reviews the prevalence of CKD in different regions around the world and by demographic subgroups, the outcomes associated with CKD that have underpinned the classification system, and recognized risk factors for CKD. Throughout the text, we discuss strengths and limitations of the current data available and highlight areas that require further study.

With the advent of GFR estimating equations and consensus definitions for CKD, there have been many studies evaluating the prevalence of CKD from around the world. A review published in the Lancet in 2013 provided CKD prevalence estimates from 18 countries.[23] The prevalence of GFR <60 mL/min/1.73 m^2, estimated by the MDRD or CKD-EPI equations, often exceeded 10%. The prevalence of proteinuria frequently exceeded 5%. In the US, robust prevalence data have been published from the 1988–1994 and 1999–2004 phases of the National Health and Nutrition Examination Survey (NHANES).[24] NHANES is a stratified, cluster probability sample that, coupled with the use of sampling weights, provides nationally representative prevalence estimates. CKD was defined using GFR estimated from S[Cr] (calibrated to a central reference standard) and persistent albuminuria. Overall, it was estimated that 13% of US adults had evidence of CKD. Of US adults with reduced GFR, the majority had mildly or moderately decreased GFR (30–59 mL/min/1.73 m^2), with only 0.35% having severely decreased GFR or kidney failure.

The European CKD Burden Consortium recently published prevalence data from various cohorts across Europe.[25] In addition to demonstrating overall high prevalence of CKD, the investigators observed considerable heterogeneity in included studies, for example, varying sample sizes and response rates, use or nonuse of a sampling frame, and lack of standardization of assays used to measure or cystatin C.[26] Notwithstanding these methodological differences, it is likely that there are population-specific factors that contribute to varying prevalence estimates. Therefore, it is important to accurately define the prevalence of CKD in well-characterized and representative samples to meaningfully compare prevalence estimates between different regions. Another limitation of most prevalence studies is the lack of a repeat assessment of GFR or ACR to confirm the chronic nature of the abnormality. Albumin excretion is subject to substantial intraindividual variation,[27] and both GFR and ACR can be affected by changes in body composition.[28] Use of a single GFR or ACR value to define the presence or absence of CKD can thus lead to substantial misclassification.[29]

CKD AND OUTCOMES

Although kidney failure is the most commonly recognized outcome for patients with kidney disease, CKD has also been strongly associated with an increased risk of several other important outcomes, most notably all-cause and CV mortality. CKD has thus been the focus of intensive research efforts to better understand the mechanisms driving poor outcomes in people with kidney disease.

CKD and All-Cause Mortality

CKD is associated with an increase in the absolute risk of all-cause mortality.[30] Life expectancy is reduced in the setting of either reduced GFR or increased ACR.[31,32] For example, individuals aged 30 years with evidence of severely increased ACR (≥300 mg/g) may have a shortening of life expectancy by as much as 18 years compared with their age-matched peers without albuminuria.[31] The CKD-PC pooled data on 1.2 million adults from general population cohorts and reported multivariable-adjusted hazard ratios (95% confidence interval (CI)) for all-cause mortality of 1.18 (1.05–1.32), 1.57 (1.39–1.78), and 3.14 (2.39–4.13) for GFR levels of 60, 30, and 15 mL/min/1·73 m^2, respectively, each vs. a reference GFR of 95 mL/min/1.73 m^2.[6] Results for GFR were nonlinear, tending

toward a U-shaped relationship, likely explained by low creatinine generation due to diminished muscle mass or malnutrition in the context of competing comorbid illness. In contrast, the association between ACR and mortality was linear. Hazard ratios (95% CI) were 1.20 (1.15–1.26), 1.63 (CI 1.50–1.77), and 2.22 (1.97–2.51) for ACR values of 10 mg/g, 30 mg/g, and 300 mg/g, respectively, each compared with an ACR of 5 mg/g. Although the interaction of GFR and ACR was not statistically significant, the highest risk of mortality was observed among those with a combination of low GFR and high ACR.

CKD and Cardiovascular Disease

Kidney disease has long been implicated as a risk factor for CV disease. Recent epidemiological studies have quantified this risk according to level of GFR and/or albuminuria. In a landmark study, Go and colleagues reported a graded increase in the risk of CV disease with diminishing GFR among patients in the Kaiser Permanente Northern California health system.[33] Leveraging data from >1.2 million individuals in the general population, the CKD-PC observed an increased risk for CV mortality associated with decreased GFR and increased albuminuria.[6] In this analysis, higher risk for CV mortality became evident at GFR values below 75 mL/min/1.73 m^2. There was no such threshold for ACR, indicating that even small increases in albuminuria are independently associated with CV mortality. The CKD-PC reported similar results for 266,975 individuals at high risk for CKD (history of hypertension, diabetes, or CV disease).[9] In this population, the risk of CV mortality started to increase below a GFR of 60 mL/min/1.73 m^2 and was statistically significant at a GFR of 45 mL/min/1.73 m^2 (HR 1.73, 95% CI 1.49–2.00). Again, ACR demonstrated a linear risk relationship with CV mortality with no evidence of a threshold effect.

The higher risk of CV disease among individuals with kidney disease is often attributed to shared risk factors such as diabetes and hypertension. This assumption was challenged in two meta-analyses that demonstrated that the relative risk of CV mortality according to either lower GFR or higher ACR was similar in participants with and without diabetes or hypertension.[34,35] Furthermore, the risk of myocardial infarction among people with CKD is comparable with the risk posed by diabetes mellitus, a recognized coronary heart disease equivalent. For example, in a population of nearly 1.3 million people without a prior myocardial infarction, the incidence rate (95% CI) for acute myocardial infarction was 5.4 (5.2–5.7) per 1000 patient years for people with diabetes and 6.9 (6.6–7.2) per 1000 patient years for people with CKD.[36] The incidence rate was twofold higher for CKD compared with diabetes when CKD was defined by stricter criteria: GFR <45 mL/min/1.73 m^2 with proteinuria. Similarly, CKD has been associated with a substantially higher risk of recurrent coronary events than established risk factors such as diabetes, metabolic syndrome, or cigarette smoking.[37] The totality of the data supports calls for CKD to be regarded as a coronary heart disease risk equivalent,[38] and for GFR and ACR to be included in CV risk prediction algorithms.[39]

CKD and Renal Outcomes

Both reduced GFR and increased ACR are strong risk factors for progression of kidney disease and the development of ESRD. Among general population and high-risk cohorts, the risk of renal outcomes appears to increase at GFR values below 75 mL/min/1.73 m^2 and to rise exponentially at lower GFR values.[8] Among CKD populations, a GFR threshold for increased risk is not as readily identified; however, each 15 mL/min/1.73 m^2 reduction in GFR (below a GFR of 45 mL/min/1.73 m^2) is associated with a sixfold increased risk of ESRD.[7] Similar to mortality outcomes, the risk relationship between ACR and ESRD is monotonic across the range of ACR.[8] The association between GFR or ACR and ESRD does not appear to vary by diabetes or hypertensive status, arguing against a clustering of risk factors driving ESRD risk.[34,35] These findings support the use of GFR and ACR to identify individuals at higher risk of kidney outcomes, including the development of kidney failure risk prediction tools for clinical practice.[40]

CKD and Other Outcomes

CKD has been examined as a risk factor for several other clinical outcomes. In keeping with the strong association between CKD and CV endpoints, CKD has been identified as an independent predictor of specific CV conditions such as atrial fibrillation, stroke, heart failure, and peripheral arterial disease.[41–45] In general, ACR appears to be a stronger predictor of outcome than GFR in these studies. CKD is also related to higher risk of infection, hospitalizations, fractures, and frailty.[33,46–49]

GLOBAL BURDEN OF CKD

Defining the Global Burden of Disease

The Global Burden of Disease (GBD) was initiated in 1992 as a collaborative effort between the World Bank and the World Health Organization (WHO). The purpose of this study was to address three primary goals:

(1) provide information on nonfatal health outcomes for debates on international health policy, (2) develop unbiased epidemiological assessments for major disorders, and (3) quantify the burden of disease with a measure that could be used for cost-effectiveness analysis.[50] The WHO first reported the GBD for 1990 using disability-adjusted life years (DALYs), which is a time-based measure that combines years of life lost due to morbidity and premature mortality.[51] Since the first report in 1990, there have been subsequent waves of the GBD study. Compared with prior GBD studies, the scope of the 2015 GBD study is expanded and includes over 300 diseases in 195 countries and territories from 1980 to 2015.[52]

In 1990, CKD was ranked 27th in the list of causes of total number of global deaths. CKD increased to the 12th leading cause of death by 2015. Mortality due to CKD rose between 2005 and 2015 by 32% to 1.2 million deaths worldwide, with an estimated annual death rate of 19.2 per 100,000. Since 1990, only deaths from complications of HIV infection have increased at a faster rate than deaths from CKD. Furthermore, the global burden of mortality associated with CKD may be substantially higher than reported in the GBD study. A study conducted in the US and Australia found that many deaths among people with diabetes and CKD did not mention CKD.[53] This study estimated that mortality from diabetes-related renal disease may be up to 9 times higher than the reported rate. The contribution of CKD to DALYs increased from 30th in 1990 to 20th in 2015.[54] In several world regions (high-income Asia Pacific, high-income North America, central Latin America, Southeast Asia, and Oceania), CKD was ranked in the top 10 for DALYs.[55]

CKD IN POPULATION SUBGROUPS

Like most chronic disease, CKD is not uniformly distributed in the population. Over the past decade, notable differences in the prevalence of CKD by demographic factors have been reported. We review differences in CKD prevalence and CKD-outcome associations by demographic factors, as well as the major risk factors for CKD.

Age

One of the most controversial aspects of the CKD classification system has been the apparently high burden of CKD among the general population of older adults. Several studies have demonstrated a steep age gradient in the prevalence of CKD. For example, in the NHANES 1999–2004 study, the prevalence of GFR <60 mL/min/1.73 m^2 increased from less than 1% among individuals aged 20–39 years to 38% among those over 70 years.[24] Similarly, the European CKD Burden Consortium reported prevalence estimates exceeding 40% among individuals aged ≥75 years.[25] Additionally, the prevalence of albuminuria increases with age. Using NHANES data, the prevalence of albuminuria (ACR >30 mg/g) was estimated at 5.8%, 11.4%, and 22.7% among US adults aged 20–49, 50–69, and ≥70 years, respectively.[56] In the Reasons for Geographic and Racial Differences in Stroke study, 25% of US adults aged ≥80 years had an ACR >30 mg/g.[57]

A number of arguments have been put forward to support an age-calibrated definition of CKD, built on the notion that decreased GFR or increased ACR in older people reflects "normal aging" rather than a disease.[58,59] It was postulated decades ago that GFR declines with advancing age. Contemporary population studies of apparently healthy adults have also demonstrated a gradual decline in estimated GFR with age.[60] An interesting population to study kidney aging are older individuals who donate a kidney. Living kidney donors are subject to a rigorous evaluation of their health status, including measurement of GFR and a kidney biopsy at the time of engraftment, providing a rich source of data regarding age-related structural and functional changes in the kidney. The prevalence of glomerulosclerosis, arteriosclerosis, interstitial fibrosis, and tubular atrophy, collectively termed nephrosclerosis, increases linearly with age.[61] This association is not explained by declines in GFR or risk factors for CKD, suggesting that these histological changes reflect a subclinical phenomenon of natural aging.[62,63] Critics of the CKD classification system also point to the discrepancy between high prevalence of the disease and comparatively low incidence of ESRD in older adults, often due to a competing risk of death from another cause.[64]

A meta-analysis of over two million participants specifically addressed the question of effect modification by age in the association between GFR and the risk of mortality or ESRD.[65] Among 33 general population and high risk of vascular disease cohorts, age was found to modify the relationship between GFR and mortality risk. Relative risks of mortality and ESRD were reduced at older age, whereas absolute risk differences were higher. Despite evidence of an interaction, GFR was independently associated with mortality and ESRD across all age categories. The increased risk of mortality generally became evident in the GFR range of 60–74 mL/min per 1.73 m^2, except in the oldest age group (>75 years) in whom the hazard ratio (with 80 mL/min per 1.73 m^2 as the reference) was statistically significant below a GFR of 56 mL/min per 1.73 m^2. In 13 CKD cohorts, the relationship between GFR and risks of ESRD and mortality did not vary substantially by age. Apart from hard outcomes, CKD has also been recognized as a contributing factor to the risk of more

proximal outcomes such as functional impairment,[66] an important patient-centered outcome for older adults.[67] Reduced GFR has been shown to be an independent predictor of poorer physical performance,[68,69] as well as a predictor of prevalent and incident frailty.[49] Even at older ages, reduced GFR is associated with a high prevalence of concurrent CKD complications such as anemia, acidosis, hyperphosphatemia, hyperparathyroidism, and hypertension.[70]

Gender

The prevalence of CKD and albuminuria appears to be higher in females. The 2016 USRDS annual report documented the prevalence of CKD in the US general population to be 13% in men and 16.5% in women.[71] In both sexes, reduced GFR and increased albuminuria are associated with higher risk of all-cause and CV mortality and ESRD. However, the slope of the risk relationship for mortality may be steeper in women.[72] Reasons for gender differences in CKD prevalence and outcomes are poorly understood.[73] Women have unique risk factors for kidney disease. Acute kidney injury (AKI), hypertension, preeclampsia, and diabetes during pregnancy are all risk factors for the development of CKD.[74,75] Furthermore, autoimmune diseases with a predilection for the kidney such as systemic lupus erythematosus, scleroderma, and rheumatoid arthritis are more common in women.[76] The potential contribution of autoimmune disease to the incidence and progression of CKD in women is an intriguing area that requires further study.[74]

Race and Ethnicity

Substantial differences have been identified in the incidence of ESRD by race or ethnicity.[77] Within the US, this takes the form of a higher incidence of ESRD among African American compared with Caucasian Americans. Around the globe, this has been investigated as differences between Asians, whites, and blacks.

Race and Ethnicity Differences in CKD in the US

According to the most recent data from USRDS, the prevalence of CKD is an estimated 16.9% in African Americans, 15.2% in Caucasians, 12.5% in Mexican Americans, 12.8% in other Hispanics, and 12.8% in other non-Hispanics. The prevalence of albuminuria is highest in African Americans (13.5%) and lowest in Caucasians (9.0%). The prevalence of ESRD is higher in African-American patients compared with other racial groups: 2.6-fold higher than Native Americans and Asians, and nearly fourfold higher than Caucasians.[71] Furthermore, analysis of NHANES data suggests that the prevalence of stages 3 and 4 CKD has stabilized in non-Hispanic whites, while it continues to rise in non-Hispanic African Americans.[78]

Genetic factors play a key role in the increased risk of CKD in African Americans. There has been increasing focus on the APOL1 gene encoding the protein apolipoprotein L1. APOL1 mutations (G1 and G2) are protective against the parasite *Trypanosoma brucei* that causes African sleeping sickness. Variants of this gene, found exclusively in individuals of recent African descent, are associated with increased risk of nondiabetic CKD, hypertensive nephropathy, and focal segmental glomerulosclerosis.[79,80] APOL1 variants also appear to increase the risk of CKD progression. In the CRIC study, participants with two copies of APOL1 risk variants were twice as likely to develop a composite renal outcome of 50% reduction in GFR or ESRD over a mean follow-up period of 9 years.[81]

Race and Ethnicity Differences in CKD Around the World

Latin America, Europe, East Asia, and the Middle East have the highest prevalence of CKD (approximately 12%), whereas South Asia (8%) and sub-Saharan African (7%) have lower prevalence estimates.[82] The incidence of ESRD also exhibits substantial regional variability, from more than 400 per million population (pmp) in Taiwan to less than 50 pmp in countries such as Russia and China.[23] It was previously estimated that >90% of all patients receiving treatment for ESRD reside in affluent countries with a large elderly population and good access to health care.[83] Using data from 25 population-based cohorts, the CKD-PC evaluated the prevalence of albuminuria and decreased GFR by race ethnicity and investigated differences in the association between these markers and clinical outcomes by race.[84] In this study, the prevalence of decreased GFR was higher among whites (16%) compared with blacks (9%) and Asians (5%). However, the prevalence of albuminuria was highest for blacks (17%) compared with whites (10%) and Asians (3%). In each race group, decreased GFR and albuminuria were associated with increased risk for all outcomes, with no evidence of effect modification by race.[84]

CKD IN THE DEVELOPING WORLD

Around 85% of the world's population live in low- and middle-income countries. Our current understanding of CKD epidemiology is predominately based on data from higher-income regions, leaving a major gap in our understanding of the scope of CKD in the developing world. The International Society of Nephrology

recently launched its "Closing the Gaps" initiative, aiming to define the current state of global kidney care and make recommendations for improvement. This initiative includes the Global Kidney Health Atlas project, a 130-country global survey seeking to characterize the current state of readiness, capacity, and ability to provide kidney health care in each country.[85] The information gathered will be invaluable to guide further initiatives to improve access to optimal care for kidney disease.

CKD prevalence is expected to grow rapidly in the developing world as rates of diabetes, hypertension, obesity, and metabolic syndrome increase.[86] Diabetic nephropathy is fast emerging as a major cause of kidney disease in the developing world. Another important contributor to CKD in these regions is the high burden of infectious diseases such as HIV, hepatitis B, malaria, and schistosomiasis that can affect the kidneys.[87] An estimated 37 million people are living with HIV worldwide. Several renal pathologic entities have been demonstrated in the HIV population including glomerular lesions such as HIV-associated nephropathy (HIVAN) and HIV-associated immune complex renal disease.[88] Early initiation of antiretroviral therapy is essential as it has been shown to reduce the risk and progression of HIV-related kidney disease.[89,90] While antiretroviral medications have dramatically reduced the risk of HIVAN, they are associated with chronic inflammation and metabolic syndrome, which are risk factors for CKD.[91] Additionally, as patients live longer with HIV infection, classic CKD risk factors such as diabetes and CV disease are becoming more common in this population.[92] CKD is associated with increased mortality and CV risk in HIV-infected patients.[93]

An emerging cause of kidney disease in low- and middle-income countries is CKD of unknown etiology (CKDu).[94] The condition was first described in plantation workers in Central and South America and is currently a leading cause of death and hospitalization in those regions.[95] Patients with CKDu do not have traditional renal risk factors such as hypertension or diabetes, suggesting the possibility of environmental factors in disease pathogenesis.[96,97] Air pollution, tobacco, pesticides, infections, heavy metals, high seasonal temperatures, and dehydration are all thought to be potential contributors.[98] The pathologic mechanism is thought to be predominately interstitial nephritis as the histological features in CKDu are interstitial inflammation and fibrosis, mononuclear cell infiltration, and tubular atrophy.[95,99] In Sri Lanka, the prevalence of CKDu was estimated at 12.9 % in males and 16.9% in females and accounts for nearly 4% of the national health care budget. In El Salvador, ESRD related to CKDu is the leading cause of in-hospital mortality.[98]

MAJOR RISK FACTORS FOR CKD

Capturing the scope of the problem of CKD lies in understanding its risk factors. Many risk factors for ESRD have also been identified to increase the risk of development of earlier stages of CKD. Several common risk factors associated with increased risk for CKD are also associated with increased risk for adverse outcomes among people with CKD.

Hypertension

Global age-standardized prevalence of hypertension in 2015 was an estimated 24.1% in men and 20.1% in women, overall equating to 1.13 billion adults.[100] Hypertension is considered both a cause and consequence of CKD. In the Framingham Heart Study, the presence of hypertension was associated with a 57% increased likelihood of incident CKD[101] The prevalence of hypertension increases with worsening kidney function and is nearly ubiquitous among patients starting renal replacement therapy. Among people with CKD, higher levels of systolic blood pressure in particular are associated with greater risk of progression to ESRD, as well as increased risk of coronary heart disease.[102–104] The optimal blood pressure target for people with CKD continues to be debated. In a prespecified subgroup analysis from the Systolic Blood Pressure Intervention Trial (SPRINT), targeting a systolic blood pressure of less than 120 mm Hg compared with 140 mm Hg was associated with reduced rates of major CV events and all-cause mortality among participants with CKD.[105] SPRINT excluded individuals with diabetes, advanced CKD, or proteinuria >1 g/day. Observational data suggest a J-shaped association between blood pressure and risk of death among CKD patients, a finding that could be confounded by the presence of underlying cardiac dysfunction in the CKD population.[106] An increasing body of literature has recognized the importance of blood pressure variability as a predictor of CV outcomes such as stroke, independent of mean or "usual" blood pressure values.[107,108] Recent data suggest that increased variability in visit-to-visit blood pressure is also a risk factor for adverse renal outcomes.[109,110]

Diabetes

The prevalence of diabetes mellitus is increasing around the globe. According to WHO 2016 data, 422 million people are living with diabetes (online reference http://www.who.int/diabetes/global-report/en/). Furthermore, impaired fasting glucose is even more prevalent (affecting more than 1 billion people

worldwide) and is associated with the development and progression of CKD.[111] According to the 2016 USRDS national report, 39% of individuals with diabetes have CKD.[71] Approximately 25% of people with CKD have diabetes, although it accounts for over 50% of ESRD cases in many countries.[56,77] Similar to hypertension, diabetes is a major risk factor for coronary heart disease, ESRD, and all-cause mortality among people with CKD.[112] Between 1990 and 2012, the number of global deaths attributed to diabetic kidney disease rose by 94%.[52]

Obesity

The global epidemic of obesity is well recognized. In 2015 worldwide, 107.7 million children and 603.7 million adults were obese.[113] Obesity is strongly related to CV disease and is also associated with an increased risk of CKD. In the Framingham Heart Study, each 4.2 kg/m^2 higher body mass index was associated with a 23% increased likelihood of incident CKD.[101] The amount of CKD attributable to obesity may be more substantial as this study adjusted for diabetes and systolic blood pressure, two major CKD risk factors that may be on the causal pathway between obesity and CKD. The mechanism of CKD in obesity is thought to be compensatory hyperfiltration and increased intraglomerular pressure.[114] Although wasting is common in more advanced CKD and obesity is protective against mortality among patients treated with maintenance dialysis, the association between obesity and outcomes in earlier stages of CKD is less clear.[115,116] When using BMI, obesity has not always been associated with CV or mortality outcomes in CKD.[117,118] However, waist circumference, which better captures abdominal adiposity, has been associated with an increased risk for all-cause mortality among patients with CKD.[118] Additionally, obese individuals often have hypertension, diabetes, and dyslipidemia, each of which are important risk factors for adverse outcomes among people with CKD. Therefore, intentional weight loss may be beneficial for preventing CKD and should be considered for overweight and obese patients with predialysis CKD.[119] The estimation of kidney function in obese patients can be problematic. Creatinine-based GFR estimating equations were not specifically derived or validated in obese patients. These formulas generally overestimate GFR in obese patients. Using cystatin C is also problematic as it is produced by adipose cells and therefore underestimates GFR.[120] CKD-EPI (creatinine) appears to the most accurate of the formulas in obese patients with GFR <60 $mL/min/1.73\,m^2$ compared with gold standard measurements of GFR.[121]

Acute Kidney Injury

AKI is defined as a transient reduction in kidney function, manifesting as decreased urine output or increased S[Cr], or both. Previous studies have demonstrated that severe AKI requiring hospitalization and short-term dialysis is associated with an increased risk of subsequent ESRD.[122] It is increasingly recognized that less severe forms of AKI can increase the risk of developing CKD, even if kidney function returns to baseline levels following the injury.[123,124] The speed of renal recovery following AKI may also be an important contributor to future CKD risk.[125] Reduced GFR and increased ACR are also strong predictors of AKI,[8] thus predisposing individuals with CKD to repeated insults which could in turn contribute to disease progression.[126] Additionally, AKI is associated with increased risk of mortality in hospitalized patients and an increased risk of CV disease including heart failure and myocardial infarction.[124,127]

CONCLUSION: SCOPE OF THE PROBLEM OF CKD

Epidemiologic data indicate the prevalence of CKD, whether defined by decreased GFR or the presence of albuminuria, is high in many regions of the world. Furthermore, the prevalence of major risk factors for CKD, including hypertension, diabetes, and obesity, is high and increasing with population aging, decline in mortality from communicable diseases, and adoption of sedentary lifestyles and a Westernized diet. Over the past 10 years, CKD has been identified as a major risk factor for CV disease, all-cause mortality, and ESRD. The risk for these adverse outcomes is higher in individuals with either reduced GFR or albuminuria, and highest if both parameters are present. Additionally, several studies have demonstrated that people with CKD have an excess risk for CV disease, exceeding that of other "high-risk" conditions such as diabetes mellitus. The emerging data regarding AKI as a predictor of CKD, as well as other adverse outcomes, emphasizes the importance of raising the awareness of kidney disease in the broader context of comorbid illness. The contribution of CKD to global mortality and disability rates has increased more than almost all other diseases over the past 20 years. Our understanding of CKD in the developing world, while improving, remains limited and has been identified as a key research priority. Although clearly challenging, public health efforts are needed to tackle the burden of CKD through greater awareness and earlier detection, better understanding of disease mechanisms, and improved access to care for all individuals.

References

1. National Kidney F. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**(2 Suppl. 1):S1–266.
2. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003;**139**(2):137–47.
3. Eckardt KU, Coresh J, Devuyst O, Johnson RJ, Kottgen A, Levey AS, et al. Evolving importance of kidney disease: from subspecialty to global health burden. *Lancet* 2013;**382**(9887): 158–69.
4. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013; **2013**(3):150.
5. Matsushita K, Ballew SH, Astor BC, Jong PE, Gansevoort RT, Hemmelgarn BR, et al. Cohort profile: the chronic kidney disease prognosis consortium. *Int J Epidemiol* 2013;**42**(6):1660–8.
6. Chronic Kidney Disease Prognosis C, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;**375**(9731): 2073–81.
7. Astor BC, Matsushita K, Gansevoort RT, van der Velde M, Woodward M, Levey AS, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int* 2011;**79**(12):1331–40.
8. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes in both general and high-risk populations. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int* 2011;**80**(1): 93–104.
9. van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2011;**79**(12):1341–52.
10. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. *Ann Intern Med* 1999;**130**(6):461–70.
11. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006;**145**(4): 247–54.
12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro 3rd AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**(9):604–12.
13. Schaeffner ES, Ebert N, Delanaye P, Frei U, Gaedeke J, Jakob O, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. *Ann Intern Med* 2012;**157**(7):471–81.
14. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function–measured and estimated glomerular filtration rate. *N Engl J Med* 2006;**354**(23):2473–83.
15. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *Am J Kidney Dis* 2002;**40**(2):221–6.
16. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012;**367**(1):20–9.
17. Shlipak MG, Mattes MD, Peralta CA. Update on cystatin C: incorporation into clinical practice. *Am J Kidney Dis* 2013;**62**(3):595–603.
18. Shlipak MG, Matsushita K, Arnlov J, Inker LA, Katz R, Polkinghorne KR, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med* 2013; **369**(10):932–43.
19. Peralta CA, Shlipak MG, Judd S, Cushman M, McClellan W, Zakai NA, et al. Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. *JAMA* 2011;**305**(15):1545–52.
20. Rule AD, Bailey KR, Lieske JC, Peyser PA, Turner ST. Estimating the glomerular filtration rate from serum creatinine is better than from cystatin C for evaluating risk factors associated with chronic kidney disease. *Kidney Int* 2013;**83**(6):1169–76.
21. Schei J, Stefansson VT, Mathisen UD, Eriksen BO, Solbu MD, Jenssen TG, et al. Residual associations of inflammatory markers with eGFR after accounting for measured GFR in a community-based cohort without CKD. *Clin J Am Soc Nephrol* 2016;**11**(2): 280–6.
22. Mathisen UD, Melsom T, Ingebretsen OC, Jenssen T, Njolstad I, Solbu MD, et al. Estimated GFR associates with cardiovascular risk factors independently of measured GFR. *J Am Soc Nephrol* 2011;**22**(5):927–37.
23. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. *Lancet* 2013;**382**(9888):260–72.
24. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. *JAMA* 2007;**298**(17):2038–47.
25. Bruck K, Stel VS, Gambaro G, Hallan S, Volzke H, Arnlov J, et al. CKD prevalence varies across the European general population. *J Am Soc Nephrol* 2016;**27**(7):2135–47.
26. Bruck K, Jager KJ, Dounousi E, Kainz A, Nitsch D, Arnlov J, et al. Methodology used in studies reporting chronic kidney disease prevalence: a systematic literature review. *Nephrol Dial Transplant* 2015;**30**(Suppl. 4):iv6–16.
27. Naresh CN, Hayen A, Weening A, Craig JC, Chadban SJ. Day-to-day variability in spot urine albumin-creatinine ratio. *Am J Kidney Dis* 2013;**62**(6):1095–101.
28. Fotheringham J, Weatherley N, Kawar B, Fogarty DG, Ellam T. The body composition and excretory burden of lean, obese, and severely obese individuals has implications for the assessment of chronic kidney disease. *Kidney Int* 2014;**86**(6):1221–8.
29. Benghanem Gharbi M, Elseviers M, Zamd M, Belghiti Alaoui A, Benahadi N, Trabelssi el H, et al. Chronic kidney disease, hypertension, diabetes, and obesity in the adult population of Morocco: how to avoid "over"- and "under"-diagnosis of CKD. *Kidney Int* 2016;**89**(6):1363–71.
30. Wen CP, Cheng TY, Tsai MK, Chang YC, Chan HT, Tsai SP, et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. *Lancet* 2008;**371**(9631):2173–82.
31. Turin TC, Tonelli M, Manns BJ, Ahmed SB, Ravani P, James M, et al. Proteinuria and life expectancy. *Am J Kidney Dis* 2013;**61**(4):646–8.
32. Turin TC, Tonelli M, Manns BJ, Ravani P, Ahmed SB, Hemmelgarn BR. Chronic kidney disease and life expectancy. *Nephrol Dial Transplant* 2012;**27**(8):3182–6.
33. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**(13):1296–305.
34. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012;**380**(9854): 1662–73.

35. Mahmoodi BK, Matsushita K, Woodward M, Blankestijn PJ, Cirillo M, Ohkubo T, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without hypertension: a meta-analysis. *Lancet* 2012; **380**(9854):1649–61.
36. Tonelli M, Muntner P, Lloyd A, Manns BJ, Klarenbach S, Pannu N, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet* 2012;**380**(9844):807–14.
37. Baber U, Gutierrez OM, Levitan EB, Warnock DG, Farkouh ME, Tonelli M, et al. Risk for recurrent coronary heart disease and all-cause mortality among individuals with chronic kidney disease compared with diabetes mellitus, metabolic syndrome, and cigarette smokers. *Am Heart J* 2013;**166**(2):373–380 e2.
38. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013;**382**(9889):339–52.
39. Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol* 2015; **3**(7):514–25.
40. Tangri N, Stevens LA, Griffith J, Tighiouart H, Djurdjev O, Naimark D, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA* 2011;**305**(15):1553–9.
41. Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, et al. Reduced kidney function as a risk factor for incident heart failure: the atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol* 2007;**18**(4): 1307–15.
42. Abramson JL, Jurkovitz CT, Vaccarino V, Weintraub WS, McClellan W. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC study. *Kidney Int* 2003;**64**(2):610–5.
43. Aguilar MI, O'Meara ES, Seliger S, Longstreth Jr WT, Hart RG, Pergola PE, et al. Albuminuria and the risk of incident stroke and stroke types in older adults. *Neurology* 2010;**75**(15): 1343–50.
44. Alonso A, Lopez FL, Matsushita K, Loehr LR, Agarwal SK, Chen LY, et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the atherosclerosis risk in communities (ARIC) study. *Circulation* 2011;**123**(25):2946–53.
45. Matsushita K, Ballew SH, Coresh J, Arima H, Arnlov J, Cirillo M, et al. Measures of chronic kidney disease and risk of incident peripheral artery disease: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol* 2017;**5**(9): 718–28.
46. James MT, Laupland KB, Tonelli M, Manns BJ, Culleton BF, Hemmelgarn BR, et al. Risk of bloodstream infection in patients with chronic kidney disease not treated with dialysis. *Arch Intern Med* 2008;**168**(21):2333–9.
47. James MT, Quan H, Tonelli M, Manns BJ, Faris P, Laupland KB, et al. CKD and risk of hospitalization and death with pneumonia. *Am J Kidney Dis* 2009;**54**(1):24–32.
48. Pimentel A, Urena-Torres P, Zillikens MC, Bover J, Cohen-Solal M. Fractures in patients with CKD-diagnosis, treatment, and prevention: a review by members of the European Calcified Tissue Society and the European Renal Association of Nephrology Dialysis and Transplantation. *Kidney Int* 2017;**92**(6):1343–55.
49. Dalrymple LS, Katz R, Rifkin DE, Siscovick D, Newman AB, Fried LF, et al. Kidney function and prevalent and incident frailty. *Clin J Am Soc Nephrol* 2013;**8**(12):2091–9.
50. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: global burden of disease study. *Lancet* 1997;**349**(9061): 1269–76.
51. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the global burden of disease study 2010. *Lancet* 2012;**380**(9859): 2163–96.
52. Mortality GBD, Causes of Death C. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the global burden of disease study 2015. *Lancet* 2016;**388**(10053): 1459–544.
53. Rao C, Adair T, Bain C, Doi SA. Mortality from diabetic renal disease: a hidden epidemic. *Eur J Public Health* 2012;**22**(2):280–4.
54. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the global burden of disease study 2015. *Lancet* 2016;**388**(10053):1603–58.
55. Jager KJ, Fraser SDS. The ascending rank of chronic kidney disease in the global burden of disease study. *Nephrol Dial Transplant* 2017;**32**(Suppl. 1_2):ii121–8.
56. Islam TM, Fox CS, Mann D, Muntner P. Age-related associations of hypertension and diabetes mellitus with chronic kidney disease. *BMC Nephrol* 2009;**10**:17.
57. Muntner P, Bowling CB, Gao L, Rizk D, Judd S, Tanner RM, et al. Age-specific association of reduced estimated glomerular filtration rate and albuminuria with all-cause mortality. *Clin J Am Soc Nephrol* 2011;**6**(9):2200–7.
58. Glassock RJ, Winearls C. CKD–fiction not fact. *Nephrol Dial Transplant* 2008;**23**(8):2695–6.
59. Glassock RJ, Winearls C. Diagnosing chronic kidney disease. *Curr Opin Nephrol Hypertens* 2010;**19**(2):123–8.
60. Wetzels JF, Kiemeney LA, Swinkels DW, Willems HL, den Heijer M. Age- and gender-specific reference values of estimated GFR in Caucasians: the Nijmegen Biomedical Study. *Kidney Int* 2007;**72**(5):632–7.
61. Rule AD, Amer H, Cornell LD, Taler SJ, Cosio FG, Kremers WK, et al. The association between age and nephrosclerosis on renal biopsy among healthy adults. *Ann Intern Med* 2010;**152**(9): 561–7.
62. Glassock RJ, Rule AD. The implications of anatomical and functional changes of the aging kidney: with an emphasis on the glomeruli. *Kidney Int* 2012;**82**(3):270–7.
63. Rule AD, Cornell LD, Poggio ED. Senile nephrosclerosis–does it explain the decline in glomerular filtration rate with aging? *Nephron Physiol* 2011;**119**(Suppl. 1):p6–11.
64. O'Hare AM, Choi AI, Bertenthal D, Bacchetti P, Garg AX, Kaufman JS, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol* 2007;**18**(10):2758–65.
65. Hallan SI, Matsushita K, Sang Y, Mahmoodi BK, Black C, Ishani A, et al. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA* 2012;**308**(22):2349–60.
66. Fried LF, Lee JS, Shlipak M, Chertow GM, Green C, Ding J, et al. Chronic kidney disease and functional limitation in older people: health, aging and body composition study. *J Am Geriatr Soc* 2006; **54**(5):750–6.
67. Fried TR, McGraw S, Agostini JV, Tinetti ME. Views of older persons with multiple morbidities on competing outcomes and clinical decision-making. *J Am Geriatr Soc* 2008;**56**(10):1839–44.
68. Roshanravan B, Robinson-Cohen C, Patel KV, Ayers E, Littman AJ, de Boer IH, et al. Association between physical

performance and all-cause mortality in CKD. *J Am Soc Nephrol* 2013;**24**(5):822–30.
69. Canney M, Sexton DJ, O'Connell MDL, Kenny RA, Little MA, O'Seaghdha CM. Kidney function estimated from cystatin C, but not creatinine, is related to objective tests of physical performance in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci* 2017;**72**(11):1554–60.
70. Bowling CB, Inker LA, Gutierrez OM, Allman RM, Warnock DG, McClellan W, et al. Age-specific associations of reduced estimated glomerular filtration rate with concurrent chronic kidney disease complications. *Clin J Am Soc Nephrol* 2011;**6**(12):2822–8.
71. Saran R, Robinson B, Abbott KC, Agodoa LY, Albertus P, Ayanian J, et al. US renal data system 2016 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2017;**69**(3 Suppl. 1):A7–8.
72. Nitsch D, Grams M, Sang Y, Black C, Cirillo M, Djurdjev O, et al. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. *Br Med J* 2013;**346**:f324.
73. Carrero JJ, Hecking M, Chesnaye NC, Jager KJ. Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. *Nat Rev Nephrol* 2018;**14**(3):151–64.
74. Piccoli GB, Liu ZH, Levin A. Women and kidney diseases: reflection on world kidney day and international Woman's day. *Arch Argent Pediatr* 2018;**116**(2):e273–8.
75. Dehmer EW, Phadnis MA, Gunderson EP, Lewis CE, Bibbins-Domingo K, Engel SM, et al. Association between gestational diabetes and incident maternal CKD: the coronary artery risk development in young adults (CARDIA) study. *Am J Kidney Dis* 2018;**71**(1):112–22.
76. Ortona E, Pierdominici M, Maselli A, Veroni C, Aloisi F, Shoenfeld Y. Sex-based differences in autoimmune diseases. *Ann Ist Super Sanita* 2016;**52**(2):205–12.
77. USRDS. *USRDS 2009 annual data report: atlas of end-stage renal disease in the United States*. Bethesda, MD. 2010.
78. Murphy D, McCulloch CE, Lin F, Banerjee T, Bragg-Gresham JL, Eberhardt MS, et al. Trends in prevalence of chronic kidney disease in the United States. *Ann Intern Med* 2016;**165**(7):473–81.
79. Madhavan SM, O'Toole JF, Konieczkowski M, Ganesan S, Bruggeman LA, Sedor JR. APOL1 localization in normal kidney and nondiabetic kidney disease. *J Am Soc Nephrol* 2011;**22**(11):2119–28.
80. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010;**329**(5993):841–5.
81. Parsa A, Kao WH, Xie D, Astor BC, Li M, Hsu CY, et al. APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med* 2013;**369**(23):2183–96.
82. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. *PLoS One* 2016;**11**(7):e0158765.
83. De Vecchi AF, Dratwa M, Wiedemann ME. Healthcare systems and end-stage renal disease (ESRD) therapies–an international review: costs and reimbursement/funding of ESRD therapies. *Nephrol Dial Transplant* 1999;**14**(Suppl. 6):31–41.
84. Wen CP, Matsushita K, Coresh J, Iseki K, Islam M, Katz R, et al. Relative risks of chronic kidney disease for mortality and end-stage renal disease across races are similar. *Kidney Int* 2014;**86**(4):819–27.
85. Bello AK, Levin A, Tonelli M, Okpechi IG, Feehally J, Harris D, et al. Assessment of global kidney health care status. *JAMA* 2017;**317**(18):1864–81.
86. Sharma S, Sarnak MJ. Epidemiology: the global burden of reduced GFR: ESRD, CVD and mortality. *Nat Rev Nephrol* 2017;**13**(8):447–8.
87. George C, Mogueo A, Okpechi I, Echouffo-Tcheugui JB, Kengne AP. Chronic kidney disease in low-income to middle-income countries: the case for increased screening. *BMJ Glob Health* 2017;**2**(2):e000256.
88. Swanepoel CR, Atta MG, D'Agati VD, Estrella MM, Fogo AB, Naicker S, et al. Kidney disease in the setting of HIV infection: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. *Kidney Int* 2018;**93**(3):545–59.
89. Atta MG, Gallant JE, Rahman MH, Nagajothi N, Racusen LC, Scheel PJ, et al. Antiretroviral therapy in the treatment of HIV-associated nephropathy. *Nephrol Dial Transplant* 2006;**21**(10):2809–13.
90. Yahaya I, Uthman OA, Uthman MM. Interventions for HIV-associated nephropathy. *Cochrane Database Syst Rev* 2013;(1):CD007183.
91. Cohen SD, Kopp JB, Kimmel PL. Kidney diseases associated with human immunodeficiency virus infection. *N Engl J Med* 2018;**378**(17):1655–6.
92. Kopp JB, Winkler C. HIV-associated nephropathy in African Americans. *Kidney Int Suppl* 2003;(83):S43–9.
93. Choi AI, Li Y, Deeks SG, Grunfeld C, Volberding PA, Shlipak MG. Association between kidney function and albuminuria with cardiovascular events in HIV-infected persons. *Circulation* 2010;**121**(5):651–8.
94. Barsoum RS. Chronic kidney disease in the developing world. *N Engl J Med* 2006;**354**(10):997–9.
95. Fischer RSB, Vangala C, Truong L, Mandayam S, Chavarria D, Granera Llanes OM, et al. Early detection of acute tubulointerstitial nephritis in the genesis of Mesoamerican nephropathy. *Kidney Int* 2018;**93**(3):681–90.
96. Kumaresan J, Seneviratne R. Beginning of a journey: unraveling the mystery of chronic kidney disease of unknown aetiology (CKDu) in Sri Lanka. *Global Health* 2017;**13**(1):43.
97. Haas M. Mesoamerican nephropathy: pathology in search of etiology. *Kidney Int* 2018;**93**(3):538–40.
98. Lunyera J, Mohottige D, Von Isenburg M, Jeuland M, Patel UD, Stanifer JW. CKD of uncertain etiology: a systematic review. *Clin J Am Soc Nephrol* 2016;**11**(3):379–85.
99. Jayatilake N, Mendis S, Maheepala P, Mehta FR, Team CKNRP. Chronic kidney disease of uncertain aetiology: prevalence and causative factors in a developing country. *BMC Nephrol* 2013;**14**:180.
100. Collaboration NCDRF. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 2017;**389**(10064):37–55.
101. Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D. Predictors of new-onset kidney disease in a community-based population. *JAMA* 2004;**291**(7):844–50.
102. Anderson AH, Yang W, Townsend RR, Pan Q, Chertow GM, Kusek JW, et al. Time-updated systolic blood pressure and the progression of chronic kidney disease: a cohort study. *Ann Intern Med* 2015;**162**(4):258–65.
103. Bell E, Gao L, Judd S, Glasser S, McClellan M, Gutierrez O, et al. Blood pressure indexes and end-stage renal disease risk in adults with chronic kidney disease. *Am J Hypertens* 2012;**25**(7):789–96.
104. Muntner P, He J, Astor BC, Folsom AR, Coresh J. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. *J Am Soc Nephrol* 2005;**16**(2):529–38.

105. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol* 2017;**28**(9):2812−23.
106. Kovesdy CP, Bleyer AJ, Molnar MZ, Ma JZ, Sim JJ, Cushman WC, et al. Blood pressure and mortality in U.S. veterans with chronic kidney disease: a cohort study. *Ann Intern Med* 2013;**159**(4): 233−42.
107. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet* 2010;**375**(9718):938−48.
108. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010;**375**(9718):895−905.
109. Whittle J, Lynch AI, Tanner RM, Simpson LM, Davis BR, Rahman M, et al. Visit-to-Visit variability of BP and CKD outcomes: results from the ALLHAT. *Clin J Am Soc Nephrol* 2016; **11**(3):471−80.
110. Gosmanova EO, Mikkelsen MK, Molnar MZ, Lu JL, Yessayan LT, Kalantar-Zadeh K, et al. Association of systolic blood pressure variability with mortality, coronary heart disease, stroke, and renal disease. *J Am Coll Cardiol* 2016;**68**(13):1375−86.
111. Fox CS, Larson MG, Leip EP, Meigs JB, Wilson PW, Levy D. Glycemic status and development of kidney disease: the Framingham Heart Study. *Diabetes Care* 2005;**28**(10):2436−40.
112. Brancati FL, Whelton PK, Randall B, Neaton J, Stamler J, Klag MJ. Risk of end-stage renal disease in diabetes mellitus: a prospective cohort study of men screened for MRFIT. *JAMA* 1997;**278**(23): 2069−74.
113. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, et al. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 2017; **377**(1):13−27.
114. D'Agati VD, Chagnac A, de Vries AP, Levi M, Porrini E, Herman-Edelstein M, et al. Obesity-related glomerulopathy: clinical and pathologic characteristics and pathogenesis. *Nat Rev Nephrol* 2016;**12**(8):453−71.
115. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Horwich TB. Survival advantages of obesity in dialysis patients. *Am J Clin Nutr* 2005;**81**(3):543−54.
116. Johansen KL, Young B, Kaysen GA, Chertow GM. Association of body size with outcomes among patients beginning dialysis. *Am J Clin Nutr* 2004;**80**(2):324−32.
117. Madero M, Sarnak MJ, Wang X, Sceppa CC, Greene T, Beck GJ, et al. Body mass index and mortality in CKD. *Am J Kidney Dis* 2007;**50**(3):404−11.
118. Kramer H, Shoham D, McClure LA, Durazo-Arvizu R, Howard G, Judd S, et al. Association of waist circumference and body mass index with all-cause mortality in CKD: the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study. *Am J Kidney Dis* 2011;**58**(2):177−85.
119. Eknoyan G. Obesity and chronic kidney disease. *Nefrologia* 2011; **31**(4):397−403.
120. Vupputuri S, Fox CS, Coresh J, Woodward M, Muntner P. Differential estimation of CKD using creatinine- versus cystatin C-based estimating equations by category of body mass index. *Am J Kidney Dis* 2009;**53**(6):993−1001.
121. Lemoine S, Guebre-Egziabher F, Sens F, Nguyen-Tu MS, Juillard L, Dubourg L, et al. Accuracy of GFR estimation in obese patients. *Clin J Am Soc Nephrol* 2014;**9**(4):720−7.
122. Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM, et al. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. *JAMA* 2009;**302**(11):1179−85.
123. Jones J, Holmen J, De Graauw J, Jovanovich A, Thornton S, Chonchol M. Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. *Am J Kidney Dis* 2012;**60**(3):402−8.
124. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med* 2014;**371**(1):58−66.
125. Heung M, Steffick DE, Zivin K, Gillespie BW, Banerjee T, Hsu CY, et al. Acute kidney injury recovery pattern and subsequent risk of CKD: an analysis of veterans health administration data. *Am J Kidney Dis* 2016;**67**(5):742−52.
126. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int* 2012;**81**(5):442−8.
127. Moore PK, Hsu RK, Liu KD. Management of acute kidney injury: core curriculum 2018. *Am J Kidney Dis* 2018; **72**(1):136−48.

QUESTIONS AND ANSWERS

Question 1

Which of the following is the recommended initial approach to identifying whether a patient has CKD?

A. A one-time S[Cr] measurement. Calculating eGFR should then be performed using the CKD-EPI equation
B. Serial assessments of S[Cr] (to calculate eGFR) and urinary albumin excretion, over a period of at least 3 months
C. S[Cr] should be used to calculate eGFR. If eGFR is <60 mL/min/1.73 m^2, then albuminuria should be assessed
D. Measure serial cystatin C and use this to calculate eGFR over a period of at least 3 months
E. Measure GFR using inulin clearance

Answer: B

KDIGO 2012 guidelines describe CKD as abnormalities in kidney structure or function, present for at least 3 months. A one-time measurement of S[Cr] may result in a false positive. Additionally, it is recommended that GFR be estimated using an equation (e.g. the CKD-EPI equation) rather than relying on elevated S[Cr]. Several equations have been developed including the MDRD and CKD-EPI formulas. GFR equations using creatinine have limitations such as differences in creatinine generation related to dietary protein intake and muscle mass. However, when adjusted for non-GFR determinants of creatinine generation (age, sex, race), the correlation between creatinine and measured GFR is significantly improved. Other tests such as cystatin C have shown promise as alternative filtration markers to creatinine, but their use has been hampered by cost and limited availability of assays. Clearance of exogenous filtration markers such as inulin remain the gold standard for measuring GFR, but this method is expensive, time-consuming, and not practical in most cases. eGFR alone cannot be used to define CKD; albuminuria also needs to be assessed. Many patients have albuminuria with preserved GFR.

Question 2

A patient has an eGFR of 45 mL/min/1.73 m^2 and a UACR of 30 mg/mmol. Which of the following is true?

A. This patient has an increased risk for ESRD
B. This patient has an increased risk for CV mortality
C. This patient has an increased risk for death
D. This patient has an increased risk for hospitalizations
E. All of the above are true

Answer: E

Data from several studies have demonstrated that reduced GFR and increased UACR are strongly associated with an increased risk of ESRD, CV, and all-cause mortality. CKD has also been identified as an independent predictor of other outcomes such as infection, hospitalization, and frailty. In general, ACR appears to be a stronger and more consistent predictor of adverse outcomes than GFR in these studies.

Question 3

Which of the following is true regarding CKD in patients of African descent?

A. The prevalence of albuminuria is lower than that of Caucasian patients
B. African Americans are more likely than other ethnicities in the US to have CKD, but are less likely to progress to ESRD
C. Genetic variants of the APOL1 gene found almost exclusively in people of African descent are associated with an increased risk of CKD
D. Focal segmental glomerulosclerosis is the most common cause of kidney failure in African Americans

Answer: C

There are significant ethnic differences in the prevalence of CKD both worldwide and in the US. African Americans are more likely than other ethnicities in the US to have CKD and albuminuria. African Americans with CKD are also more likely to progress to ESRD. The most common causes of CKD in African Americans are diabetic and hypertensive kidney disease. Genetic factors are largely responsible for the increased CKD risk and progression in patients of African descent. Mutations in the APOL1 gene are associated with hypertensive nephropathy and FSGS. These mutations are thought to be more common in African populations because they are protective against the parasite causing African sleeping sickness.

Question 4

Which of the following statements are true regarding CKD in the developing world?

A. The rise in CKD prevalence is being driven by increased rates of diabetes, obesity and hypertension
B. We have major gaps in our understanding of the prevalence of CKD because most of our

data regarding CKD comes from developed countries

C. CKDu is an increasingly recognized cause of CKD in agricultural communities

D. None are correct

E. All are correct

Answer: E

Although the majority of the world's population live in developing nations, our understanding of CKD epidemiology in these areas is limited because most data come from high-income countries. Historically the most common causes of CKD in the developing world were chronic glomerulonephritis and interstitial nephritis, related to the high incidence of infectious diseases such as HIV that can affect the kidneys. More recently the rapid rise in CKD prevalence in developing countries has been attributed to increasing rates of diabetes, obesity, hypertension and population aging. Furthermore, CKDu is increasingly being recognized as a major contributor to renal disease, especially in middle- and low-income agricultural communities. Patients with CKDu are missing traditional risk factors for CKD but share similar histologic findings, predominately chronic interstitial nephritis, which suggests the possibility of environments causes.

Question 5

Regarding AKI which of the following statements is false?

A. AKI rarely leads to end-stage kidney disease

B. AKI confers an increased risk of CKD, even if the kidney function returns to baseline levels

C. The speed of renal recovery following AKI may be an important contributor to future CKD risk

D. Prior CKD and albuminuria significantly increase the risk of AKI

E. AKI is associated with higher mortality, future cardiac disease, hypertension, and reduced quality of life

Answer: A

AKI is associated with an increased risk of CKD, ESRD, CV events, all-cause mortality, and reduced quality of life. More severe AKI, especially if requiring dialysis or hospitalization, is associated with higher risk of subsequent CKD and ESRD. Even seemingly mild AKI increases the risk of CKD.

CHAPTER

7

Gender Issues in Chronic Kidney Disease

Joel Neugarten[a], *Jane F. Reckelhoff*[b]

[a]Albert Einstein College of Medicine, Renal Division, Montefiore Medical Center, Bronx, NY, United States; [b]Women's Health Research Center, University of Mississippi Medical Center, Jackson, MS, United States

Abstract

Gender influences the incidence, prevalence, and progression of chronic kidney disease (CKD). In numerous experimental models of renal disease, progression is accelerated in male animals. Gender dimorphism in the course of renal disease is replicated by hormonal manipulation, suggesting that the actions of sex hormones, rather than structural differences between the sexes, are responsible for gender-related differences in renal disease progression. Sex hormones influence many of the processes known to mediate progressive renal injury including cell proliferation, mesangial matrix synthesis and degradation, generation of reactive oxygen species, and the expression of profibrotic proinflammatory cytokines, hormones, and vasoactive agents. In humans, the progression of CKD is arguably more rapid in men than in women, a finding which parallels observations in experimental animals. Translation of these observations into therapeutic interventions has not yet been realized, although selective estrogen receptor modulators, which lack the detrimental effects of estrogen on reproductive tissue, have shown renoprotective effects.

The Institute of Medicine has defined "sex" as those traits that are affected by sex chromosomal complement and the presence or absence of sex steroids.[1] The concept of "gender" is more complicated and is determined by a person's self-representation as "male" or "female" and society's response to this self-representation.[1] For discussions of studies in human subjects, the term "gender" will be used, whereas the term "sex" will be used to discuss animal studies. A series of seminal studies beginning the mid-1990s evaluated whether there were gender-related differences in the prevalence and progression of chronic kidney disease (CKD).[2–4] The finding that gender disparities did indeed exist gave rise to a myriad of studies in both humans and animals to evaluate the mechanisms that may be responsible for these sex/gender differences.

GENDER PROGRESSION OF CHRONIC KIDNEY DISEASE

In most experimental models, male animals show accelerated progression of renal disease.[4] Hormonal manipulation replicates the effects of gender on the course of experimental renal disease and suggests that female sex hormones may slow the progression of renal disease, whereas male hormones promote renal disease progression.[4] These observations also suggest that sex hormones themselves, rather than genetically determined structural differences, determine the greater susceptibility of the male kidney to progressive renal injury.

Unlike experimental models, studies describing the relationship between gender and renal disease progression in humans have yielded conflicting results. There have been no large well-designed prospective studies specifically evaluating the rate of decline of renal function in men compared with women. In this context, we performed a meta-analysis involving 11,345 subjects from 68 studies to determine the effect of gender on the progression of nondiabetic renal disease.[2] In individuals with autosomal dominant polycystic kidney disease, IgA nephropathy, membranous nephropathy, or CKD of unspecified etiology, progression was more rapid in men than in women. However, our meta-analysis was limited by the heterogeneity of study endpoints, failure to adequately account for confounding factors and lack of knowledge of menopausal status.

Among the studies evaluated in our meta-analysis was the Modification of Diet in Renal Disease study,[5] which included 840 participants, nearly 40% of whom were women, assigned to various dietary protein and blood pressure (BP) groups. As compared with men, the rate of deterioration of glomerular filtration rate

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00007-3

(GFR) was slower in women below the age of 55, but this difference was no longer significant after adjusting for differences in BP, urinary protein excretion, and HDL levels.

Similarly, Cattran and coworkers[6] reported a reduced rate of decline in kidney function and/or increased kidney survival in younger women with membranous nephropathy or focal and segmental glomerulosclerosis compared with men. The beneficial effect of female gender persisted after correction for BP and proteinuria. In contrast, these investigators failed to find any effect of gender on the progression of IgA nephropathy.

The Ramipril Efficacy in Nephropathy Study, a multicenter, randomized, double-blind, placebo-controlled trial performed in subjects with chronic nondiabetic, proteinuric renal disease, found that the rate of decline of GFR was faster in women compared with men in the placebo arm, whereas in the Ramipril-treated arm, progression was slower and the reduction in proteinuria greater in women.[7] Angiotensin-converting enzyme inhibitor (ACEI) therapy was uniformly renoprotective in women, regardless of angiotensin-converting enzyme (ACE) polymorphism, but in men ACEI therapy was renoprotective only in those with the DD genotype. The authors concluded that men with chronic proteinuric renal disease are at increased risk of progression of CKD due to their lesser response to ACEI therapy.

Numerous longitudinal studies have shown that the rate of decline in kidney function was more rapid in men than in woman.[4] Population-based, observational studies from the US, Europe, and Japan, including several mass screening studies, have identified male sex as a predictor of poor renal outcome.[8–14] Despite certain methodological limitations, these studies are consistent with observations in experimental animals showing a faster rate of progression of renal disease in males.

The Chronic Renal Insufficiency Cohort Study followed 3939 participants with a baseline estimated GFR (eGFR) of 20–70 mL/min/1.73 m^2 for a median period of 6.9 years and found that men were at higher risk of a 50% decline in eGFR ((HR 1.19, CI 1.06, 1.35), incident stage 5 CKD, incident end-stage renal disease (ESRD) (HR 1.39, CI 1.15, 1.69), and death (HR 1.79, CI 1.35, 2.27)) than women in fully adjusted models.[15] The rate of decline in eGFR was also greater in men than in women ($\Delta = 0.33$ mL/min/1.73 m^2/year), but this difference failed to achieve statistical significance in a fully adjusted model. Although menopausal status was not ascertained, the data failed to support a renoprotective role for estrogen, because sex-related differences in incident ESRD rates tended to be greater among older compared with younger subjects.

In contrast, other studies have concluded that there is no difference between men and women in the rate of progression of CKD, or that women progress at a faster rate than do men. Jafar and coworkers[16] performed a patient-level meta-analysis which evaluated 1650 nondiabetic subjects enrolled in 11 randomized studies evaluating the efficacy of ACEI therapy on the progression of renal disease over a mean duration of follow-up of 2.2 years. The authors concluded that after correction for differences in systolic BP and urinary protein excretion, women have a worse renal prognosis, showing a greater relative risk of doubling of serum creatinine (S[Cr]), renal replacement therapy (RRT), or death due to kidney disease compared with men. However, most of the female participants in these studies were postmenopausal, which may explain why these findings differ from those reported by our earlier meta-analysis.

The Chronic Kidney Disease Prognosis Consortium performed several patient-level meta-analyses, with varying degrees of patient overlap, which examined the role of gender in CKD progression.[17–20] Male gender was determined to be a risk factor for CKD progression in all but one of these studies. In the first of these patient-level meta-analyses, Nitsch et al.[17] studied more than 2 million subjects from 48 general population, high cardiovascular risk, and CKD cohorts. The primary endpoint was RRT or death due to kidney disease during a mean duration of follow-up of 2.3–24.9 years. The authors found that lower eGFR and albuminuria were associated with all-cause mortality and cardiovascular mortality, and that the risk was higher for men than women at all levels of eGFR and albumin:creatinine ratio (ACR). However, the slope of the risk relationship was steeper in women than in men in both the general population and the high cardiovascular risk cohorts. In all three cohorts, lower eGFR and higher ACR were associated with increased risk of developing ESRD, but the risk was similar between men and women. Results did not change when subjects less than 50 years of age were compared with those greater than 65 years of age. Despite the size of this meta-analysis and its robust methodology, the conclusion that gender has no impact on renal disease progression is subject to limitations imposed by competing mortality. Men are more likely to die a nonrenal death at any given level of eGFR or ACR, and the risks of both death and progression to ESRD increase at lower eGFR and higher ACR levels. Thus, the gender disparity in the risk of death disproportionately affects men at greatest risk for progression to ESRD and ultimately reduces the number of men at

risk for progression to ESRD. These factors limit the validity of conclusions about the role of gender in renal disease progression which derive from studies where ESRD is the sole outcome measure. Also relevant to interpretation of these data are results from a general population observational study performed by Japanese investigators which found that the cumulative incidence of ESRD did not differ between the sexes until four years after initial screening.[14] Very few of the general population and high cardiovascular risk cohorts studied by Nitsch et al.[17] were followed for more than three years, suggesting that a longer duration of follow-up may have been required to demonstrate sexual dimorphism in the progression to ESRD in these cohorts.

In a subsequent publication, the CKD Prognosis Consortium performed another patient-level meta-analysis of 731,357 subjects from CKD cohorts.[18] The primary outcome was RRT or renal transplantation with a median duration of follow-up of four years. Using a pooled eight-variable model, the risk of progression to RRT or renal transplantation was significantly greater in men than women (HR 1.34, CI 1.24, 1.44). However, a significant limitation of this study was the fact that nearly 435,000 subjects were derived from a Veterans Administration cohort severely deficient in women. Similar results, showing a worse renal prognosis in men, were obtained by these investigators when their analysis was restricted to patients with stages 4 and 5 CKD.[19] Grams et al.[20] studied over 5 million healthy subjects from 7 general population cohorts and found the risk of progression to ESRD was 50% greater in men than in women.

CKD, defined as an eGFR <60 mL/min/1.73 m^2, is more common in women than in men. Numerous population-based studies from across the globe have shown that the percent of women that suffer from CKD is greater than that of men in nearly every country studied and in all age groups except 20–29 years of age.[21–23] Data from the National Health and Nutrition Examination Survey (NHANES) of the civilian noninstitutional population of the US between 2005 and 2010 indicate that the prevalence of an eGFR less than 60 mL/min/1.723 m^2 is 7.7% in women vs. 5.6% in men and the prevalence of ACR >30 mg/g creatinine is 10.2% in women vs. 8.6% in men.[24] Similar results were obtained in later NHANES surveys.[25]

Any discussion of the relationship between sex and the prevalence and progression of CKD must first address the adequacy of the measures commonly used to quantify renal function in men relative to women. Glassock and Winearls[26] as well as numerous other investigators have suggested that CKD be defined according to sex-specific percentiles rankings that take into account sex-specific reductions in GFR associated with normal aging instead of using a single GFR threshold to define normality. They argue that a single threshold fails to adequately demarcate increased risk for adverse events across the gender and age spectrum, and that this practice leads to an overdiagnosis of CKD in women, especially in elderly women.

Similarly, numerous investigators have suggested that we use sex-specific cutoffs for urine albumin:creatinine ratio (UACR) to define the upper limit of normal in the healthy population.[27,28] Data from NHANES II collected between 1988 and 1994 showed that mean urinary albumin concentration was not different between men and women.[27] However, when UACR was used as the measure, the prevalence of microalbuminuria was greater in women than in men. This result is explained by the fact that men generally have a larger muscle mass and excrete more creatinine than do women. The NHANES II data were reanalyzed using sex-specific ACR cutoffs suggested by Warram et al.[28] (17 mg/g for men vs. 25 mg/g for women) which correspond to the 95th percentile values for healthy men and women. This reanalysis yielded identical albumin excretion rates, expressed as mcg/minute, in men and women. Thus, applying sex-specific ACR cutoff values to the NHANES II cohort leads to the conclusion that the prevalence of microalbuminuria is similar in men and women.

Additional concerns arise relating to the predictive performance of the MDRD and CKD-EPI equations to estimate GFR in men vs. women. The measure of interest is the difference in bias between men and women, where bias represents the difference between the actual and estimated GFR. Studies have generally yielded inconsistent results. Adding to the complexity in interpretation of available data are observations that differences in bias between men and women vary with age and baseline GFR. Moreover, interpretation of the data is limited by the small size of many of these studies. However, if our analysis is informed by study size, it is fair to conclude that the difference in bias between the sexes is small (weighted average of Δ bias for MDRD $= -1.42$ mL/min/1.73 m^2, n $= 8940$, range $= -5.1$ to $+7.77$; weighted average of Δ bias for CKD-EPI $= +1.93$ mL/min/1.73 m^2, n $= 8036$, range $= -2.7$ to $+10.8$ mL/min/1.73 m^2).[29]

GENDER AND THE TRANSITION TO ESRD

Despite the greater prevalence of CKD in women, ESRD registry data and cohort studies from around the world clearly establish that the incidence rate of ESRD is greater in men than in women.[30–34] The Dialysis Outcomes and Practice Pattern Study (DOPPS), an international prospective cohort study of dialysis practices in high-income countries, showed that, after

adjustment for the representation of each sex in the general population, the proportion of women in the incident dialysis population is less than men in every participating country.[35] The incidence rate of reported ESRD in the US, per million population, adjusted for age and race, is approximately 60% greater in men compared with women.[24] It is unlikely that the slightly higher eGFR at which men initiate RRT alone can account for this disparity in incidence rates (discussed below).[36–38]

Two explanations may account for the finding that women are less likely to initiate dialysis despite being more likely to suffer from CKD: (1) women with CKD progress more slowly to ESRD than men and/or (2) women start dialysis later than men and as a result are more likely to die in stage 5 CKD without ever being dialyzed. The DOPPS investigators propose that differences among countries in the age-adjusted proportion of women starting dialysis suggest that psychosocial and economic factors, rather than, or in addition to, biologic factors, are responsible for the fact that fewer women start dialysis than men. They speculate that women, especially those that are elderly and in poor health, are less likely to initiate dialysis than are men of similar circumstance.

This controversy raises several interrelated questions: (1) whether or not men and women have equal access to dialysis and (2) whether or not there exists a large pool of women with stage 5 CKD who are not being dialyzed and who have a high mortality.

Analysis of US Renal Data System (USRDS) data from 1995 to 2009 shows that women consistently initiate dialysis later than men at an adjusted eGFR that is 1 mL/min/1.73 m^2 lower than men and that this difference in eGFR between the sexes has not changed over the 15-year period studied.[37] Data from Europe parallel these observations.[38] Similarly, the DOPPS found that women initiate dialysis later than men at an eGFR 0.5 mL/min/1.73 m^2 lower than men and that this eGFR difference existed in all countries studied.[35] However, the differences in bias between the sexes for the MDRD and CKD-EPI equations used to estimate GFR are comparable or exceed the difference in eGFR observed between men and women at the start of dialysis. Thus, the difference in eGFR that exists between the sexes at the start of dialysis may merely reflect imprecision in the equations used to estimate GFR.

Multiple alternative explanations have been proposed to explain the observation that women start dialysis at a lower eGFR than men. These explanations focus on gender-related disparities in health care delivery. Although women are more likely to suffer from CKD than men, they are less aware of their CKD diagnosis, seek medical care later than men, are less likely to be given an ICD-10 diagnosis of CKD, are less likely to be referred to consult a nephrologist, and are underrepresented in CKD clinics.[35,39–41] In addition, at initiation of dialysis, women are less well educated and are more likely to be uninsured or unemployed.[36,39,40,42] All these factors may contribute to unequal access for women to RRT. However, in contrast to these observations, the USRDS has recently reported that the proportion of women receiving pre-ESRD care and the duration of such care is similar to that of men. However, the URSDS data pertain only to women who actually start dialysis and do not reflect the status of women who defer dialysis.[43]

In addition, it has been suggested that women, particularly elderly women, are more likely to choose conservative care rather than RRT.[41,44] Faruque et al.[45] followed 7901 patients with stage 5 CKD not on dialysis for a mean of 11 months. They confirmed that women were less likely to start dialysis than men, and that this disparity was most pronounced among the elderly where men were more than twice as likely to initiate dialysis. In another large study, women, particularly older women, were 50% more likely to choose conservative care.[41] However, many other studies of stage 5 CKD fail to show any significant difference between the sexes in the number of those with stage 5 CKD who elect conservative care. Interpretation of the data is limited by the small number of subjects in many of these studies.

The DOPPS investigators further suggest that later initiation of dialysis in women as compared with men leads to a large pool of women with stage 5 CKD and that a higher death rate among these women contributes to the higher incidence of men starting dialysis.[44,46,47] However, available data are inconclusive.

Go et al.[48] studied over 1 million patients enrolled in an integrated health care plan and found that the percentage of patients with an eGFGR <15 mL/min/1.73 m^2 who are not being dialyzed was slightly higher in women than in men. However, after adjustment for the proportion of men and women enrolled in the health plan, the opposite was true; among enrollees with an eGFR <15 mL/min/1.73 m^2, a greater percent of men than women were not being dialyzed. These data argue against the hypothesis that women are deprived of equal access to RRT. Similarly, the Stockholm Creatinine Measurements project which analyzed creatinine measurements in over 1 million adults found that stage 5 CKD without dialysis was more common in men than in women.[40] However, both these analyses were limited to individuals who have undergone S[Cr] measurements, and data from the USRDS suggest that women are less likely to undergo a S[Cr] measurement than are men. Using ESRD registry data and administrative codes for kidney disease on death certificates, Australian investigators concluded that women, especially

elderly women, are less likely to initiate dialysis than men.[41] In contrast, using a similar approach in a case-control study nested in NHANES, American investigators found no disparity in the provision of RRT based on sex.[49] However, both studies may be criticized for methodological flaws.

Turin has shown that the survival advantage enjoyed by women in the general population is attenuated as GFR declines and is lost when the GFR falls to 15–29 mL/min/1.73 m^2, where no significant difference is observed.[50] No data were reported regarding 5 CKD not on dialysis. Nevertheless, the survival advantage of women in earlier stages of CKD would tend to mask any renoprotective effect of female gender on the progression of renal disease where the outcome measure is ESRD. Men with progressive CKD are more likely to die before reaching dialysis than are women, reducing the population of men at risk to develop ESRD, which in turn would decrease the number of men starting dialysis. In contrast, the DOPPS investigators suggest that the relationship between the competing risks of death and dialysis in men vs. women with early CKD is reversed in stage 5 CKD.[44,46,47] They argue that women with stage 5 CKD are less likely to initiate RRT than men, have a higher mortality than men and are more likely to die without ever reaching dialysis. This in turn might contribute to the predominance of men in the incident dialysis population. However, available data are contradictory. Moreover, even if this hypothesis were true, it would not necessarily eliminate the impact of competing mortality in earlier stages of CKD on sex-stratified ESRD rates.

Faruque et al.[45] followed 7901 patients with stage 5 CKD not on dialysis for a mean of 11 months. They found that men, not women, with stage 5 CKD were more likely to die without initiating dialysis in adjusted analysis; however, this was not the case in unadjusted analysis. In a patient-level meta-analysis of 28 cohorts containing over 185,000 subjects with stage 4 or 5 CKD, Evans et al.[19] reported that in adjusted analyses male sex was associated with death without RRT. Several smaller studies that examine survival in late-stage CKD have yielded conflicting results.[51,52]

If women are more likely to suffer from stage 3 CKD then men and the progression of CKD is less rapid in women, this would lead to a higher proportion of men with advanced stages of CKD compared with early stages of CKD. This is precisely what was observed in the NHANES population.[53] Similarly, prevalence data from the National Health Examination Survey in Italy (n = 7652) and the Stockholm Creatinine Measurements project (n = 1,128,058) also found that the excess of women with CKD was attenuated in later stages of CKD as compared with stage 3 CKD.[40,54]

Although the age- and race-adjusted prevalence of ESRD on dialysis is greater in men than in women, women on dialysis show a modest survival advantage compared with men.[24,35] The prevalence of most primary, immune-mediated glomerular diseases is also greater in men.[4] Among patients with idiopathic membranous nephropathy, IgA nephropathy, and childhood minimal change disease, males outnumber females by 2–3 to 1.[4] Because most male animals exhibit reduced immune responsiveness and testosterone, administration is immunosuppressive, the mechanisms responsible for these gender disparities in immunologic-mediated renal diseases remain to be elucidated.[55]

GENDER AND DIABETIC CHRONIC KIDNEY DISEASE

Because ESRD due to diabetes makes up a substantial fraction of all incident and prevalent ESRD, the influence of gender on the development and progression of diabetic nephropathy merits separate consideration. Sexual dimorphism in the progression of diabetic nephropathy is even less well established than in nondiabetic CKD.

The impact of gender on the course of type 1 diabetic nephropathy in humans is controversial. Arguably, the preponderance of data support the conclusion that men with type I diabetes have a worse renal prognosis than do women despite the existence of contrary data. Numerous cross-sectional and longitudinal studies in individuals with type I diabetes show a greater prevalence of albuminuria, a greater risk of developing microalbuminuria, and a greater risk of progressing from micro- to macroalbuminuria in men compared with women.[56–58] In particular, a large study from Germany of 27,805 type I diabetics reported that male gender was associated with the development of microalbuminuria.[57] However, numerous other studies fail to demonstrate gender differences in the development and progression of albuminuria in type 1 diabetics.

Studies evaluating the effect of gender on the rate of decline of renal function in type 1 diabetics have also yielded conflicting results.[4,56,58–61] A retrospective analysis of the rate of decline of GFR in 59 normotensive type I diabetics with albuminuria showed more rapid progression in men.[61] In a prospective, observational study of 199 proteinuric type 1 diabetics, men had a significantly greater rate of decline in GFR than did women; however, this difference did not persist after adjustment for other progression factors.[60] In contrast, the Collaborative Captopril Study Group performed a prospective, double-blind, randomized placebo-controlled trial of the effect of captopril on the progression of nephropathy in type I diabetes (n = 409) and reported no effect of gender on renal disease progression.[59]

In evaluating these inconsistent data, lessons learned from several population-based longitudinal studies must be considered.[62–64] Finnish Diabetic Nephropathy Study investigators found no gender-related differences in the cumulative incidence of ESRD in patients diagnosed with type I diabetes before the age of 10.[62] In contrast, in those diagnosed after the age of 10, the cumulative incidence of ESRD was nearly twice as great in men. A gender-related difference in the risk of developing ESRD became significant only after a duration of diabetes exceeding 40 years. Other population-based studies from Sweden and the US confirm the observation that stratification by age at onset of diabetes and a lengthy follow-up period are required to demonstrate sexual dimorphism in the progression of nephropathy in type 1 diabetics.[63,64] Thus, differences among studies in the mean age of onset of diabetes, the intensity of metabolic control, and the duration of follow-up may make it more difficult to demonstrate sex differences in the progression of diabetic CKD. Adding to this complexity, sexual hormone synthesis and metabolism is dysregulated in both type 1 and type 2 diabetes mellitus.[65]

There is also limited and inconsistent data regarding the contribution of gender to the development and progression of nephropathy in type 2 diabetes.[56,58] Studies evaluating the effect of gender on the prevalence, incidence, and progression of albuminuria and on the rate of decline of renal function in type 2 diabetics have yielded conflicting results. In the placebo arm of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study, a multicenter, randomized, double-blind, placebo-controlled trial of the effect of Losartan on the progression of type II diabetes mellitus ($n = 1513$), male gender was found to be renoprotective by univariate but not by multivariate analysis.[66] However, most of the female subjects enrolled in this trial were postmenopausal, and interpretation of the data is confounded by gender differences in baseline characteristics; at baseline women had significantly more proteinuria and lower eGFR than did men. The Collaborative Study Group performed a multicenter, randomized, double-blind, placebo-controlled trial of the effects of Irbesartan on the progression of nephropathy in 1715 hypertensive type 2 diabetics.[67] The investigators found that albuminuria progressed more rapidly in women, and that women benefited less from irbesartan therapy than did men. Again, most female subjects in this trial were postmenopausal.

ESRD registry data show a similar pattern of sexual dimorphism among incident diabetic dialysis patients as has been observed in the general dialysis population. In 2010, the incident rate of reported diabetic ESRD in the US, adjusted for age and race, was nearly 25% greater in men than in women. Unadjusted UK registry data indicate an 80% greater incidence rate for diabetes-related ESRD in men than in women.[32] Similar data have been reported from Germany.[68] This male predominance persists into the postmenopausal age range in all these populations.[32,68] It should be noted, however, that registry data generally do not differentiate between types 1 and 2 diabetic nephropathy.

There is mounting evidence that sex hormone synthesis and metabolism is disturbed in diabetes mellitus.[65] However, data are conflicting as to the nature of this dysregulation. There are also data to suggest that aberrant sex hormone metabolism may influence the development and progression of diabetic nephropathy.[65] Maric et al.[65] examined the relationship between sex hormone levels and nephropathy in type 1 diabetes among male participants in the Finnish Diabetic Nephropathy Study. Uncomplicated type 1 diabetes was associated with a low serum testosterone level even after correction for multiple metabolic factors. Although sex hormone levels were not correlated with the development of microalbuminuria in a Cox regression model, reduced baseline testosterone levels predicted progression from micro- to macroalbuminuria. Higher testosterone levels and higher estrogen levels were each independent risk factors for progression from macroalbuminuria to ESRD.

FACTORS CONTRIBUTING TO GENDER DIFFERENCES IN RENAL DISEASE PROGRESSION

Numerous mechanisms have been suggested to explain the protective effect of female gender on the progression of renal disease including differences between the sexes in BP, renal structure, lifestyle factors, systemic and renal hemodynamics, and lipid metabolism, as well as direct effects of sex hormones on mesangial cell proliferation and matrix accumulation and the synthesis and release of cytokines, vasoactive agents, and growth factors (Table 7.1).

Lifestyle Factors

Lifestyle factors that influence CKD progression differ between men and women. Men are more likely to smoke, suffer from poorly controlled hypertension and hyperlipidemia, exhibit poor dietary habits, comply less with dietary restrictions, and ingest increased quantities of sodium, protein, calories, phosphorus, and potassium.[47] On the other hand, men with medical comorbidities are more likely to receive aggressive therapy.[69] Adding further complexity to this issue is the observation that risk factors may influence the rate of

TABLE 7.1 Factors Contributing to Gender Dimorphism in Chronic Kidney Disease Progression

Hypertension
Glomerular size/number
Glomerular hemodynamics
Cytokines/hormones
Nitric oxide
Angiotensin II
Endothelin
Transforming growth factor-beta
Metalloproteinases-2 and -9
Reactive oxygen species
Direct effects of sex hormone
Cell proliferation
Matrix synthesis and degradation
Apoptosis
Lipids
Lifestyle factors
Diet
Cigarette smoking
Environmental exposures
Obesity

progression of CKD differently in men and women. In this regard, several studies have identified a gender-specific risk pattern in the progression of CKD where, for example, smoking and hypertriglyceridemia accelerate CKD in men but not in women.[70–73]

Direct Effects of Sex Hormones on Cellular Biology

In a study that directly addresses the renoprotective role of estrogen, Kattah et al.[74] found that women who underwent bilateral oophorectomy before the age of 50 were at higher risk to develop CKD than women with intact ovaries.

Cell Proliferation and Mesangial Matrix Accumulation

Serum-stimulated mesangial cell proliferation is inhibited by physiologic concentrations of estrogen by a receptor-mediated mechanism.[4,75]

The accumulation of glomerular extracellular matrix reflects the balance between matrix synthesis and matrix degradation, both of which are influenced by sex hormones. Transforming growth factor-beta (TGF-beta) plays a central role in stimulating mesangial matrix synthesis and in promoting progressive renal injury. Although not a universal finding, circulating TGF-beta levels appear to be lower in women than in men.[76] In numerous animal models of renal disease, administration of estrogen decreases, whereas administration of testosterone increases glomerular and kidney expression of TGF-beta. Estradiol also decreases TGF-beta mRNA expression in cultured podocytes isolated from db/db diabetic mice.[77] In contrast, neither estrogen nor testosterone alters the expression of TGF-beta in cultured mesangial cells isolated from normal male rats nor does testosterone alter the expression of TGF-beta in podocytes isolated from female estrogen receptor knockout mice.[4,78] Many of the effects of estrogen on TGF-beta expression may be indirect. In this regard, estrogen suppresses and testosterone upregulates the synthesis and/or peripheral activity of two potent inducers of TGF-beta expression, angiotensin II and endothelin-1.[4]

The actions of TGF-beta depend, in part, on transcriptional effects mediated by cooperation between Smad proteins and the transcription factor Specificity Protein 1 (Sp1).[79] We have shown that activation of protein kinase CK2, a ubiquitous serine/threonine protein kinase involved in signal transduction and transcriptional regulation, mediates TGF-beta-simulated type IV collagen gene transcription by increasing the quantity of free Sp1 available to transactivate the collagen IV promoter.[79] Estradiol reversed TGF-beta stimulated type IV collagen gene transcription by preventing TGF-beta-induced activation of CK2[79] (Figure 7.1). We also demonstrated that TGF-beta induces mesangial cell apoptosis *via* upregulation of CK2 activity, which in turn leads to phosphorylation of p53 and initiation of an apoptotic cascade.[80] Again we showed that estrogen reverses this process by preventing TGF-beta-induced activation of CK2.

In transfected human embryonic kidney cells exposed to estrogen, estrogen receptor alpha forms a ternary complex with Smad2/Smad3 and the ubiquitin ligase Smurf. Formation of this complex enhances ubiquination and degradation of these Smad proteins.[81] These interactions inhibit the TGF-beta signaling cascade and explain the finding that estrogen decreased the expression of total and phosphorylated Smad2/3 in kidneys from diabetic rats.[46] In addition, estradiol reversed the increased expression of TGF-beta receptors types I and II in these diabetic animals[82] (Figure 7.1).

We have also shown that estradiol suppresses mesangial cell type I collagen gene transcription and protein synthesis *via* a mitogen-activated protein kinase/AP 1-mediated mechanism, stimulates mesangial cell metalloproteinase 2 activity *via* a mitiogen-activated protein kinase/AP 2-mediated mechanism,

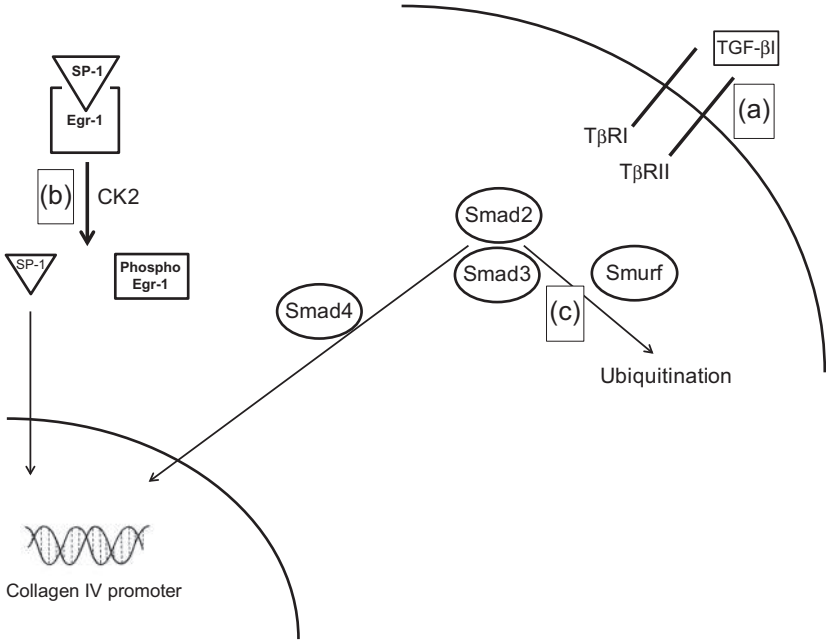


FIGURE 7.1 Interactions between estradiol and TFG-beta. (a) Estradiol downregulates TGF-beta R I and TGF-beta R II. (b) ER-alpha promotes formation of a complex between Smad2/Smad3 and Smurf leading to enhanced ubiquination. (c) Estradiol reverses TGF-beta-induced stimulation of CK2 enzyme activity which in turn limits the availability of free Sp1 to bind to the collagen IV promoter. Abbreviations used: *CK2*, protein kinase CK2; *ER*, estrogen receptor; *Smurf*, Smad ubiquitin regulatory factor; *Sp1*, specificity protein 1; *TGF-βR*, TGF-β receptor.

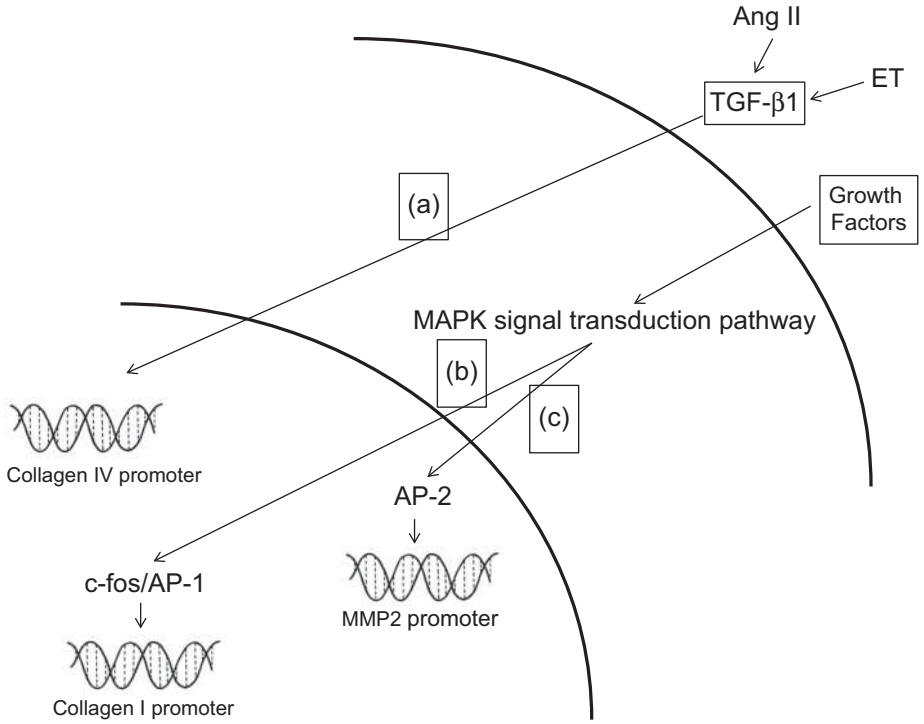


FIGURE 7.2 Estradiol alters the balance between mesangial matrix synthesis and degradation. (a) Estradiol inhibits AII-stimulated and ET-1-stimulated mesangial cell type IV collagen synthesis by interfering with the actions of TGF-beta on the collagen IV promoter. (b) Estradiol increases mesangial matrix degradation by stimulating MMP-2 synthesis *via* stimulation of the MAPK signal transduction pathway and upregulation of AP-2 activity. (c) Estradiol suppresses mesangial cell type I collagen synthesis by upregulating c-fos/AP-1 activity *via* stimulation of the MAPK signal transduction pathway. Abbreviations used: *Ang II*, angiotensin II; *AP*, activator protein; *ET*, endothelin; *MAPK*, mitogen-activated protein kinase; *MMP*, metalloproteinase; *TGF*, transforming growth factor.

and stimulates metalloproteinase 9 activity[83,84] (Figure 7.2). These actions shift the balance of matrix metabolism away from matrix accumulation and glomerulosclerosis.

Alb/TGF-beta mice overexpress TGF-beta and develop proteinuria and progressive renal injury. We have demonstrated that estradiol, by preventing CK2 activation, reverses the injurious effects of TGF-beta and ameliorates renal injury in this model.[85]

Nitric Oxide

Nitric oxide (NO) contributes to the development and progression of renal injury in numerous experimental models.[75,85–87] In cultured glomerular and vascular endothelial cells, physiological concentrations of estrogen cause a rapid release of NO *via* estrogen receptor α.[75,86] The promoter region of the endothelial nitric oxide synthase (eNOS) gene contains an estrogen responsive element, which may mediate estrogen-induced upregulation of eNOS mRNA and protein levels.[75,86] Estradiol also increases eNOS activity by increasing release of intracellular calcium.[75,86] In addition, estradiol increases local PGE_2 and prostacyclin levels, which in turn activate NO synthase.[75,86] As a consequence of these actions, female rats express higher levels of renal eNOS than males, an effect that is reversed by ovariectomy.[87] Although chronic NO inhibition in rats induces systolic hypertension in both sexes, only male rats develop proteinuria, which is prevented by orchiectomy.[88] Aging male rats show a greater reduction in renal NOS protein and enzyme activity as compared with females, which may contribute to greater age-dependent kidney damage in males.[89]

Reactive Oxygen Species

Enhanced generation of reactive oxygen species (ROS) has been shown to contribute to renal damage in experimental models of renal disease. Estrogen blunts the upregulation of nicotinamide adenosine dinucleotide phosphate oxidase activity induced by renal injury, which in turn suppresses the generation of superoxide anion, the major ROS produced by the kidney.[90] In contrast, testosterone increases oxidative stress either directly or indirectly. Testosterone inhibits antioxidant enzymes and amplifies the generation of ROS in response to numerous renal insults.[90] In several experimental models of hypertension, reversal of renal injury by estrogen and exacerbation of renal injury by testosterone is mediated by the ability of sex hormones to modulate ROS generation.[90]

Apoptosis

Testosterone induces podocyte apoptosis *in vivo* and *in vitro via* an androgen receptor-dependent mechanism which is independent of TGF-beta signaling.[78] Testosterone also promotes apoptosis of human proximal tubular cells by stimulating the c-Jun amino-terminal kinase signal transduction pathway associated with upregulation of Fas/Fas ligand and caspase-dependent apoptotic pathways.[91,92] In contrast, estrogen protects podocytes from apoptosis induced by testosterone, TGF-beta, TNF-alpha, and puromycin aminonucleoside *in vitro*.[78,93] This protective effect may be mediated by activation of the ERK or PI3K-AKT signal transduction pathways or by reduced generation of ROS.[78,93] In addition, we have shown that estrogen antagonizes TGF-beta-induced mesangial cell apoptosis by inhibiting activation of CK2 which in turn inhibits phosphorylation of p53.[80]

Kidney Structure and Renal Hemodynamics

Men tend to have larger kidneys than women. In addition, several studies in humans found that men have 10–15% more glomeruli than do women.[94] However, we previously suggested that body surface area (BSA), and not gender, is an independent determinant of kidney weight, glomerular size, and total glomerular volume.[95] As men are generally larger than women, these parameters also tend to be greater in men.

Munger and Baylis[96] suggested that an increased renal vascular resistance in female rats may protect their glomeruli from hyperfiltration-induced injury by blunting elevations in glomerular capillary pressure associated with renal insults. In this regard, female rats subjected to unilateral nephrectomy and fed a high-protein diet have lower glomerular capillary pressures and excrete less protein than similarly treated male rats.[4]

Early studies found a higher inulin clearance in healthy men than in healthy women.[97] However, with several notable exceptions, later studies have shown no difference in GFR between the sexes after correction for BSA.[4,98,99] Authors that reported a lower normalized GFR in women have suggested that these observed differences may merely reflect error introduced by indexing GFR by a constant BSA, which may fail to adequately correct for differences in kidney size or account for differences in physiologic demand between the sexes. In addition, neither testosterone nor estrogen directly affects GFR or renal blood flow in humans.[4]

Despite similar GFR, glomerular hemodynamic responses to vasoactive agents differ in men vs. women. Men respond to an infusion of AII by maintaining their GFR at the expense of an increased filtration fraction, suggesting an increase in glomerular capillary pressure.[100] In contrast, women showed a decrease in GFR and effective renal plasma flow (ERPF) without any change in filtration fraction, suggesting no increase in glomerular capillary pressure. As a result, men with CKD may be more likely to develop hyperfiltration

than women. Moreover, this gender dimorphism may contribute to renoprotection in females by blunting elevations in glomerular capillary pressure which in turn would reduce glomerular hemodynamic stress.

Studies of renal hemodynamic responses to angiotensin receptor blockade suggest that men may require higher doses of angiotensin receptor blockers (ARBs) than women and that the BP response to therapy may not adequately gauge renin-angiotensin system blockade.[101] Similarly, in Caucasian subjects with nondiabetic glomerular disease, ACEIs were more effective in reducing the rate of progression of CKD and led to a greater reduction in proteinuria in woman compared with men.[7] However, other investigators have reported the opposite. The Collaborative Study Group found that hypertensive women with diabetic nephropathy benefited less from ARB therapy than did men.[67] Moreover, a meta-analysis of efficacy studies in hypertensive cohorts concluded that ACEI and ARB therapy are more effective in reducing cardiovascular events in men than in women.[102] In addition, ACEI therapy of congestive heart failure has been reported to be more effective in reducing mortality in men than in women.[103,104] Whether gender differences in the response to ACEI/ARB therapy contributes to sexual dimorphism in the progression of CKD remains unclear.

Studies performed in normotensive, nonproteinuric type I diabetic adolescents found gender-related differences in the renal hemodynamic response to clamped euglycemia and clamped hyperglycemia.[105] During clamped euglycemia, males showed a higher ERPF and a lower renal vascular resistance than females. During clamped hyperglycemia, males did not exhibit any change in renal hemodynamics, whereas females showed a decrease in ERPF and increases in renal vascular resistance and filtration fraction, suggesting an increase in glomerular capillary pressure. It was suggested that these gender-related differences in the response of the renal microvasculature to hyperglycemia may explain the lack of a consistent protective effect of female gender on the course of nephropathy in type I diabetes.

Women with uncomplicated type 1 diabetes show exaggerated renal responses to cyclooxygenase 2 (COX-2) inhibition, characterized by decreased ERPF and increased filtration fraction, suggesting that women are more dependent on vasodilatory prostaglandins to maintain renal hemodynamics than are men.[106] COX-2 inhibition also eliminated gender-related differences in the response to angiotensin II (Ang II), indicating that vasodilatory prostaglandins may play a greater role in counteracting the effects of Ang II on the renal microvasculature of diabetic women compared with diabetic men.

In the rat, regional renal blood flow autoregulation is more efficient and papillary blood flow is lower in males.[4,75] A role for vasodilatory prostaglandins in mediating these effects is suggested by the finding that cyclooxygenase inhibitors abolish gender-related differences in regional renal blood flow autoregulatory capacity and in papillary blood flow rate.[4,75]

HYPERTENSION

The link between hypertension and renal insufficiency was recognized as early as the mid-1800s when Richard Bright noticed that individuals with renal disease also had hypertension.[107] The interaction between the kidney and hypertension sets up a vicious cycle in which renal injury causes hypertension, and hypertension causes further renal injury. Evidence that renal disease and hypertension are interconnected is shown by the many studies showing that the use of antihypertensive medications slows the progression of renal injury.[108] The mechanisms responsible for hypertension are multifactorial, and thus the mechanisms by which hypertension causes renal injury are also multifactorial. Similarly, the roles played by sex steroids in mediating gender differences in hypertension and renal injury have not been completely elucidated.[109,110]

Hypertension in all animal models studied is due to a hypertensive shift in the pressure-natriuresis relationship such that a higher BP is required to allow "normal" levels of sodium to be excreted. Reductions in GFR due to injury cause an increase in sodium reabsorption and hypertension.[109–112] Whether estrogens attenuate sodium reabsorption directly has not been determined to our knowledge. However, in studies in male rats, androgens increase proximal tubule sodium reabsorption directly *via* the androgen receptor, and this response is mediated by the RAS as blockade with AT1 receptor antagonists attenuated the response.[113] Thus, androgens could be prohypertensive.

In hypertensive animals, such as spontaneously hypertensive rats (SHRs), androgens promote hypertension and renal injury and castration of males attenuates the hypertension to level found in females.[114] Estrogens do not have a protective effect on hypertension in this model because ovariectomy does not increase BP in the females. With aging, androgens also promote increases in BP in Dahl salt-sensitive rats, castration attenuates the hypertension, but in females, ovariectomy promotes increases in BP.[114,115]

One mechanism by which hypertension is thought to occur is due to increases in ROS. Antioxidants reduce BP in male SHR but have no effect in females.[116] Prooxidants, such as molsidomine, increase BP in male SHR, but not females.[116] Because estradiol increases endothelial NO, and reductions in NO by interaction with superoxide are thought to contribute to the ROS-mediated increases BP, females were given L-NAME

and molsidomine in the hopes that blockade of NO synthesis would then cause BP to increase further with molsidomine. However, BP in females still did not respond.[116] Thus, the hypertension in female SHR is not controlled by ROS, whereas in males, the opposite is true. The role of oxidative stress in mediating hypertension in humans is not clear, however. No clinical trials to date have shown that antioxidant therapy alone decreases BP. However, this may be due to the fact that a competent NO system is necessary for antioxidants to be able to reduce BP.[117] Most hypertensive individuals have endothelial dysfunction and thus have reduced NO production, and antioxidants would not be effective in lowering their BPs. In addition, none of the studies to date have separated depressor response to antioxidants by gender. Thus, hypertensive men may benefit from antioxidant therapy and women may not, as in the animal studies. Thus, additional studies are needed to determine if there are gender differences in the depressor response to chronic antioxidant therapy.

Angiotensin II hypertension is also sex dependent. In rats given slow pressor doses of Ang II along with ACEIs to reduce the endogenous production of Ang II, the BP increases to higher levels in females than males.[118] Addition of high salt diet has no further effect to increase BP in females but causes a salt-dependent increase in the BP in males. In rats not given ACEIs, males exhibit a greater increase in BP than females. In contrast, male mice develop higher elevations in BP in response to Ang II than do females, regardless of whether they are given ACEIs.[119,120] Sex steroids affect the components of the RAS. Renal synthesis of angiotensinogen is increased with androgens,[121,122] and estrogens stimulate liver angiotensinogen synthesis but attenuate expression of AT1 receptors and ACE.[122,123] Estrogens also upregulate ACE2 to produce vasodilator Ang (1−7).[124]

Aging in both men and women is characterized by increases in BP,[125,126] and the prevalence of hypertension in postmenopausal women is higher than in men.[125,127−130] In the US, more than 75% of women over 60 years of age are hypertensive.[131,132] Nondipping of BP at night is associated with increased target organ damage (including renal injury) in both men and women.[133,134] However, there is evidence that nondipping in women, in general, is associated with greater target organ damage than in men,[133,134] and postmenopausal women are more likely than premenopausal women to exhibit nocturnal nondipping of BP.[134]

The mechanisms responsible for hypertension in aging hypertensive animal models also show sex differences. For example, in male SHR, albuminuria and glomerular sclerosis is present by 16 months of age.[135] In contrast, female SHR have little proteinuria or histologic evidence of glomerular or tubular injury despite the fact that their BP increases with aging to the same or higher levels than in age-matched males.[136] The mechanisms responsible for the hypertension in aging male SHR are mainly the RAS because AT1 receptor blockade, but not endothelin ETA receptor blockade, normalizes the BP old males and young females.[137,138] In old females, although blockade of the RAS, ETA receptor, 20-HETE synthesis, and renal denervation attenuate the hypertension, none of these maneuvers alone normalizes the BP. Combined administration of an AT1 receptor antagonist, an ETA receptor blocker, and a 20-HETE synthesis inhibitor reduces the BP toward normal levels but mean arterial pressure remains above 100 mm Hg.[139] These data suggest that more studies are necessary to determine the mechanisms responsible for hypertension in postmenopausal women to protect them from developing renal disease with aging. There is evidence that hypertension is not as well controlled in aging women as in aging men, despite the fact that women see their care providers more regularly than men and are typically more compliant in taking their medications.[140] The observations from animal studies suggest that the reason for the gender difference in BP control in aging individuals may be due to differences in mechanisms and further suggest that novel drug therapies may need to be developed to treat women.

THERAPEUTIC IMPLICATIONS

Several observational and three randomized, placebo-controlled studies have examined the effects of hormone replacement therapy and oral contraceptive therapy on renal function and proteinuria in diabetic and nondiabetic women. The results are contradictory and cannot be entirely explained by differences in estrogen dose, route of administration, or the nature of concomitantly administered progestins. Moreover, healthy user bias complicates interpretation of observations studies because women who take hormone therapy differ in relevant characteristics from those who do not take hormone therapy.

Jackson and coworkers have suggested that many of the beneficial effects of estradiol on cellular processes that influence real disease progression are mediated by nonestrogenic metabolites that lack feminizing properties, particularly catecholestradiols.[141] These agents inhibit mesangial cell proliferation and collagen synthesis *in vitro* and ameliorate oxidative stress and progressive renal injury in several models of experimental renal disease by estrogen receptor-independent mechanism. Whether these agents might exert a similar effect on progressive renal injury in humans without adverse effects on reproductive tissues has not been explored.

Selective estrogen receptor modulators (SERMs) are agents that mimic many of the beneficial effects of estrogen on bone and vascular tissue without reproducing estrogens deleterious effects on reproductive tissue. SERMs replicate the effects of estradiol on mesangial cell biology and are renoprotective in models of experimental renal injury.[142] The Raloxifene in Diabetic Nephropathy study, a double-blind, placebo-controlled trial in postmenopausal women with type 2 diabetes and evidence of renal involvement randomized to receive either Raloxifene or placebo for six months, reported that urinary protein excretion decreased in patients receiving Raloxifene but not in the placebo group.[143] We performed a *post hoc* analysis of the Multiple Outcomes of Raloxifene Evaluation trial, a multicenter, randomized, double-blind, placebo-controlled trial of Raloxifene vs. placebo on the risk of fractures in nondiabetic postmenopausal women, and found that women in the Raloxifene group had a slower rate of increase in S[Cr] and a significantly slower rate of decline in eGFR during three years of follow-up.[144]

CONCLUSION AND FUTURE DIRECTIONS

In experimental models of renal disease, there is a clear sexual dimorphism, with male animals showing a worse renal prognosis. However, in humans, a larger number of variables make the issue of gender and real disease progression more challenging. There have been no dedicated well-designed prospective studies evaluating the rate of decline in renal function in men vs. women. Individual studies that have taken gender into account when analyzing factors contributing to renal disease progression have often included small numbers of subjects with a short duration of follow-up. Although far from a universal finding, the predominance of data supports the conclusion that male gender is associated with accelerated progression of nondiabetic CKD. A similar case can be made for sexual dimorphism in the course of diabetic nephropathy; however, the evidence for this conclusion is even less robust.

Interpretation of data is confounded by uncertainty about the appropriate cutoff to define the normal range of GFR and ACR with respect to gender and age. This is especially relevant in cross-sectional studies examining the incidence and prevalence of CKD. Moreover, questions arise regarding the magnitude of differences between the sexes in the bias of equations used to estimate GFR. Inconsistent data may also reflect differences in the populations studied with respect to duration of follow-up, hormonal status, demographic features, disease-modifying therapy, lipid levels, and BP control, as well as differences in study methodology, most notably differences in outcome measures. In the case of diabetic nephropathy, inconsistent data may also reflect differences in the age of onset of diabetes and in the intensity of glycemic control. At present, insufficient data are available to adequately address these concerns. These issues merit serious consideration in any discussion of the relationship between gender and CKD.

We are not aware of any ongoing studies to investigate the effects of hormone replacement therapy, SERMs, or estradiol metabolites on the course of CKD in humans.[111] We speculate that a lack of enthusiasm to explore these novel therapeutic approaches arises from the dampening effect of the Woman's Health Initiative Study which raised concerns about the relationship between hormonal therapy and elevated risk of breast cancer and thromboembolic events.

Acknowledgments

The authors wish to acknowledge the contribution of Sharon R. Silbiger, MD (1960–2012), to this body of work and thank the American Heart Association (JN) and National Institutes of Health National Heart, Lung, and Blood Institute RO1 HL135089, PO1 HL51971, P20GM121334 (JFR) for support.

References

1. Wizemann TMP ML. Exploring the biological contributions to human health: does sex matter? In: *Committee on understanding the biology of sex and gender differences, Board on Health Sciences Policy, Institute of Medicine*. National Acad Press; 2001. p. 1–288.
2. Neugarten J, Acharya A, Silbiger SR. Effect of gender on the progression of nondiabetic renal disease: a meta-analysis. *J Am Soc Nephrol* 2000;**11**:319–29.
3. Neugarten J, Silbiger SR. Effects of sex hormones on mesangial cells. *Am J Kidney Dis* 1995;**26**:147–51.
4. Silbiger SR, Neugarten J. The impact of gender on the progression of chronic renal disease. *Am J Kidney Dis* 1995;**25**:515–33.
5. Coggins CH, Breyer Lewis J, Caggiula AW, Castaldo LS, Klahr S, Wang SR. Differences between women and men with chronic renal disease. *Nephrol Dial Transplant* 1998;**13**:1430–7.
6. Cattran DC, Reich HN, Beanlands HJ, Miller JA, Scholey JW, Troyanov S, Genes G, Glomerulonephritis G. The impact of sex in primary glomerulonephritis. *Nephrol Dial Transplant* 2008;**23**: 2247–53.
7. Ruggenenti P, Perna A, Zoccali C, Gherardi G, Benini R, Testa A, Remuzzi G. Chronic proteinuric nephropathies. II. Outcomes and response to treatment in a prospective cohort of 352 patients: differences between women and men in relation to the ACE gene polymorphism. Gruppo Italiano di Studi Epidemologici in Nefrologia (Gisen). *J Am Soc Nephrol* 2000;**11**:88–96.
8. Babayev R, Whaley-Connell A, Kshirsagar A, Klemmer P, Navaneethan S, Chen SC, Li S, McCullough PA, Bakris G, Bomback A, Investigators K. Association of race and body mass index with ESRD and mortality in CKD stages 3-4: results from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2013;**61**:404–12.
9. Chang WX, Arai S, Tamura Y, Kumagai T, Ota T, Shibata S, Fujigaki Y, Shen ZY, Uchida S. Time-dependent risk factors

associated with the decline of estimated GFR in CKD patients. *Clin Exp Nephrol* 2016;**20**:58–70.
10. Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int* 2006;**69**:375–82.
11. Evans M, Fryzek JP, Elinder CG, Cohen SS, McLaughlin JK, Nyren O, Fored CM. The natural history of chronic renal failure: results from an unselected, population-based, inception cohort in Sweden. *Am J Kidney Dis* 2005;**46**:863–70.
12. Hallan SI, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR. Combining GFR and albuminuria to classify CKD improves prediction of ESRD. *J Am Soc Nephrol* 2009;**20**:1069–77.
13. Haroun MK, Jaar BG, Hoffman SC, Comstock GW, Klag MJ, Coresh J. Risk factors for chronic kidney disease: a prospective study of 23,534 men and women in Washington County, Maryland. *J Am Soc Nephrol* 2003;**14**:2934–41.
14. Iseki K, Iseki C, Ikemiya Y, Fukiyama K. Risk of developing end-stage renal disease in a cohort of mass screening. *Kidney Int* 1996;**49**:800–5.
15. Ricardo AC, Yang W, Sha D, Appel LJ, Chen J, Krousel-Wood M, Manoharan A, Steigerwalt S, Wright J, Rahman M, Rosas SE, Saunders M, Sharma K, Daviglus ML, Lash JP, Investigators C. Sex-related disparities in CKD progression. *J Am Soc Nephrol* 2019;**30**(1):137–46.
16. Jafar TH, Schmid CH, Stark PC, Toto R, Remuzzi G, Ruggenenti P, Marcantoni C, Becker G, Shahinfar S, De Jong PE, De Zeeuw D, Kamper AL, Strangaard S, Levey AS. The rate of progression of renal disease may not be slower in women compared with men: a patient-level meta-analysis. *Nephrol Dial Transplant* 2003;**18**:2047–53.
17. Nitsch D, Grams M, Sang Y, Black C, Cirillo M, Djurdjev O, Iseki K, Jassal SK, Kimm H, Kronenberg F, Oien CM, Levey AS, Levin A, Woodward M, Hemmelgarn BR. Chronic kidney disease prognosis C: associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. *BMJ* 2013;**346**:f324.
18. Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC, Chodick G, Collins AJ, Djurdjev O, Elley CR, Evans M, Garg AX, Hallan SI, Inker LA, Ito S, Jee SH, Kovesdy CP, Kronenberg F, Heerspink HJ, Marks A, Nadkarni GN, Navaneethan SD, Nelson RG, Titze S, Sarnak MJ, Stengel B, Woodward M, Iseki K, Consortium CKDP. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *J Am Med Assoc* 2016;**315**:164–74.
19. Evans M, Grams ME, Sang Y, Astor BC, Blankestijn PJ, Brunskill NJ, Collins JF, Kalra PA, Kovesdy CP, Levin A, Mark PB, Moranne O, Rao P, Rios PG, Schneider MP, Shalev V, Zhang H, Chang AR, Gansevoort RT, Matsushita K, Zhang L, Eckardt KU, Hemmelgarn B, Wheeler DC. Risk factors for prognosis in patients with severely decreased GFR. *Kidney Int Rep* 2018;**3**:625–37.
20. Grams ME, Sang Y, Levey AS, Matsushita K, Ballew S, Chang AR, Chow EK, Kasiske BL, Kovesdy CP, Nadkarni GN, Shalev V, Segev DL, Coresh J, Lentine KL, Garg AX, Chronic Kidney Disease Prognosis C. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med* 2016;**374**:411–21.
21. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FD. Global prevalence of chronic kidney disease – a systematic review and meta-analysis. *PLoS One* 2016;**11**:e0158765.
22. Mills KT, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, Chen J, He J. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int* 2015;**88**:950–7.
23. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. *BMC Public Health* 2008;**8**:117.
24. U.S. Renal Data System. *USRDS 2012 annual report: atlas of chronic kidney disease and end stage renal disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diaseases; 2012.
25. Murphy D, McCulloch CE, Lin F, Banerjee T, Bragg-Gresham JL, Eberhardt MS, Morgenstern H, Pavkov ME, Saran R, Powe NR, Hsu CY, Centers for Disease C. Prevention chronic kidney disease surveillance T: trends in prevalence of chronic kidney disease in the United States. *Ann Intern Med* 2016;**165**:473–81.
26. Glassock RJ, Winearls C. An epidemic of chronic kidney disease: fact or fiction? *Nephrol Dial Transplant* 2008;**23**:1117–21.
27. Mattix HJ, Hsu CY, Shaykevich S, Curhan G. Use of the albumin/creatinine ratio to detect microalbuminuria: implications of sex and race. *J Am Soc Nephrol* 2002;**13**:1034–9.
28. Warram JH, Gearin G, Laffel L, Krolewski AS. Effect of duration of type I diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. *J Am Soc Nephrol* 1996;**7**:930–7.
29. Neugarten J, Golestaneh L. Gender and renal disease progression. Mayo Clin Proc [in press].
30. Chadban SJ, Briganti EM, Kerr PG, Dunstan DW, Welborn TA, Zimmet PZ, Atkins RC. Prevalence of kidney damage in Australian adults: the AusDiab kidney study. *J Am Soc Nephrol* 2003;**14**: S131–138.
31. Fernandez-Prado R, Fernandez-Fernandez B, Ortiz A. Women and renal replacement therapy in Europe: lower incidence, equal access to transplantation, longer survival than men. *Clin Kidney J* 2018;**11**:1–6.
32. Gilg J, Castledine C, Fogarty D. UK Renal Registry 14th annual report: Chapter 1 UK RRT incidence in 2010: national and centre-specific analyses. *Nephron Clin Pract* 2012;**120**(Suppl. 1): c1–27.
33. Iseki K, Nakai S, Shinzato T, Nagura Y, Akiba T. Patient Registration Committee of the Japanese Society for Dialysis T: increasing gender difference in the incidence of chronic dialysis therapy in Japan. *Ther Apher Dial* 2005;**9**:407–11.
34. Xu R, Zhang LX, Zhang PH, Wang F, Zuo L, Wang HY. Gender differences in age-related decline in glomerular filtration rates in healthy people and chronic kidney disease patients. *BMC Nephrol* 2010;**11**:20.
35. Hecking M, Bieber BA, Ethier J, Kautzky-Willer A, Sunder-Plassmann G, Saemann MD, Ramirez SP, Gillespie BW, Pisoni RL, Robinson BM, Port FK. Sex-specific differences in hemodialysis prevalence and practices and the male-to-female mortality rate: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *PLoS Med* 2014;**11**:e1001750.
36. Kausz AT, Obrador GT, Arora P, Ruthazer R, Levey AS, Pereira BJ. Late initiation of dialysis among women and ethnic minorities in the United States. *J Am Soc Nephrol* 2000;**11**:2351–7.
37. Li Y, Jin Y, Kapke A, Pearson J, Saran R, Port FK, Robinson BM. Explaining trends and variation in timing of dialysis initiation in the United States. *Medicine (Baltim)* 2017;**96**:e6911.
38. Stel VS, Tomson C, Ansell D, Casino FG, Collart F, Finne P, Ioannidis GA, De Meester J, Salomone M, Traynor JP, Zurriaga O, Jager KJ. Level of renal function in patients starting dialysis: an ERA-EDTA Registry study. *Nephrol Dial Transplant* 2010;**25**:3315–25.
39. Coresh J, Byrd-Holt D, Astor BC, Briggs JP, Eggers PW, Lacher DA, Hostetter TH. Chronic kidney disease awareness, prevalence, and trends among U.S. adults, 1999 to 2000. *J Am Soc Nephrol* 2005;**16**:180–8.
40. Gasparini A, Evans M, Coresh J, Grams ME, Norin O, Qureshi AR, Runesson B, Barany P, Arnlov J, Jernberg T, Wettermark B, Elinder CG, Carrero JJ. Prevalence and recognition of chronic kidney disease in Stockholm healthcare. *Nephrol Dial Transplant* 2016;**31**:2086–94.

41. Sparke C, Moon L, Green F, Mathew T, Cass A, Chadban S, Chapman J, Hoy W, McDonald S. Estimating the total incidence of kidney failure in Australia including individuals who are not treated by dialysis or transplantation. *Am J Kidney Dis* 2013;**61**:413–9.
42. Xue JL, Eggers PW, Agodoa LY, Foley RN, Collins AJ. Longitudinal study of racial and ethnic differences in developing end-stage renal disease among aged medicare beneficiaries. *J Am Soc Nephrol* 2007; **18**:1299–306.
43. United States Renal Data System. *USRDS annual data report: epidemiology of kidney disease in the United States*. 2016.
44. Carrero JJ, Hecking M, Chesnaye NC, Jager KJ. Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. *Nat Rev Nephrol* 2018;**14**:151–64.
45. Faruque LI, Hemmelgarn BR, Wiebe N, Manns BJ, Ravani P, Klarenbach S, Pelletier R, Tonelli M. Alberta Kidney Disease N: factors associated with initiation of chronic renal replacement therapy for patients with kidney failure. *Clin J Am Soc Nephrol* 2013;**8**:1327–35.
46. Carrero JJ, Hecking M, Ulasi I, Sola L, Thomas B. Chronic kidney disease, gender, and access to care: a global perspective. *Semin Nephrol* 2017;**37**:296–308.
47. Cobo G, Hecking M, Port FK, Exner I, Lindholm B, Stenvinkel P, Carrero JJ. Sex and gender differences in chronic kidney disease: progression to end-stage renal disease and haemodialysis. *Clin Sci (Lond)* 2016;**130**:1147–63.
48. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**:1296–305.
49. Powe NR, Tarver-Carr ME, Eberhardt MS, Brancati FL. Receipt of renal replacement therapy in the United States: a population-based study of sociodemographic disparities from the Second National Health and Nutrition Examination Survey (NHANES II). *Am J Kidney Dis* 2003;**42**:249–55.
50. Turin TC, Tonelli M, Manns BJ, Ravani P, Ahmed SB, Hemmelgarn BR. Chronic kidney disease and life expectancy. *Nephrol Dial Transplant* 2012;**27**:3182–6.
51. Conway B, Webster A, Ramsay G, Morgan N, Neary J, Whitworth C, Harty J. Predicting mortality and uptake of renal replacement therapy in patients with stage 4 chronic kidney disease. *Nephrol Dial Transplant* 2009;**24**:1930–7.
52. Holland DC, Lam M. Predictors of hospitalization and death among pre-dialysis patients: a retrospective cohort study. *Nephrol Dial Transplant* 2000;**15**:650–8.
53. United States Renal Data System. *USRDS annual data report: epidemiology of kidney disease in the United States. One-chronic kidney disease in the adult NHANES population*. 2009.
54. De Nicola L, Donfrancesco C, Minutolo R, Lo Noce C, Palmieri L, De Curtis A, Iacoviello L, Zoccali C, Gesualdo L, Conte G, Vanuzzo D, Giampaoli S, Group A-SR. Prevalence and cardiovascular risk profile of chronic kidney disease in Italy: results of the 2008-12 National Health Examination Survey. *Nephrol Dial Transplant* 2015;**30**:806–14.
55. Klein SL. Immune cells have sex and so should journal articles. *Endocrinology* 2012;**153**:2544–50.
56. Maric C, Sullivan S. Estrogens and the diabetic kidney. *Gend Med* 2008;**5**(Suppl. A):S103–113.
57. Raile K, Galler A, Hofer S, Herbst A, Dunstheimer D, Busch P, Holl RW. Diabetic nephropathy in 27,805 children, adolescents, and adults with type 1 diabetes: effect of diabetes duration, A1C, hypertension, dyslipidemia, diabetes onset, and sex. *Diabetes Care* 2007;**30**:2523–8.
58. Seliger SL, Davis C, Stehman-Breen C. Gender and the progression of renal disease. *Curr Opin Nephrol Hypertens* 2001;**10**:219–25.
59. Breyer JA, Bain RP, Evans JK, Nahman Jr NS, Lewis EJ, Cooper M, McGill J, Berl T. Predictors of the progression of renal insufficiency in patients with insulin-dependent diabetes and overt diabetic nephropathy. The Collaborative Study Group. *Kidney Int* 1996;**50**:1651–8.
60. Hovind P, Tarnow L, Oestergaard PB, Parving HH. Elevated vascular endothelial growth factor in type 1 diabetic patients with diabetic nephropathy. *Kidney Int Suppl* 2000;**75**:S56–61.
61. Jacobsen P, Rossing K, Tarnow L, Rossing P, Mallet C, Poirier O, Cambien F, Parving HH. Progression of diabetic nephropathy in normotensive type 1 diabetic patients. *Kidney Int Suppl* 1999;**71**: S101–105.
62. Harjutsalo V, Maric C, Forsblom C, Thorn L, Waden J, Groop PH, FinnDiane Study G. Sex-related differences in the long-term risk of microvascular complications by age at onset of type 1 diabetes. *Diabetologia* 2011;**54**:1992–9.
63. Mollsten A, Svensson M, Waernbaum I, Berhan Y, Schon S, Nystrom L, Arnqvist HJ, Dahlquist G, Swedish Childhood Diabetes Study G, Diabetes Incidence Study in S, Swedish Renal R. Cumulative risk, age at onset, and sex-specific differences for developing end-stage renal disease in young patients with type 1 diabetes: a nationwide population-based cohort study. *Diabetes* 2010;**59**:1803–8.
64. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Drash AL, Ellis D, LaPorte RE, Kuller LH. Prevalence of complications in IDDM by sex and duration. Pittsburgh epidemiology of diabetes complications study II. *Diabetes* 1990;**39**:1116–24.
65. Maric C, Forsblom C, Thorn L, Waden J, Groop PH, FinnDiane Study G. Association between testosterone, estradiol and sex hormone binding globulin levels in men with type 1 diabetes with nephropathy. *Steroids* 2010;**75**:772–8.
66. Keane WF, Brenner BM, de Zeeuw D, Grunfeld JP, McGill J, Mitch WE, Ribeiro AB, Shahinfar S, Simpson RL, Snapinn SM, Toto R, Investigators RS. The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: the RENAAL study. *Kidney Int* 2003;**63**:1499–507.
67. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I, Collaborative Study G. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**:851–60.
68. Icks A, Haastert B, Genz J, Giani G, Hoffmann F, Trapp R, Koch M. Incidence of renal replacement therapy (RRT) in the diabetic compared with the non-diabetic population in a German region, 2002-08. *Nephrol Dial Transplant* 2011;**26**:264–9.
69. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ* 2006;**332**: 73–8.
70. Chang PY, Chien LN, Lin YF, Wu MS, Chiu WT, Chiou HY. Risk factors of gender for renal progression in patients with early chronic kidney disease. *Medicine (Baltim)* 2016;**95**:e4203.
71. Halbesma N, Brantsma AH, Bakker SJ, Jansen DF, Stolk RP, De Zeeuw D, De Jong PE, Gansevoort RT, group P. Gender differences in predictors of the decline of renal function in the general population. *Kidney Int* 2008;**74**:505–12.
72. Pscheidt C, Nagel G, Zitt E, Kramar R, Concin H, Lhotta K. Sex- and time-dependent patterns in risk factors of end-stage renal disease: a large Austrian cohort with up to 20 years of follow-up. *PLoS One* 2015;**10**:e0135052.
73. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, Narita M, Koyama A. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int* 2007;**71**:159–66.
74. Kattah AG, Smith CY, Gazzuola Rocca L, Grossardt BR, Garovic VD, Rocca WA. CKD in patients with bilateral oophorectomy. *Clin J Am Soc Nephrol* 2018;**13**:1649–58.

75. Neugarten JS SR, Golestaneh L. Gender and kidney disease. In: Brenner BM, editor. *Brenner and rector's the kidney.* Amsterdam, Netherlands: Elsevier; 2008. p. 674–80.
76. Lin Y, Nakachi K, Ito Y, Kikuchi S, Tamakoshi A, Yagyu K, Watanabe Y, Inaba Y, Kazuo T, Jacc Study G. Variations in serum transforming growth factor-beta1 levels with gender, age and lifestyle factors of healthy Japanese adults. *Dis Markers* 2009;**27**:23–8.
77. Catanuto P, Doublier S, Lupia E, Fornoni A, Berho M, Karl M, Striker GE, Xia X, Elliot S. 17 beta-estradiol and tamoxifen upregulate estrogen receptor beta expression and control podocyte signaling pathways in a model of type 2 diabetes. *Kidney Int* 2009;**75**:1194–201.
78. Doublier S, Lupia E, Catanuto P, Periera-Simon S, Xia X, Korach K, Berho M, Elliot SJ, Karl M. Testosterone and 17beta-estradiol have opposite effects on podocyte apoptosis that precedes glomerulosclerosis in female estrogen receptor knockout mice. *Kidney Int* 2011;**79**:404–13.
79. Zdunek M, Silbiger S, Lei J, Neugarten J. Protein kinase CK2 mediates TGF-beta1-stimulated type IV collagen gene transcription and its reversal by estradiol. *Kidney Int* 2001;**60**:2097–108.
80. Negulescu O, Bognar I, Lei J, Devarajan P, Silbiger S, Neugarten J. Estradiol reverses TGF-beta1-induced mesangial cell apoptosis by a casein kinase 2-dependent mechanism. *Kidney Int* 2002;**62**: 1989–98.
81. Ito I, Hanyu A, Wayama M, Goto N, Katsuno Y, Kawasaki S, Nakajima Y, Kajiro M, Komatsu Y, Fujimura A, Hirota R, Murayama A, Kimura K, Imamura T, Yanagisawa J. Estrogen inhibits transforming growth factor beta signaling by promoting Smad2/3 degradation. *J Biol Chem* 2010;**285**:14747–55.
82. Dixon A, Maric C. 17beta-Estradiol attenuates diabetic kidney disease by regulating extracellular matrix and transforming growth factor-beta protein expression and signaling. *Am J Physiol Renal Physiol* 2007;**293**:F1678–1690.
83. Guccione M, Silbiger S, Lei J, Neugarten J. Estradiol upregulates mesangial cell MMP-2 activity via the transcription factor AP-2. *Am J Physiol Renal Physiol* 2002;**282**:F164–169.
84. Neugarten J, Medve I, Lei J, Silbiger SR. Estradiol suppresses mesangial cell type I collagen synthesis via activation of the MAP kinase cascade. *Am J Physiol* 1999;**277**:F875–881.
85. Blush J, Lei J, Ju W, Silbiger S, Pullman J, Neugarten J. Estradiol reverses renal injury in Alb/TGF-beta1 transgenic mice. *Kidney Int* 2004;**66**:2148–54.
86. Dubey RK, Jackson EK. Estrogen-induced cardiorenal protection: potential cellular, biochemical, and molecular mechanisms. *Am J Physiol Renal Physiol* 2001;**280**:F365–388.
87. Neugarten J, Ding Q, Friedman A, Lei J, Silbiger S. Sex hormones and renal nitric oxide synthases. *J Am Soc Nephrol* 1997;**8**:1240–6.
88. Verhagen AM, Attia DM, Koomans HA, Joles JA. Male gender increases sensitivity to proteinuria induced by mild NOS inhibition in rats: role of sex hormones. *Am J Physiol Renal Physiol* 2000;**279**:F664–670.
89. Erdely A, Greenfeld Z, Wagner L, Baylis C. Sexual dimorphism in the aging kidney: effects on injury and nitric oxide system. *Kidney Int* 2003;**63**:1021–6.
90. Neugarten J. Estrogen and oxidative stress. *Gend Med* 2007;**4**:31–2.
91. Verzola D, Gandolfo MT, Salvatore F, Villaggio B, Gianiorio F, Traverso P, Deferrari G, Garibotto G. Testosterone promotes apoptotic damage in human renal tubular cells. *Kidney Int* 2004; **65**:1252–61.
92. Verzola D, Villaggio B, Procopio V, Gandolfo MT, Gianiorio F, Fama A, Tosetti F, Traverso P, Deferrari G, Garibotto G. Androgen-mediated apoptosis of kidney tubule cells: role of c-Jun amino terminal kinase. *Biochem Biophys Res Commun* 2009; **387**:531–6.
93. Kummer S, Jeruschke S, Wegerich LV, Peters A, Lehmann P, Seibt A, Mueller F, Koleganova N, Halbenz E, Schmitt CP, Bettendorf M, Mayatepek E, Gross-Weissmann ML, Oh J. Estrogen receptor alpha expression in podocytes mediates protection against apoptosis in-vitro and in-vivo. *PLoS One* 2011;**6**:e27457.
94. Nyengaard JR, Bendtsen TF. Glomerular number and size in relation to age, kidney weight, and body surface in normal man. *Anat Rec* 1992;**232**:194–201.
95. Neugarten J, Kasiske B, Silbiger SR, Nyengaard JR. Effects of sex on renal structure. *Nephron* 2002;**90**:139–44.
96. Munger K, Baylis C. Sex differences in renal hemodynamics in rats. *Am J Physiol* 1988;**254**:F223–231.
97. Delanaye P, Schaeffner E, Ebert N, Cavalier E, Mariat C, Krzesinski JM, Moranne O. Normal reference values for glomerular filtration rate: what do we really know? *Nephrol Dial Transplant* 2012;**27**:2664–72.
98. Inker LA, Shafi T, Okparavero A, Tighiouart H, Eckfeldt JH, Katz R, Johnson WC, Dermond N, Tariq Z, Benayache I, Post WS, Coresh J, Levey AS, Shlipak MG. Effects of race and sex on measured GFR: the multi-ethnic study of atherosclerosis. *Am J Kidney Dis* 2016;**68**:743–51.
99. Poggio ED, Rule AD, Tanchanco R, Arrigain S, Butler RS, Srinivas T, Stephany BR, Meyer KH, Nurko S, Fatica RA, Shoskes DA, Krishnamurthi V, Goldfarb DA, Gill I, Schreiber Jr MJ. Demographic and clinical characteristics associated with glomerular filtration rates in living kidney donors. *Kidney Int* 2009;**75**:1079–87.
100. Miller JA, Anacta LA, Cattran DC. Impact of gender on the renal response to angiotensin II. *Kidney Int* 1999;**55**:278–85.
101. Miller JA, Cherney DZ, Duncan JA, Lai V, Burns KD, Kennedy CR, Zimpelmann J, Gao W, Cattran DC, Scholey JW. Gender differences in the renal response to renin-angiotensin system blockade. *J Am Soc Nephrol* 2006;**17**:2554–60.
102. Rabi DM, Khan N, Vallee M, Hladunewich MA, Tobe SW, Pilote L. Reporting on sex-based analysis in clinical trials of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker efficacy. *Can J Cardiol* 2008;**24**:491–6.
103. Hudson M, Rahme E, Behlouli H, Sheppard R, Pilote L. Sex differences in the effectiveness of angiotensin receptor blockers and angiotensin converting enzyme inhibitors in patients with congestive heart failure–a population study. *Eur J Heart Fail* 2007;**9**:602–9.
104. Keyhan G, Chen SF, Pilote L. Angiotensin-converting enzyme inhibitors and survival in women and men with heart failure. *Eur J Heart Fail* 2007;**9**:594–601.
105. Cherney DZ, Sochett EB, Miller JA. Gender differences in renal responses to hyperglycemia and angiotensin-converting enzyme inhibition in diabetes. *Kidney Int* 2005;**68**:1722–8.
106. Cherney DZ, Scholey JW, Nasrallah R, Dekker MG, Slorach C, Bradley TJ, Hebert RL, Sochett EB, Miller JA. Renal hemodynamic effect of cyclooxygenase 2 inhibition in young men and women with uncomplicated type 1 diabetes mellitus. *Am J Physiol Renal Physiol* 2008;**294**:F1336–1341.
107. Bright R. Tabular view of the morbid appearance in 100 cases connected with albuminous urine, with observations. *Guy's Hospital Rep* 1846;**1**:380–400.
108. Sandberg K. Mechanisms underlying sex differences in progressive renal disease. *Gend Med* 2008;**5**:10–23.
109. Liu PY, Death AK, Handelsman DJ. Androgens and cardiovascular disease. *Endocr Rev* 2003;**24**:313–40.
110. Tamler R. Diabetes, obesity, and erectile dysfunction. *Gend Med* 2009;**6**(Suppl. 1):4–16.
111. Hall JE, Guyton AC, Brands MW. Pressure-volume regulation in hypertension. *Kidney Int Suppl* 1996;**55**:S35–41.

112. Hall JE, Guyton AC, Brands MJ. Control of sodium excretion and arterial pressure by intrarenal mechanisms and the renin-angiotensin system. In: Laragh JH, Brenner BM, editors. *Hypertension, pathophysiology, diagnosis, and management*. 2nd ed. New York: Raven Press; 1995. p. 1452–75.
113. Kienitz T, Quinkler M. Testosterone and blood pressure regulation. *Kidney Blood Press Res* 2008;**31**:71–9.
114. Reckelhoff JF, Zhang H, Granger JP. Testosterone exacerbates hypertension and reduces pressure-natriuresis in male spontaneously hypertensive rats. *Hypertension* 1998;**31**:435–9.
115. Reckelhoff JF, Zhang H, Srivastava K. Gender differences in development of hypertension in spontaneously hypertensive rats: role of the renin-angiotensin system. *Hypertension* 2000;**35**: 480–3.
116. Sartori-Valinotti JC, Iliescu R, Fortepiani LA, Yanes LL, Reckelhoff JF. Sex differences in oxidative stress and the impact on blood pressure control and cardiovascular disease. *Clin Exp Pharmacol Physiol* 2007;**34**:938–45.
117. Yanes L, Romero D, Iliescu R, Cucchiarelli VE, Fortepiani LA, Santacruz F, Bell W, Zhang H, Reckelhoff JF. Systemic arterial pressure response to two weeks of Tempol therapy in SHR: involvement of NO, the RAS, and oxidative stress. *Am J Physiol Regul Integr Comp Physiol* 2005;**288**:R903–908.
118. Sartori-Valinotti JC, Iliescu R, Yanes LL, Dorsett-Martin W, Reckelhoff JF. Sex differences in the pressor response to angiotensin II when the endogenous renin-angiotensin system is blocked. *Hypertension* 2008;**51**:1170–6.
119. Venegas-Pont M, Sartori-Valinotti JC, Glover PH, Reckelhoff JF, Ryan MJ. Sexual dimorphism in the blood pressure response to angiotensin II in mice after angiotensin-converting enzyme blockade. *Am J Hypertens* 2010;**23**:92–6.
120. Xue B, Pamidimukkala J, Hay M. Sex differences in the development of angiotensin II-induced hypertension in conscious mice. *Am J Physiol Heart Circ Physiol* 2005;**288**:H2177–2184.
121. Chen YF, Naftilan AJ, Oparil S. Androgen-dependent angiotensinogen and renin messenger RNA expression in hypertensive rats. *Hypertension* 1992;**19**:456–63.
122. Ellison KE, Ingelfinger JR, Pivor M, Dzau VJ. Androgen regulation of rat renal angiotensinogen messenger RNA expression. *J Clin Invest* 1989;**83**:1941–5.
123. Ji H, Menini S, Zheng W, Pesce C, Wu X, Sandberg K. Role of angiotensin-converting enzyme 2 and angiotensin(1-7) in 17beta-oestradiol regulation of renal pathology in renal wrap hypertension in rats. *Exp Physiol* 2008;**93**:648–57.
124. Nickenig G, Baumer AT, Grohe C, Kahlert S, Strehlow K, Rosenkranz S, Stablein A, Beckers F, Smits JF, Daemen MJ, Vetter H, Bohm M. Estrogen modulates AT1 receptor gene expression in vitro and in vivo. *Circulation* 1998;**97**:2197–201.
125. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ. Comparative Risk Assessment Collaborating G: selected major risk factors and global and regional burden of disease. *Lancet* 2002;**360**:1347–60.
126. Mosca L, Banka CL, Benjamin EJ, Berra K, Bushnell C, Dolor RJ, Ganiats TG, Gomes AS, Gornik HL, Gracia C, Gulati M, Haan CK, Judelson DR, Keenan N, Kelepouris E, Michos ED, Newby LK, Oparil S, Ouyang P, Oz MC, Petitti D, Pinn VW, Redberg RF, Scott R, Sherif K, Smith Jr SC, Sopko G, Steinhorn RH, Stone NJ, Taubert KA, Todd BA, Urbina E, Wenger NK, Expert Panel/Writing G, American Heart A, American Academy of Family P, American College of O, Gynecologists, American College of Cardiology F, Society of Thoracic S, American Medical Women's A, Centers for Disease C, Prevention, Office of Research on Women's H, Association of Black C, American College of P, World Heart F, National Heart L, Blood I, American College of Nurse P. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation* 2007;**115**:1481–501.
127. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, Roccella EJ, National Heart L, Blood Institute Joint National Committee on Prevention DE, Treatment of High Blood P, National High Blood Pressure Education Program Coordinating C. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *J Am Med Assoc* 2003;**289**:2560–72.
128. Kim JK, Alley D, Seeman T, Karlamangla A, Crimmins E. Recent changes in cardiovascular risk factors among women and men. *J Womens Health (Larchmt)* 2006;**15**:734–46.
129. Ong KL, Cheung BM, Man YB, Lau CP, Lam KS. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. *Hypertension* 2007;**49**:69–75.
130. Ong KL, Tso AW, Lam KS, Cheung BM. Gender difference in blood pressure control and cardiovascular risk factors in Americans with diagnosed hypertension. *Hypertension* 2008;**51**: 1142–8.
131. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D. Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension* 1995;**25**: 305–13.
132. Routledge FS, McFetridge-Durdle JA, Dean CR. Stress, menopausal status and nocturnal blood pressure dipping patterns among hypertensive women. *Can J Cardiol* 2009;**25**: e157–163.
133. Forman JP, Stampfer MJ, Curhan GC. Diet and lifestyle risk factors associated with incident hypertension in women. *J Am Med Assoc* 2009;**302**:401–11.
134. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH, American Heart A, Obesity Committee of the Council on Nutrition Physical Activity, and Metabolism. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2006;**113**:898–918.
135. Reckelhoff JF, Granger JP. Role of androgens in mediating hypertension and renal injury. *Clin Exp Pharmacol Physiol* 1999;**26**: 127–31.
136. Fortepiani LA, Zhang H, Racusen L, Roberts 2nd LJ, Reckelhoff JF. Characterization of an animal model of postmenopausal hypertension in spontaneously hypertensive rats. *Hypertension* 2003; **41**:640–5.
137. Yanes LL, Romero DG, Cucchiarelli VE, Fortepiani LA, Gomez-Sanchez CE, Santacruz F, Reckelhoff JF. Role of endothelin in mediating postmenopausal hypertension in a rat model. *Am J Physiol Regul Integr Comp Physiol* 2005;**288**:R229–233.
138. Yanes LL, Romero DG, Iles JW, Iliescu R, Gomez-Sanchez C, Reckelhoff JF. Sexual dimorphism in the renin-angiotensin system in aging spontaneously hypertensive rats. *Am J Physiol Regul Integr Comp Physiol* 2006;**291**:R383–390.
139. Lima R, Yanes LL, Davis DD, Reckelhoff JF. Roles played by 20-HETE, angiotensin II and endothelin in mediating the hypertension in aging female spontaneously hypertensive rats. *Am J Physiol Regul Integr Comp Physiol* 2013;**304**:R248–251.
140. Reckelhoff JF, Wofford M. Hypertension in women. In: Goldman MB, Troisi R, Rexrode KM, editors. 2nd ed. New York: Elsevier; 2013. p. 1–11.
141. Tofovic SP, Dubey R, Salah EM, Jackson EK. 2-Hydroxyestradiol attenuates renal disease in chronic puromycin aminonucleoside nephropathy. *J Am Soc Nephrol* 2002;**13**:2737–47.
142. Neugarten J, Acharya A, Lei J, Silbiger S. Selective estrogen receptor modulators suppress mesangial cell collagen synthesis. *Am J Physiol Renal Physiol* 2000;**279**:F309–318.

143. Hadjadj S, Gourdy P, Zaoui P, Guerci B, Roudaut N, Gautier JF, Chabin M, Mauco G, Ragot S, Group RS. Effect of raloxifene – a selective oestrogen receptor modulator – on kidney function in post-menopausal women with Type 2 diabetes: results from a randomized, placebo-controlled pilot trial. *Diabet Med* 2007;**24**:906–10.
144. Melamed ML, Blackwell T, Neugarten J, Arnsten JH, Ensrud KE, Ishani A, Cummings SR, Silbiger SR. Raloxifene, a selective estrogen receptor modulator, is renoprotective: a post-hoc analysis. *Kidney Int* 2011;**79**:241–9.
145. ERA-EDA registry annual report; 2010. www.espn-reg.org.
146. Carrero JJ, de Jager DJ, Verduijn M, Ravani P, De Meester J, Heaf JG, Finne P, Hoitsma AJ, Pascual J, Jarraya F, Reisaeter AV, Collart F, Dekker FW, Jager KJ. Cardivascular and noncardiovascular mortality among men and women starting dialysis. *Clin J Am Soc Nephrol* 2011;**6**:1722–30.
147. www.cdc.gov/diabetes/statitics/esrd.

QUESTIONS AND ANSWERS

Question 1

A 45-year-old woman with CKD presents to your office with nausea, vomiting, and anorexia. She is found to have an eGFR of 8 mL/min and is referred for initiation of chronic maintenance hemodialysis.

Which one of the following is true regarding the relationship between gender and CKD?

A. The incidence rate of ESRD is greater in men than in women
B. The prevalence of ESRD is greater in women than in men
C. The prevalence of stages 3–5 CKD not requiring dialysis in the US population is greater in men than in women
D. The prevalence of proteinuria in the US population is greater in men than women
E. Male gender confers a survival advantage in ESRD

Answer: A

The incidence rate of ESRD in the US is 60% greater in men compared with women.[24,30,32–34,38,145,146] B is incorrect. Both the incidence and prevalence of ESRD is greater in men than women. C and D are incorrect. Despite the fact that the prevalence of stages 3–5 CKD is greater in women than in men, the incidence of ESRD is greater in men. NHANES data indicate that the prevalence of an eGFR less than 60 mL/min/1.723 m^2 is 7.7% in women vs. 5.6% in men and the prevalence of ACR >30 mg/g creatinine is 10.2% in women vs. 8.6% in men.

Question 2

A 50-year-old woman with long-standing diabetes mellitus presents to your office for evaluation of hypertension, microalbuminuria, and an eGFR of 47 mL/min.

Which one of the following is true regarding the relationship between gender and diabetic nephropathy?

A. Sex hormone metabolism is dysregulated in diabetes mellitus
B. There is no gender disparity in the renal hemodynamic response to hyperglycemia
C. The incidence of diabetes-related ESRD is greater in women than in men
D. The prevalence of diabetes-related ESRD is greater in women than in men
E. Women initiate RRT at a higher GFR than do men

Answer: A

There is substantial evidence that sex hormone synthesis and metabolism is disturbed in diabetes mellitus. However, data are conflicting as to the nature of this dysregulation. B is incorrect. During clamped hyperglycemia, males do not exhibit any change in renal hemodynamics, whereas females show a decrease in ERPF and increases in renal vascular resistance and filtration fraction. C and D are incorrect. Both the incidence and prevalence of diabetes-related ESRD is greater in men than in women. The incident rate of diabetes-related ESRD in the US is 24% greater in men. E is incorrect. Women initiate renal replacement therapy at a lower GFR than do men both in Europe and the US.[24,32,38,65,68,105,147]

Question 3

Which one of the following is true regarding the effect of estrogen on the TGF-beta signaling cascade?

A. Estrogen reduces the bioavailability of the transcription factor SP1 to transactivate the type IV collagen gene promoter
B. Estrogen decreases ubiquitization and degradation of Smad2/3
C. Estrogen increases the density of TGF-beta receptors types I and II in experimental diabetes
D. Estrogen increases the synthesis and release of TGF-beta by mesangial cells and podocytes in experimental models of renal disease
E. Estrogen increases the expression of endothelin which in turn increases generation of TGF-beta

Answer: A

TGF-beta activates a serine/threonine protein kinase, protein kinase CK2, which leads to an increase in the quantity of free Sp1 available to transactivate the collagen IV promoter. Estradiol reverses TGF-beta stimulated type IV collagen gene transcription by preventing TGF-beta-induced activation of CK2. B is incorrect. Estrogen receptor alpha forms a ternary complex with Smad2/Smad3 and the ubiquitin ligase Smurf which in turn enhances ubiquitization and degradation of these Smad proteins and inhibits TGF-beta signal transduction. C is incorrect. Estradiol reverses the increased expression of TGF-beta receptors types I and II in experimental diabetes. D is incorrect. Estrogen decreases TGF-beta expression by mesangial cells and podocytes in numerous models of experimental renal disease. E is incorrect. Estrogen decreases and testosterone increases endothelin expression.[4,79,81,82]

Question 4

Which one of the following statements about the effects of sex hormones on mesangial cell and podocyte apoptosis is false?

A. Testosterone induces apoptosis in podocytes
B. Testosterone induces apoptosis in proximal tubule cells
C. Estrogen reverses TGF-beta-induced apoptosis in mesangial cells
D. Estrogen reverses podocyte apoptosis in an experimental model of renal disease induced by puromycin aminonucleoside
E. Testosterone reverses TGF-beta-induced podocyte apoptosis

Answer: E

Estrogen protects podocytes from apoptosis induced by testosterone, TGF-beta, TNF-alpha, and puromycin aminonucleoside. In addition, estrogen antagonizes TGF-beta-induced mesangial cell apoptosis. Testosterone induces podocyte apoptosis *in vivo* and *in vitro* and also promotes apoptosis of human proximal tubular cells.[80,91–93]

Question 5

Which one of the following is true regarding the effect of sex hormones on the generation of ROS?

A. Estrogen increases the generation of ROS
B. Estrogen upregulates NADPH oxidase
C. Interactions between testosterone and ROS mediate the renoprotective effects of testosterone
D. Testosterone upregulates cellular antioxidant defense systems
E. Interactions between sex hormones and the generation of ROS influence the course of several experimental models of hypertension

Answer: E

Enhanced generation of ROS has been shown to contribute to renal damage in experimental models of renal disease. In several experimental models of hypertension, reversal of renal injury by estrogen and exacerbation of injury by testosterone is mediated by the ability of sex hormones to modulate ROS generation. A and B are incorrect. Estrogen blunts the upregulation of nicotinamide adenosine dinucleotide phosphate oxidase activity induced by renal injury, which in turn suppresses the generation of superoxide anion, the major ROS produced by the kidney. C and D are incorrect. Testosterone increases oxidative stress and promotes renal injury. Testosterone inhibits antioxidant enzymes and amplifies the generation of ROS in response to renal insults.[90]

Question 6

A 60-year-old man with a history of long-standing hypertension presents for management of uncontrolled hypertension.

Which one of the following is true regarding the effect of gender on the renin-angiotensin axis and on the development and severity of hypertension?

A. The prevalence of hypertension is greater in premenopausal women compared with age-matched men
B. The prevalence of hypertension is greater in postmenopausal women compared with age-matched men
C. Estrogen reduces angiotensinogen levels
D. Estrogen increases the density of AT-1 receptors
E. The renal hemodynamic response to angiotensin II infusion is equivalent in men and women

Answer: B

The prevalence of hypertension is greater in postmenopausal women compared with age-matched men, but this relationship is reversed in premenopausal women. C and D are incorrect. Sex steroids affect the components of the renin-angiotensin system. Estrogens stimulate liver angiotensinogen synthesis but attenuate expression of AT1 receptors and ACE, whereas androgens increase renal synthesis of angiotensinogen. Estrogens also upregulate ACE2 to produce angiotensin (1–7), which has vasodilatory properties. E is incorrect. Men respond to an infusion of angiotensin II by maintaining their GFR at the expense of an increased filtration fraction. In contrast, women show a decrease in GFR and ERPF without any change in filtration fraction.[100,123,125,127–130]

CHAPTER

8

Ethnicity and Chronic Kidney Disease—United States

Keith C. Norris[a], *Allen R. Nissenson*[a,b]

[a]Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA, United States; [b]DaVita, Inc., Denver, CO, United States

Abstract

Chronic kidney disease (CKD) is a noncommunicable disease that is now well recognized as a major cause of premature morbidity and mortality. Racial/ethnic minorities have an increased prevalence of key risk factors such as diabetes mellitus and hypertension, as well as being 1.5–3 times more likely than their non-Hispanic White counterparts to reach end-stage renal disease (ESRD). While the term race represents a social/political construct, its association with health is complex. The term race is actually a misnomer as *Homo sapiens* is the only extant human species, so there is only one race. Thus, variations in groups of humans that share similar physical appearances, language, culture, and/or biology linked to ancestral geographic origins might more appropriately be classified as ethnicity. Understanding how the race/ethnicity interacts to influence CKD and ESRD risk, progression, and complications in the US is critical to advancing the care of all patients with kidney disease.

INTRODUCTION

We don't see things as they are, we see them as we are **Anais Nin (1903–1977)**

Chronic kidney disease (CKD) is epidemic in the US. CKD is a noncommunicable disease that is now well recognized as a major cause of premature morbidity and mortality.[1] Multiple aspects of CKD, ranging from the risk and development to progression and complications, differ by race/ethnicity and are among the starkest examples of health disparities in the US.[2,3] This is highlighted by racial/ethnic minorities having a nearly 2-fold higher incidence rate of diabetes mellitus (DM), the leading cause of CKD, as well as a 1.5- to 3-fold greater incidence of end-stage renal disease (ESRD) compared with their age-adjusted non-Hispanic White peers.[4,5] This chapter describes the current status of CKD and ESRD risk, complications, and care in the US and explores the social and biologic factors that interact to influence racial/ethnic differences in CKD/ESRD risk and outcomes.

HEALTHY PEOPLE 2020

The elimination of racial and ethnic disparities across all stages of CKD is widely recognized in nephrology as an important approach to understand and ultimately improve overall patient outcomes.[2,6–8] It is also one of the target areas for Healthy People 2020, our nation's blueprint for health.[9] The finding of increased rates of ESRD among racial/ethnic minorities Americans in the late 1970s and early 1980s[10–12] prompted the need to better understand the issues underlying both ESRD incidence and quality care for all groups of patients receiving renal replacement therapy (RRT).[13–16] A response to these early findings was the introduction of national ESRD performance measures and quality standards.[17,18] These national performance measures have led to a substantial improvement in the quality of care and a reduction in disparities for patients receiving RRT.[17,18] However, our work has just begun. In evaluating kidney disease-related racial/ethnic disparities, it is critical that we view this issue through two distinct lenses, one viewing race as a social construct and one as ancestral biological variants. Thus, outcomes for patients in varying settings with or at risk for CKD are influenced by the social determinants of health, juxtaposed with geo-evolutionary risk and resilience gene variants. Through this understanding, the nephrology community can move closer to creating more effective

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00008-5

solutions to eliminate disparities and to use the lessons learned to improve outcomes for all patients.

DEFINING RACE AND ETHNICITY

The concept and use of the terms race and ethnicity are deeply integrated into our nation's social fabric. There is no generally agreed on definition for these terms, but it is clear that they carry complex nuances reflecting social position, political status, culture, economics, and history juxtaposed with differing frequencies of particular gene variants that reflect ancestral geographic origins.[19] Race and ethnicity can mean different things to different people, may have different implications in different settings, and a person's designation can change in a particular place and/or time. Historically, the use of the term race in the US derives from Carl Linnaeus, the father of modern taxonomy. Linnaeus designated four major "racial" groups by geographic region (Europe, Asia, Americas, and Africa), and then assigned each racial category select personality traits, skills, and abilities,[20] with the more desirable traits ascribed to White Europeans and the least desirable traits ascribed to Black Africans. This designation was viewed as an actual scientific fact and helped to establish the "scientific" foundation for racism.[21] By contrast, the actual science, including recent DNA analysis of different groups of people, confirmed that there are in fact no distinct populations within or that differ from modern *Homo sapiens*.[22] However, the US Census reporting still uses the original Linnaeus-based race categories—White, American Indian or Alaska Native, Asian, and Black or African American—with a fifth category added in 2000 for Native Hawaiian or other Pacific Islander.[23–25] The US Office of Management and Budget uses two major ethnic categories for each person: (1) not Hispanic or Latino and (2) Hispanic or Latino, regardless of race.[23,24] Clearly a decision to divide the world into two ethnic groups also has no scientific merit. These categories thus reflect not scientific differences among groups but the social, political, cultural, economic, and historical influences that provide access and opportunity in a society and its impact on multiple dimensions of being, including health.

A scientifically accurate view that humans are a single race is held by the Pan American Health Organization/World Health Organization, which does not use the term race and uses the term ethnicity to capture differences between groups of individuals that share common linguistic, cultural, and ancestral backgrounds.[26] Consistent with this, the terms "ethnicity" and "race" will be used as the combined term race/ethnicity in this chapter, not only recognizing that different races do not exist but different ethnic groups do but also acknowledging that the use of the term race persists in the US for categorizing people by governmental agencies, including health and educational systems.[26]

RACE/ETHNICITY AND HEALTH

Racial/ethnic minorities now comprise nearly 40% of the US population,[27] highlighting the importance of optimizing minority health to improve the overall health of our nation. However, given the political and social underpinnings of race and ethnicity in the US, and the persistence of structural racism, it is not surprising that minorities continue to suffer from worse health outcomes in most domains. This is because health outcomes stratified by race/ethnicity are strongly influenced by a group's social position/exclusion, marginalization, discrimination, and the associated socioecologic determinants of health such as residential segregation,[28] educational and income inequalities,[29–32] imbalance in community-level assets, access to care,[6] health care resources,[33–35] and exposure to environmental toxins.[7,36] Additional factors include health system barriers, unconscious provider biases, medical mistrust, patient beliefs and behaviors, and stereotype threat.[37–40] Stereotype threat is a more recently recognized concept in health care and refers to the fear of being judged by, and/or confirming through one's own actions, negative group stereotypes that operate within the domain of health care, such as inferior intelligence, lower social status, greater likelihood of engaging in risky behaviors, and less deserving of high quality care.[39] Despite the passing of civil rights legislation in the 1960s, the above issues are promulgated by judicial and institutional policies, practices, and beliefs that maintain many of the racialized precivil rights structural elements and thus perpetuate many of the persisting disparities by race/ethnicity and gender.

CKD PREVALENCE AND MAJOR CHRONIC KIDNEY DISEASE RISK FACTORS

Based on estimates from the National Health and Nutrition Examination Survey (NHANES), the overall prevalence of CKD in the US has slowly increased, and this increase is present in all racial/ethnic groups. The 1988-1994 NHANES compared with the 2011-2012 NHANES estimated prevalence of CKD stages 1–4 for

TABLE 8.1 Select Chronic Kidney Disease Risk Factors by Ethnicity

	Hispanic	Asian	Native American	Black/African American	White
Prevalence of age-adjusted diagnosed diabetes for adults aged 18 years or older, 2013–2015 (%)[46]	12.1	8	15.1	12.7	7.4
Age-adjusted prevalence of hypertension among adults aged 18 and over, 2015–2016 (%)[47,48]	27.8	25.0	26.4	40.3	27.8
Age-adjusted prevalence of controlled hypertension among adults with hypertension aged 18 and over, 2015–2016 (%)[47]	45	37.4	Not available	44.6	50.8
Prevalence of overweight/obese (age-adjusted) (%)[27]	69.9	42	70.5	72	64.1

TABLE 8.2 Select Socioeconomic Factors by Race/Ethnicity

	Hispanic	Asian	Native American	Black/African American	White
Self-reported overall health status as fair or poor[27]	25.2	10.8	28.7	22.1	16.4
% Below federal poverty level[27]	16	9	22	20	8
Uninsured, nonelderly[27]	19	7	22	11	7
Graduation rate from public high school (%)[50]	79	91	72	76	88
No personal doctor or health care provider[27]	39	23	29.2	22.3	18

non-Hispanic Whites at 11.8 vs. 14.1%, non-Hispanic Blacks 13.7 vs. 17.3%, and for other 10.1 vs. 12.7%.[41] However, when the estimates were restricted to CKD stages 3 and 4, the authors found the rates for non-Hispanic Whites at 5.4 vs. 8.0%, non-Hispanic Blacks 3.7 vs. 6.2%, and for other 2.2 vs. 3.6%.[41] These findings suggest White patients with CKD are more likely to progress to stages 3 and 4 but appear less likely to progress to ESRD, especially because racial/ethnic minorities have a higher mortality rate among persons with CKD, especially those below 65 years of age.[42]

Diabetes and hypertension are the two leading causes of patients progressing to ESRD.[43] In addition, obesity/overweight is an emerging CKD risk factor as well as a noncommunicable public health epidemic, whereas albuminuria is an important CKD progression factor. Compared with their White peers, most racial/ethnic minorities have a higher prevalence of diabetes, hypertension, and obesity/overweight, as well as albuminuria (Table 8.1).[27,44,45]

SOCIAL DETERMINANTS OF HEALTH

The self-reported overall health status varies by race/ethnicity, with 20.5% of African Americans, 25.6% of Hispanics, 27% of Native Americans, 9% of Asians, and 15.7% of Whites reporting fair or poor health status.[27] This discrepancy is driven in part by many of the social determinants of health, which disproportionally affect minority and low-income populations adversely. Social determinants of health include factors such as access to providers/care, educational attainment, income, insurance, and community-level assets and deficits.[3,49] In general, compared with their White peers, racial/ethnic minorities are more likely to report having no personal doctor or health care provider, be below the federal poverty line, be uninsured, and have lower graduation rates at public high schools (Table 8.2).[27,50]

These adverse social characteristics are highly relevant for patients with CKD. An analysis of participants with or at risk for CKD in the National Kidney Foundation

Kidney Early Evaluation Program (KEEP) screening program found uninsured KEEP participants were 72% more likely to develop ESRD and 82% more likely to die than those with private insurance.[51] Similarly, Choi et al. found a nearly 20% higher adjusted relative risk of death for KEEP participants with CKD and less than high school education, compared with those with high school education or greater, followed over a mean follow-up period of 3.9 years.[31] A situation similar to limited educational attainment exists regarding low levels of literacy. An analysis of participants in the Chronic Renal Insufficiency Cohort study found 28% of African Americans and 5% of Whites had limited health literacy.[52] Limited health literacy in patients with CKD has been associated with increased hospitalizations, emergency department use, cardiovascular events, and mortality.[53] Cavanagh and colleagues found limited health literacy in dialysis patients was associated with a 54% higher risk for death and was more likely in be present in males, racial/ethnic minorities, and those with fewer years of education.[54] Thus, adverse social determinants of health have a major impact on CKD outcomesand they remain disproportionately prevalent in many racial/ethnic minority communities.

CKD QUALITY OF CARE

The Agency for Healthcare Research and Quality examined racial/ethnic differences in 182 national quality measures and reported areas where there was improvement, no difference or worsening. They found, compared with White patients, no difference or worsening in 87% of quality measures for Blacks, 78% for Hispanics, 87% for American Indian/Alaskan Natives, 76% for Native Hawaiian/Pacific Islanders, and 66% for Asians.[55] In addition, Blacks, Hispanics, and American Indian/Alaskan Natives had worsening in more than twice as many quality of care measures than they had improvement.[55] Details regarding improvement, no difference, or worsening of quality measures by race/ethnicity are provided in Table 8.3.

However, for CKD and major CKD-specific quality care metrics, there has been more substantial improvement noted by Healthy People 2020 (Table 8.4).[43,56] This includes a substantial increase in and reduced disparity over the last 10–12 years in the percent of racial/ethnic minorities diagnosed with DM who obtained an annual evaluation of urinary albumin, the percent of persons with DM and CKD who received a more comprehensive medical assessment and received recommendation regarding medical treatment with inhibitors of the renin angiotensin system, the percent of patients receiving care from a nephrologist at least 12 months prior to the start of RRT and others (Table 8.4). Because the number of patients receiving RRT has increased while the number of kidney transplants has remained flat, the percent of all patients receiving a kidney transplant has progressively fallen (Table 8.4).

Interestingly, despite an overall decline in the death rate for patients receiving dialysis treatments, the death rate for White dialysis patients remains above the Healthy People 2020 target level (Table 8.4). The reason for this observation is not clear, but a possible survival bias could lead to healthier minorities reaching dialysis or other resilience factors in the setting of chronic disease could account for the observed differences.[42,57–61]

ESRD TREATMENT MODALITIES

Despite a fairly similar prevalence of the early stages of CKD, and a lower prevalence of CKD stages 3 and 4, racial/ethnic minorities are 1.5–3 times more likely than their non-Hispanic White peers to progress to ESRD and require RRT.[4,5,41] In the US, the preferred options for RRT are kidney transplantation or home dialysis,[62] yet, racial/ethnic minorities are less likely to receive RRT with either a kidney transplant or home dialysis therapy.[63] These findings highlight the continuing need for efforts to achieve greater equity in the use of the preferred ESRD treatment options.

TABLE 8.3 Agency for Healthcare Research and Quality Racial/Ethnic Differences in 182 National Quality Measures Compared with Whites (Not all Measures Included all Groups, so Totals May Not = 182)

Change in Quality Metrics	Hispanic	Asian	American Indian/ Alaskan Natives	Black/African American	Native Hawaiian/ Pacific Islanders
Improved (n)	37	55	12	23	12
No difference (n)	66	76	50	82	24
Worsened (n)	65	32	31	77	14

TABLE 8.4 Healthy People 2020 (HP 2020) Select Markers of Chronic Kidney Disease (CKD) Care by Race/Ethnicity

	Hispanic	Asian	Native American	Black/African American	White	HP 2020 Target
% Persons with diagnosed DM who obtain an annual urinary microalbumin measurement	50.5 (2015)	53.4 (2015)	30.1 (2015)	46.0 (2015)	47.5 (2015)	37 (2015)
	31.5 (2006)	33.8 (2006)	19.8 (2006)	29.5 (2006)	31.4 (2006)	31 (2006 average)
% Persons with DM and CKD who receive medical evaluation with serum creatinine, lipids, and A1c, microalbuminuria, and eye exams	32.1 (2015)	32.9 (2015)	18.0 (2015)	27.6 (2015)	30.2 (2015)	25.3 (2015)
	20.3 (2006)	26.2 (2006)	12.4 (2006)	18.8 (2006)	21.4 (2006)	21.2 (2006 average)
% Persons with DM and CKD who receive recommended medical treatment with ACEI or ARB	77.1 (2015)	76.5 (2015)	74.4 (2015)	72.3 (2015)	70.2 (2015)	76.3 (2015)
	69.1 (2006)	70.3 (2006)	60.2 (2006)	66.7 (2006)	62.2 (2006)	63.6 (2006 average)
% CKD patients receiving nephrologist care at least 12 months before start of renal replacement therapy	28.1 (2015)	37.6 (2015)	34.9 (2015)	32 (2015)	37 (2015)	30.4 (2015)
	19.8 (2006)	23.9 (2006)	27.3 (2006)	23.2 (2006)	27.9 (2006)	26.4 (2006 average)
Rate of new cases of ESRD/million population	492 (2015)	314.9 (2015)	376 (2015)	895 (2015)	312.1 (2015)	352 (2015)
	21.1 (2006)	355.4 (2006)	526.9 (2006)	1114 (2006)	294 (2006)	398.9 (2006 average)
% Patients receiving a kidney transplant within 3 years of ESRD	11.0 (2012)	16.2 (2012)	7.2 (2012)	7 (2012)	16.2 (2012)	20.1 (2012)
	14.7 (2006)	19.1 (2006)	10.0 (2006)	9.1 (2006)	21 (2006)	17.2 (2006 average)
Number of deaths per 1000 patient years for persons on dialysis	128.5 (2015)	126.4 (2015)	152.9 (2015)	135.8 (2015)	207.4 (2015)	187.4 (2015)
	156.9 (2006)	153.7 (2006)	171.1 (2006)	170.9 (2006)	258.1 (2006)	216.7 (2006 average)

ACEI, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin II receptor blocker; *DM*, diabetes mellitus; *ESRD*, end-stage renal disease.
Source: USRDS 2017.[43]

ESRD QUALITY CARE METRICS

Ongoing quality improvement measures have eliminated individual-level racial/ethnic disparities for most metrics such as dialysis adequacy and anemia. Interestingly, disparities persist at the facility level, with lower levels of dialysis adequacy and higher rates of anemia reported in patients treated in dialysis facilities within neighborhoods with a higher proportion of African Americans.[64,65] These disparities persist even after controlling for neighborhood-level socioeconomic status and other factors in some,[64] but not all, studies.[65] Interestingly, when examining facility-level hemoglobin (Hb) targets by the percentage of African-Americans patients per facility, rather than by neighborhood, there was no difference in anemia-related quality measures.[65]

These findings reinforce the need to better understand and further explore the social determinants of health that drive facility/community-level outcomes to further advance efforts to achieve equity in treatment care at dialysis facilities, regardless of facility location or patient case mix.

IMPACT OF CHANGES IN ESRD REGULATORY PRACTICES ON RACIAL/ETHNIC DISPARITIES

Although there has been progressive improvement in quality care for racial/ethnic minorities over the last 25 years, concerns have been raised that these gains may have been negated by the implementation of the 2011 Medicare ESRD prospective payment system (PPS) and the simultaneous FDA-mandated manufacturer label changes to lower recommended Hb targets. Either of these could lead to more restricted erythrocyte-stimulating agent (ESA) use, increased rates of anemia, and subsequently worse outcomes.[66,67] Medicare ESRD PPS changes could also lead to poorer bone and mineral disorder (BMD) outcomes.[67] Anemia and BMDs are of particular concern, given the historically higher doses of ESA and vitamin D needed to maintain target Hb and parathyroid hormone (PTH) levels, respectively, in Blacks. A pre-post PPS analysis by Turenne and colleagues of over 7000 patients treated at 132 dialysis facilities from the Dialysis Outcomes and

Practice Patterns Study Practice Monitor found overall mean Hb levels fell from 11.5 to 11.0 g/dL and mean EPO dose declined from 20,506 to 14,777 U/week, with no meaningful differences by race/ethnicity.[68]

Similar to the potential impact of anemia management and outcomes, the PPS is likely to affect the dosing of vitamin D and related medications used to treat BMDs. The dose of vitamin D needed to maintain target PTH levels and the relationship between PTH levels, serum phosphate levels, and fibroblast growth factor 23, and bone fractures, bone histology, or mortality differs across racial/ethnic groups.[68–73] Following the implementation of 2011 Medicare ESRD PPS cost-saving measures, Turenne et al. found mean serum iPTH increased from 340 to 435 pg/mL, but these changes did not differ by race/ethnicity.[68]

In addition, Wang et al. examined cardiovascular outcomes following the PPS and ESA labeling changes in 2011 and found no overall difference before and after the changes among fee-for-service Medicare patients, with the exception of an 18% reduction in cardiovascular events that was observed in a secondary analysis of Black patients, suggesting the new policies had no adverse impact overall or by race/ethnicity, with a possible beneficial effect on Black patients.[74]

PRE-ESRD NEPHROLOGIST CARE AND VASCULAR ACCESS

Several markers of pre-ESRD care are linked to outcomes for patients receiving RRT, and the lack of or delay in establishing pre-ESRD care is associated with increased risk of death following transition to RRT.[75–77] Unfortunately, there has been little change over the last 15–20 years in the disparities related to pre-ESRD nephrology care.[75–79] Despite the introduction of the ESRD (and pre-ESRD) quality care initiatives in the early 1990s, Gillespie et al. reported in 2015 that more than 12 months of pre-ESRD care was less frequent in African Americans, Asians, Native Americans, and Hispanics.[76] These findings are reinforced by a report from Yan et al. who found a lower state-level probability of Blacks having received nephrologist care 12 months prior to dialysis, more so in younger Black patients.[80] The finding was attenuated for older Blacks, who were more likely to have had Medicare insurance coverage during the per-ESRD period, suggesting insurance has a major influence on racial disparities in the pre-ESRD period.[80]

Although the use of an arteriovenous fistula (AVF) at first hemodialysis treatment is associated with superior clinical outcomes, the use of an AVF at the first dialysis treatment remains a major area of racial/ethnic and gender disparities in dialysis care.[81,82] Analyzing a cohort of nearly 400,000 dialysis patients, Zarkowsky et al. found Hispanic and Black patients were less likely to initiate hemodialysis with an AVF than their non-Hispanic White peers, independent of insurance status, despite having fewer comorbidities and being younger.[83] Like pre-ESRD nephrologist visits, factors in addition to insurance, such as medical mistrust, health system barriers, health literacy, provider and patient biases, social determinants, and others that could account for these differences, require further investigation to create policies which might eliminate or diminish pre-ESRD disparities.[7,38,40,83,84]

SURVIVAL ON DIALYSIS

Despite higher rates of lower quality of ESRD care, observational data have consistently shown that racial/ethnic minorities receiving dialysis treatments have greater survival rates than their peer majority groups, even after adjusting for age, gender, and transplantation.[57–60,85–90] The observation that minority groups treated with dialysis have greater survival than their majority peers is not limited to the US.[86–88] In the US, Hispanics have a higher adjusted survival rate than non-Hispanics at every age, whereas the Black-White survival difference appears to vary by age, as there are significantly better survival rates for Blacks above 40 or 50 years of age compared with Whites, but younger Black and White patients have similar survival rates.[57,58,60] Asians also have a higher survival rates than Whites,[91] but due to fewer numbers of Asian ESRD patients, few comparative subgroup analyses have been feasible to date.

Community factors also influence dialysis outcomes. Facilities located in communities with higher proportions of Black patients (typically characterized by lower community SES and fewer health-related community assets) have poorer survival outcomes among both Black and non-Black patients.[35,64,65,92] These findings reinforce the notion that intertwined social and economic influences may have important implications for ESRD patient outcomes.

CONCLUSION

Social and to a lesser extent biological factors appear to contribute to the more frequent need for RRT for racial/ethnic minorities, where access to and quality of care, patient behaviors, control of medical risk factor conditions, and other factors combine with CKD risk alleles to influence CKD development and progression.[3,38] Once progression to ESRD has occurred, the impact of risk factors in different race/ethnic groups may vary substantially for different quality measures and

outcomes. The impact of longstanding racialized policies and practices on the social positioning of racial/ethnic groups, and associated barriers such as limited finances, inadequate health insurance, medical distrust, unconscious provider biases, that may result in differential clinical practice decision-making and related factors influencing patients' beliefs and behaviors together, may contribute to persistent disparities in the likelihood of receiving different care for CKD, pre-ESRD, and RRT.[2,6,7,29,33,84] Importantly, as the medical and health sciences professions identify health-related differences between racial groups, the lessons learned should not only prompt new biomedical advances including personalized medicine but also stimulate advocacy for social and health policy level changes that can promote equity while ensuring the highest quality of care within our health systems and dialysis facilities, to ultimately achieve health equity and improve outcomes for all patients.[93–95]

Funding/Support

KN is supported in part by NIH research grants UL1TR000124 and P30AG021684.

Financial Disclosures

Neither of the other authors declare any relevant conflicts of interest.

References

1. Eknoyan G, Lameire N, Eckardt K, et al. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013;**3**:5–14.
2. Nicholas SB, Kalantar-Zadeh K, Norris KC. Racial disparities in kidney disease outcomes. *Semin Nephrol* 2013;**33**(5):409–15.
3. Nicholas SB, Kalantar-Zadeh K, Norris KC. Socioeconomic disparities in chronic kidney disease. *Adv Chron Kidney Dis* 2015;**22**(1):6–15.
4. USRDS. United States Renal Data System. *2015 USRDS annual data report: epidemiology of kidney disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2015.
5. Hsu CY, Lin F, Vittinghoff E, Shlipak MG. Racial differences in the progression from chronic renal insufficiency to end-stage renal disease in the United States. *J Am Soc Nephrol* 2003;**14**(11):2902–7.
6. Powe NR. Let's get serious about racial and ethnic disparities. *J Am Soc Nephrol* 2008;**19**(7):1271–5.
7. Norris K, Nissenson AR. Race, gender, and socioeconomic disparities in CKD in the United States. *J Am Soc Nephrol* 2008;**19**(7):1261–70.
8. Norris KC, Agodoa LY. Unraveling the racial disparities associated with kidney disease. *Kidney Int* 2005;**68**(3):914–24.
9. US Department of Health and Human Services: Healthy people 2020: chronic kidney disease. Available from: https://www.healthypeople.gov/2020/topics-objectives/topic/chronic-kidney-disease.
10. Rostand SG, Kirk KA, Rutsky EA, Pate BA. Racial differences in the incidence of treatment for end-stage renal disease. *N Engl J Med* 1982;**306**(21):1276–9.
11. Dillard MG, Callender CO. End-stage renal disease in blacks: a national or international problem? *J Natl Med Assoc* 1984;**76**(12):1157–8.
12. Easterling RE. Racial factors in the incidence and causation of end-stage renal disease (ESRD). *Trans Am Soc Artif Intern Organs* 1977;**23**:28–33.
13. Wright Jr JT, Kusek JW, Toto RD, et al. Design and baseline characteristics of participants in the African American Study of Kidney Disease and hypertension (AASK) pilot study. *Contr Clin Trials* 1996;**17**(4 Suppl. l):3s–16s.
14. Feldman HI, Klag MJ, Chiapella AP, Whelton PK. End-stage renal disease in US minority groups. *Am J Kidney Dis* 1992;**19**(5):397–410.
15. Norris K, Owen Jr B. Minorities and ESRD: have we seen improvements in care? *Nephrol News Issues* 1997;**11**(2):66–8.
16. Reddan DN, Szczech LA, Klassen PS, Owen Jr WF. Racial inequity in America's ESRD program. *Semin Dial* 2000;**13**(6):399–403.
17. Sehgal AR. Impact of quality improvement efforts on race and sex disparities in hemodialysis. *J Am Med Assoc* 2003;**289**(8):996–1000.
18. Owen Jr WF, Szczech LA, Frankenfield DL. Healthcare system interventions for inequality in quality: corrective action through evidence-based medicine. *J Natl Med Assoc* 2002;**94**(8 Suppl. l):83s–91s.
19. Collins FS. What we do and don't know about 'race', 'ethnicity', genetics and health at the dawn of the genome era. *Nat Genet* 2004;**36**(11 Suppl. l):S13–15.
20. Linnaeus C. *Systema naturae*. 1735.
21. Harawa NT, Ford CL. The foundation of modern racial categories and implications for research on black/white disparities in health. *Ethn Dis* 2009;**19**(2):209–17.
22. Marshall E. DNA studies challenge the meaning of race. *Science* 1998;**282**(5389):654–5.
23. Directive OS. 15. Standards for maintaining, collecting, and presenting federal data on race and ethnicity. *Fed Regist* 1997:30.
24. Registrar F. Revisions to the standards for the classification of federal data on race and ethnicity. *Fed Regist* 1997;**62**:58781–90.
25. Pew Research Center. *What census calls us: a historical timeline*. 2015. Available from: http://www.pewsocialtrends.org/interactives/multiracial-timeline/.
26. Ethnicity and Health. Pan American Health Organization/World Health Organization. In: *132nd session of the executive committee. Washington, D.C., USA*; 23–27 June 2003. Available from: http://www1.paho.org/english/gov/ce/ce132-16-e.pdf.
27. Kaiser Family Foundation. *State health facts*. 2018. https://www.kff.org/state-category/minority-health/.
28. Bruce MA, Beech BM, Sims M, et al. Social environmental stressors, psychological factors, and kidney disease. *J Investig Med* 2009;**57**(4):583–9.
29. De La Cruz-Viesca M, Chen Z, Ong PM, Hamilton D, William Jr AD. *The color of wealth in Los Angeles*. Los Angeles: Report produced by Duke University, The New School, and University of California; 2016.
30. Plantinga LC, Johansen KL, Schillinger D, Powe NR. Lower socioeconomic status and disability among US adults with chronic kidney disease, 1999-2008. *Prev Chronic Dis* 2012;**9**:E12.
31. Choi AI, Weekley CC, Chen SC, et al. Association of educational attainment with chronic disease and mortality: the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2011;**58**(2):228–34.
32. Young BA. The interaction of race, poverty, and CKD. *Am J Kidney Dis* 2010;**55**(6):977–80.
33. Mode NA, Evans MK, Zonderman AB. Race, neighborhood economic status, income inequality and mortality. *PLoS One* 2016;**11**(5):e0154535.

34. Kimmel PL, Fwu CW, Eggers PW. Segregation, income disparities, and survival in hemodialysis patients. *J Am Soc Nephrol* 2013;**24**(2): 293–301.
35. Rodriguez RA, Sen S, Mehta K, Moody-Ayers S, Bacchetti P, O'Hare AM. Geography matters: relationships among urban residential segregation, dialysis facilities, and patient outcomes. *Ann Intern Med* 2007;**146**(7):493–501.
36. Crews DC, Liu Y, Boulware LE. Disparities in the burden, outcomes, and care of chronic kidney disease. *Curr Opin Nephrol Hypertens* 2014;**23**(3):298–305.
37. World Health Organization. *A conceptual framework for action on the social determinants of health*. 2010.
38. Boulware LE, Cooper LA, Ratner LE, LaVeist TA, Powe NR. Race and trust in the health care system. *Publ Health Rep* 2003;**118**(4): 358–65.
39. Abdou CM, Fingerhut AW, Jackson JS, Wheaton F. Healthcare stereotype threat in older adults in the health and retirement study. *Am J Prev Med* 2016;**50**(2):191–8.
40. Narva AS, Norton JM, Boulware LE. Educating patients about CKD: the path to self-management and patient-centered care. *Clin J Am Soc Nephrol* 2016;**11**(4):694–703.
41. Murphy D, McCulloch CE, Lin F, et al. Trends in prevalence of chronic kidney disease in the United States. *Ann Intern Med* 2016; **165**(7):473–81.
42. Mehrotra R, Kermah D, Fried L, Adler S, Norris K. Racial differences in mortality among those with CKD. *J Am Soc Nephrol* 2008;**19**(7):1403–10.
43. Saran R, Robinson B, Abbott KC, et al. US renal data system 2017 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2018;**71**(3S1):A7.
44. Greenburg AD. 1:1 Valerie Schreiner. VP product management/ product marketing. Blackboard. *Wainhouse Res Bull* 2013;**14**(5): 7–11.
45. Bryson CL, Ross HJ, Boyko EJ, Young BA. Racial and ethnic variations in albuminuria in the US Third National Health and Nutrition Examination Survey (NHANES III) population: associations with diabetes and level of CKD. *Am J Kidney Dis* 2006;**48**(5):720–6.
46. Centers for Disease Control and Prevention. *National diabetes statistics report*. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2017.
47. Fryar CD, Ostchega Y, Hales CM, Zhang G, Kruszon-Moran D. Hypertension prevalence and control among adults: United States, 2015–2016. *NCHS Data Brief* 2017;(289):1–8.
48. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation* 2018;**137**(12):e67–492.
49. National Center for Health Statistics. *Health, United States, 2015: with special feature on racial and ethnic health disparities*. 2016. Hyattsville, MD.
50. *National center for education statistics public high school graduation rates*. 2018. https://nces.ed.gov/programs/coe/indicator_coi.asp.
51. Jurkovitz CT, Li S, Norris KC, et al. Association between lack of health insurance and risk of death and ESRD: results from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2013;**61**(4 Suppl. 2):S24–32.
52. Ricardo AC, Yang W, Lora CM, et al. Limited health literacy is associated with low glomerular filtration in the Chronic Renal Insufficiency Cohort (CRIC) study. *Clin Nephrol* 2014;**81**(1): 30–7.
53. Taylor DM, Fraser S, Dudley C, Oniscu GC, Tomson C, Ravanan R, Roderick P. ATTOM investigators. Health literacy and patient outcomes in chronic kidney disease: a systematic review. *Nephrol Dial Transplant* 2018;**33**(9):1545–58.
54. Cavanaugh KL, Wingard RL, Hakim RM, et al. Low health literacy associates with increased mortality in ESRD. *J Am Soc Nephrol* 2010; **21**(11):1979–85.
55. Cash E, Salmon P, Weissbecker I, et al. Mindfulness meditation alleviates fibromyalgia symptoms in women: results of a randomized clinical trial. *Ann Behav Med* 2015;**49**(3):319–30.
56. Healthy People - Development of the National Health Promotion and Disease Prevention Objectives for 2030 @ https://www.healthypeople.gov/2020/About-Healthy-People/Development-Healthy-People-2030.
57. Kucirka LM, Grams ME, Lessler J, et al. Association of race and age with survival among patients undergoing dialysis. *J Am Med Assoc* 2011;**306**(6):620–6.
58. Yan G, Norris KC, Yu AJ, et al. The relationship of age, race, and ethnicity with survival in dialysis patients. *Clin J Am Soc Nephrol* 2013;**8**(6):953–61.
59. Kalantar-Zadeh K, Kovesdy CP, Norris KC. Racial survival paradox of dialysis patients: robust and resilient. *Am J Kidney Dis* 2012;**60**(2):182–5.
60. Rhee CM, Lertdumrongluk P, Streja E, et al. Impact of age, race and ethnicity on dialysis patient survival and kidney transplantation disparities. *Am J Nephrol* 2014;**39**(3):183–94.
61. Laster M, Norris KC. Lesson learned in mortality and kidney transplant outcomes among pediatric dialysis patients. *J Am Soc Nephrol* 2017;**28**(5):1334–6.
62. Robinson BM, Akizawa T, Jager KJ, Kerr PG, Saran R, Pisoni RL. Factors affecting outcomes in patients reaching end-stage kidney disease worldwide: differences in access to renal replacement therapy, modality use, and haemodialysis practices. *Lancet* 2016;**388**(10041):294–306.
63. Mehrotra R, Soohoo M, Rivara MB, et al. Racial and ethnic disparities in use of and outcomes with Home dialysis in the United States. *J Am Soc Nephrol* 2016;**27**(7):2123–34.
64. Saunders MR, Chin MH. Variation in dialysis quality measures by facility, neighborhood, and region. *Med Care* 2013;**51**(5):413–7.
65. Hall YN, Xu P, Chertow GM, Himmelfarb J. Characteristics and performance of minority-serving dialysis facilities. *Health Serv Res* 2014;**49**(3):971–91.
66. Chertow GM, Liu J, Monda KL, et al. Epoetin Alfa and outcomes in dialysis amid regulatory and payment reform. *J Am Soc Nephrol* 2016;**27**(10):3129–38.
67. Shen JI, Norris KC. ESRD payment reform: first do no harm. *J Am Soc Nephrol* 2016;**27**(10):2924–6.
68. Turenne MN, Cope EL, Porenta S, et al. Has dialysis payment reform led to initial racial disparities in anemia and mineral metabolism management? *J Am Soc Nephrol* 2015;**26**(3):754–64.
69. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; **42**(4 Suppl. 3):S1–201.
70. Kalantar-Zadeh K, Miller JE, Kovesdy CP, et al. Impact of race on hyperparathyroidism, mineral disarrays, administered vitamin D mimetic, and survival in hemodialysis patients. *J Bone Miner Res* 2010;**25**(12):2724–34.
71. Gupta A, Kallenbach LR, Zasuwa G, Divine GW. Race is a major determinant of secondary hyperparathyroidism in uremic patients. *J Am Soc Nephrol* 2000;**11**(2):330–4.
72. Wolf M, Betancourt J, Chang Y, et al. Impact of activated vitamin D and race on survival among hemodialysis patients. *J Am Soc Nephrol* 2008;**19**(7):1379–88.
73. Gutierrez OM, Mannstadt M, Isakova T, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008;**359**(6):584–92.
74. Wang C, Kane R, Levenson M, Kelman J, Wernecke M, Lee JY, Kozlowski S, Dekmezian C, Zhang Z, Thompson A, Smith K, Wu YT, Wei Y, Chillarige Y, Ryan Q, Worrall C, MaCurdy TE, Graham DJ. Association between changes in CMS reimbursement policy and drug labels for erythrocyte-stimulating agents with outcomes for older patients undergoing hemodialysis covered by fee-for-service medicare. *JAMA Intern Med* 2016;**176**(12):1818–25.

75. Kinchen KS, Sadler J, Fink N, et al. The timing of specialist evaluation in chronic kidney disease and mortality. *Ann Intern Med* 2002; **137**(6):479–86.
76. Gillespie BW, Morgenstern H, Hedgeman E, et al. Nephrology care prior to end-stage renal disease and outcomes among new ESRD patients in the USA. *Clin Kidney J* 2015;**8**(6):772–80.
77. Arora P, Obrador GT, Ruthazer R, et al. Prevalence, predictors, and consequences of late nephrology referral at a tertiary care center. *J Am Soc Nephrol* 1999;**10**(6):1281–6.
78. Prakash S, Rodriguez RA, Austin PC, et al. Racial composition of residential areas associates with access to pre-ESRD nephrology care. *J Am Soc Nephrol* 2010;**21**(7):1192–9.
79. Ifudu O, Dawood M, Iofel Y, Valcourt JS, Friedman EA. Delayed referral of black, Hispanic, and older patients with chronic renal failure. *Am J Kidney Dis* 1999;**33**(4):728–33.
80. Yan G, Cheung AK, Greene T, et al. Interstate variation in receipt of nephrologist care in US patients approaching ESRD: race, age, and state characteristics. *Clin J Am Soc Nephrol* 2015;**10**(11):1979–88.
81. Patibandla BK, Narra A, Desilva R, et al. Disparities in arteriovenous fistula placement in older hemodialysis patients. *Hemodial Int* 2014;**18**(1):118–26.
82. Hod T, Desilva RN, Patibandla BK, Vin Y, Brown RS, Goldfarb-Rumyantzev AS. Factors predicting failure of AV "fistula first" policy in the elderly. *Hemodial Int* 2014;**18**(2):507–15.
83. Zarkowsky DS, Arhuidese IJ, Hicks CW, Canner JK, Qazi U, Obeid T, Schneider E, Abularrage CJ, Freischlag JA, Malas MB. Racial/ethnic disparities associated with initial hemodialysis access. *JAMA Surg* 2015;**150**(6):529–36.
84. Norton JM, Moxey-Mims MM, Eggers PW, et al. Social determinants of racial disparities in CKD. *J Am Soc Nephrol* 2016;**27**(9):2576–95.
85. Kalantar-Zadeh K, Kovesdy CP, Derose SF, Horwich TB, Fonarow GC. Racial and survival paradoxes in chronic kidney disease. *Nat Clin Pract Nephrol* 2007;**3**(9):493–506.
86. Kalantar-Zadeh K, Golan E, Shohat T, Streja E, Norris KC, Kopple JD. Survival disparities within American and Israeli dialysis populations: learning from similarities and distinctions across race and ethnicity. *Semin Dial* 2010;**23**(6):586–94.
87. Rhee CM, Kalantar-Zadeh K, Norris KC. Why minorities live longer on dialysis: an in-depth examination of the Danish nephrology registry. *Nephrol Dial Transplant* 2016;**31**(7):1027–30.
88. van den Beukel TO, Hommel K, Kamper AL, et al. Differences in survival on chronic dialysis treatment between ethnic groups in Denmark: a population-wide, national cohort study. *Nephrol Dial Transplant* 2016;**31**(7):1160–7.
89. Arce CM, Goldstein BA, Mitani AA, Winkelmayer WC. Trends in relative mortality between Hispanic and non-Hispanic whites initiating dialysis: a retrospective study of the US Renal Data System. *Am J Kidney Dis* 2013;**62**(2):312–21.
90. Pei YP, Greenwood CM, Chery AL, Wu GG. Racial differences in survival of patients on dialysis. *Kidney Int* 2000;**58**(3):1293–9.
91. Wong JS, Port FK, Hulbert-Shearon TE, et al. Survival advantage in Asian American end-stage renal disease patients. *Kidney Int* 1999; **55**(6):2515–23.
92. Zhang Y. The association between dialysis facility quality and facility characteristics, neighborhood demographics, and region. *Am J Med Qual* 2016;**31**(4):358–63.
93. Norris KC. On Race and Medicine: until health care becomes truly personalized, race and ethnicity will continue to be important clues guiding medical treatments. *Scientist* Febuary 2014;**28**(2). http://www.the-scientist.com/?articles.view/articleNo/38950/title/On-Race-and-Medicine/.
94. Williams AW. Health policy, disparities, and the kidney. *Adv Chron Kidney Dis* 2015;**22**(1):54–9.
95. Norris KC, Williams SF, Rhee CM, et al. Hemodialysis disparities in African Americans: the deeply integrated concept of race in the social fabric of our society. *Semin Dial* 2017;**30**(3):213–23.

CHAPTER

9

Ethnicity and Chronic Kidney Disease in Disadvantaged Populations—An International Perspective

Ricardo Correa-Rotter[a], *Guillermo García-García*[b], *Jonathan Chávez-Iñiguez*[b], *Juan C. Ramírez-Sandoval*[a]

[a]**Department of Nephrology and Mineral Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México City, México;** [b]**Division of Nephrology, Hospital Civil de Guadalajara, University of Guadalajara Health Science Center, Guadalajara, Jalisco, México**

Abstract

Ethnicity is a powerful element that affects the incidence, prevalence, and course of chronic kidney disease (CKD) worldwide. Complex interactions of genetic, biologic, cultural, environmental, and socioeconomic factors are associated with CKD differences among countries, including several disadvantaged communities and ethnic minorities in developed countries. Conditions that predispose to CKD such as hypertension, diabetes mellitus, or obesity can be more prevalent in these communities, caused by differences in predisposing genetic backgrounds, prenatal and perinatal care, and experiences, including low birth weights, inadequate diets, infectious diseases, or exposure to toxins. End-stage renal disease incidence tends to rise in communities with social deprivation, and provision of renal replacement therapy depends mostly on extent of national health care expenditures and economic strength. Strategies to provide renal care for all including preventive care, early referral, timely dialysis initiation, and equalizing opportunities for kidney transplantation can be achieved through a concerted effort between nephrologists, governments, patients, charitable organizations, and industry.

BACKGROUND

Ethnic diversity is strongly associated with disparities in health status of millions of persons around the world and may explain differences in the rate of incidence, prevalence, morbidity, and mortality related to chronic kidney disease (CKD) between and within countries.[1] Dramatic increases in life expectancies and widespread declines of fertility and birth rates have been particularly marked in developing nations, increasing the incidence and prevalence of chronic diseases.[2] Obesity, diabetes mellitus (DM), hypertension, and CKD are the four major comorbidities leading to mortality disparities among disadvantaged populations.[3]

Epidemiologic and demographic transitions are not consistent among emerging nations.[4] While the trends described are happening rapidly in countries such as India, China, most of Southeast Asia, and Latin America, other regions of the world, such as sub-Saharan Africa or West Africa, are still plagued by devastating epidemics of communicable diseases. Nevertheless, even in those regions, dealing with tuberculosis, AIDS, viral hepatitis, and other infectious diseases, growing urban concentrations are also struggling with an increase in CKD that was not present decades before.[5,6]

In developed countries, the growth of ethnic minorities, in addition to the extent of racial diversity and mixture between ethnic groups, increases disparities related to the prevention, diagnosis, and treatment of CKD.[7] Socioeconomic status, education, and access to health care contribute to the differences in CKD risk among ethnic minorities, yet disparities persist even when these factors are controlled for in studies, suggesting that underlying biologic, genetic, or epigenetic effects may also be important factors related to outcome.[8]

Contemporary definitions of race and ethnicity are controversial, and occasionally indistinguishable, as

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00009-7

they may be viewed as a genetic inheritance or as a social construct.[9] In this chapter, ethnicity will be defined as a community whose shared heritage offers important characteristics in common between the members of a group, including physical appearance (the old concept of "race"), subjective identification, cultural tradition, common population history, religion, and language.[10]

In this context, inequities in CKD and end-stage renal disease (ESRD) incidence and treatment vary widely in developing countries and in ethnic minorities living in developed countries. Great variations in gross national product, standards of education, health care, and nutrition can be found in one specific region or even within a country itself. Therefore, it is not appropriate to generalize about epidemiologic and risk factors in disadvantaged communities. Nevertheless, some general aspects deserve to be highlighted.

In most of the world, increased CKD incidence and prevalence are strongly associated with lower socioeconomic status and belonging to certain ethnic groups. The interplay between these factors is complex, and it is not always possible to stratify them as single entities.[11] For example, low socioeconomic status is associated with duplication of the risk of CKD in both African Americans and White Americans, compared with individuals from higher socioeconomic status, yet the absolute risk is actually higher in African Americans than in Whites Americans, independent of whether African Americans have low or high socioeconomic status.[12] In a cohort with more than 22,000 subjects, in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) cohort, lower income was strongly associated with albuminuria in African Americans compared with Whites.[13]

Lower household income may be associated with an inadequate diet.[14] The interpretation of dietary intake and its associations with CKD depends on the selected population and aspects of study design. For example, a restricted protein intake, which can be found in disadvantaged communities, is associated with lower risk of CKD.[15] In contrast, these same communities may be susceptible to adverse kidney outcomes because of other dietary factors, such as higher caloric intake,[16] salt consumption,[17] or high dietary protein intake, especially in African Americans with DM.[18]

Access to education is an important social factor that affects CKD in ethnic minority groups. In Netherlands, the Healthy Life in an Urban Setting cohort of more than 21,000 participants demonstrated that low- and mid-level education was associated with higher risk of CKD in ethnic minority groups, after adjustment for other confounders such as age or sex.[19]

Epigenetic interactions between environmental adversity and the genome, predominantly associated with malnutrition, could be a link between social factors related to ethnicity and subsequent development of CKD.[20] Low nephron number associated with low birth weight could explain, in part, differences in progressive renal injury observed in communities with lower socioeconomic status. Low birth weight in offsprings is a marker of an adaptation to a "thrifty phenotype" *in utero* in preparation for a world depleted of nutrients.[21] With exposure to high-calorie diets, maladaptive complications occur at a high frequency, ending in hypertension, DM, dyslipidemia, and obesity, as well as microalbuminuria and decreased estimated glomerular filtration rate (eGFR).[22] Poverty and deprivation during childhood are strong predictors of multiple adverse health outcomes during adulthood, such as cardiovascular disease (CVD) and type II DM.[23]

The presence of a predisposing genetic background for CKD may be associated with ethnicity. Some genetic variants such as APOL1, ELMO1, UMOD, ACTN4, and PROX1 are examples of risk factors for CKD linked to ethnic groups.[24,25]

Environmental exposure and gene interactions may be other relevant factors. Everett et al. reported that concentration of the pesticide DDT (dichlorodiphenyltrichloroethane) and its metabolites in the blood of Mexican Americans was associated with both diabetic nephropathy and DM without nephropathy.[26]

Patterns of unhealthy lifestyle behaviors differ among ethnic minorities and may modify the risk for CKD. For example, about one-third of Latin American smokers report a pattern of "intermittent smoking," which is higher compared with other ethnic groups. Nevertheless, intermittent smokers had an increased risk for CKD, similar to daily smokers.[27]

The prevalence of glomerular diseases in tropical countries is 2.5 times the rate in developed nations,[28] which could be related to the many endemic environmental, social, financial, and infectious causes which characterize regions but differ greatly between them. Noninfectious glomerulonephritides are greatly influenced by ethnicity. For example, lupus nephritis occurs more frequently in African, Caribbean, Asian, and Hispanic populations compared with White Europeans. Likewise, lupus nephritis is associated with a severe course in Asian and Hispanic individuals.[29]

DM and hypertension are the leading causes of CKD in developed and many developing countries. In contrast, infectious diseases continue to play an important role as causes of CKD and ESRD in low-income countries, probably in association with poor sanitation, inadequate supply and access to potable water, and high concentrations of disease-transmitting vectors.[30] Chronic glomerulonephritis and interstitial nephritis are currently the principal causes of CKD in the many underdeveloped nations, not only in sub-Saharan Africa but also in some Latin American and Southeast Asian nations, reflecting the high prevalence of bacterial, viral,

and parasitic infections. Several parasitic infections cause CKD through ureteral obstruction (such as schistosomiasis, in most of sub-Saharan Africa), interstitial nephritis (such as kala-azar [visceral leishmaniasis] in many African and Asian countries), glomerulonephritis associated with malaria and filariasis, in West Africa, and schistosomiasis, in Africa and Latin America.[31]

The incidence and prevalence of ESRD differ substantially across countries and regions (Figure 9.1a and b). More than 80% of all renal replacement therapy (RRT) is provided in affluent countries. In the US, the incidence rate of ESRD in ethnic minorities is 1.5–4.0 times more than its incidence in the White population, with African Americans suffering the highest rates.[32] Around the world, hemodialysis (HD) is the most prevalent mode of RRT employed, yet it may be inadequate in particular for patients living in remote nonurban areas, as happens in large parts of the developing world. In contrast, peritoneal dialysis (PD) is increasing in some countries, including China, the US, and Thailand, but has proportionally decreased in parts of Europe and in Japan.[33] The lower figures regarding RRT reported from emerging nations are largely due to patients not being accepted into dialysis or transplant programs, although where economies are growing, the numbers of patients being accepted are rising strikingly.

Projected worldwide population changes suggest that the potential number of cases of ESRD will increase disproportionately in developing countries, where the number of elderly people is increasing. This effect will be enhanced further if the trends of increasing hypertension and DM prevalence persist, competing causes of death such as stroke and CVDs are reduced, and access to treatment improves.[30]

The lack of renal registries in most developing nations hampers the publication of reliable statistics about the prevalence of ESRD. Information is mainly based on data obtained by questionnaires addressed to leading nephrologists, the dialysis industry, and from a few publications in local and international journals.[1]

AN INTERNATIONAL PERSPECTIVE REGARDING CKD

The Americas: Canada

The prevalence of CKD in Canada, determined primarily by eGFR, varies among ethnic groups. A screening program called the First Nations Community Based Screening to Improve Kidney Health and Prevent Dialysis project examined the prevalence of CKD among First Nations. They found a prevalence of 26% of CKD (defined as UACR $\geq$30 mg/g or eGFR <60 mL/min/1.73 m^2), a twofold higher prevalence of CKD in indigenous Canadians, and a prevalence of severely increased albuminuria that was fivefold higher in comparison with the general population.[34] Among Indigenous Canadian children, 11% had albumin:creatinine ratio >3 mg/mmol and 6% had an eGFR <90 mL/min/1.73 m^2.[35] Severe CKD (eGFR less than 30 mL/min/1.73 m^2) was almost twofold higher among First Nations people.[36] Zacharias et al. demonstrated that the prevalence and risk factors for albuminuria in a First Nation population is high and more prevalent in men.[37] Conley et al. studied a large community-based cohort of Caucasian, Chinese, and South Asian participants living in Alberta, to determine whether the prevalence of proteinuria varied across the three ethnic groups. While the prevalence of heavy proteinuria was higher in Chinese and South Asians compared with Caucasians regardless of eGFR (>60 mL/min/1.73 m^2 or <30 mL/min/1.73 m^2), these ethnicities experienced a decreased risk of death and similar risk of CKD.[38]

Samuel et al. demonstrated that the incidence of ESRD is higher among aboriginal (First Nations, Inuit, and Metis) children and young adults than among white children and young adults. They also showed congenital diseases were less common in aboriginal people, and glomerulonephritis was more common than in whites. An excess of glomerulonephritis, but not DM, was seen among aboriginal people aged 22–40 years. The converse was true (higher risk of DM, lower risk of glomerulonephritis) among aboriginal people aged 40 years and older.[39]

Canadian First Nations experience ESRD 2.5 to 4 times more frequently, and those with DM have 7 times the rate of diabetic ESRD compared with their non-First Nations counterparts.[40] Aboriginal Canadians (First Nations, Inuit, and Metis) are more likely to live farther from tertiary health care centers. PD may be appropriate for those who live in remote areas where there are no HD facilities.[41] Tonelli et al. evaluated the use of PD among three provinces with the highest proportion of aboriginal people.[42] After adjustment for age and comorbidity and comparison with white patients, aboriginal patients were significantly less likely to initiate therapy with PD compared with white patients and displayed a trend toward a higher risk for technique failure. This low PD use was independent of whether subjects lived remotely or in an urban location.

The Americas: Latin America

In Latin America, the prevalence and incidence of CKD has increased in all countries, yet with wide variations in rates between countries. Across the region, CKD stages 4 and 5 have increased from 119 patients per

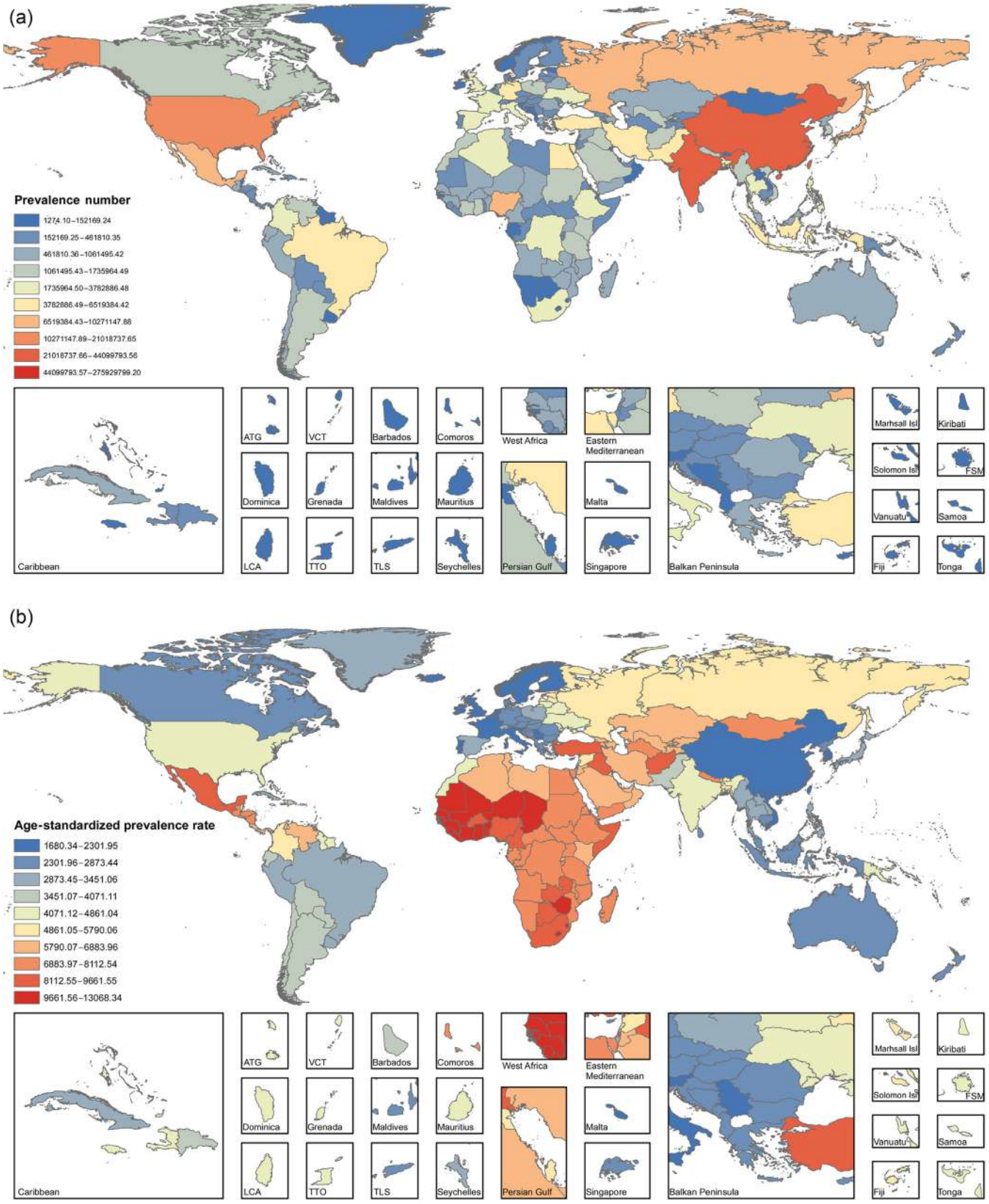


FIGURE 9.1 (a) Comparison of unadjusted end-stage renal disease (ESRD) prevalence number worldwide. Data from Japan are dialysis only. (b) Comparison of age-standardized ESRD prevalence rate worldwide. Data from Japan are dialysis only. *From U.S. Renal Data System. USRDS 2013 annual data report: atlas of end-stage renal disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2013.*

million population (pmp) in 1991 to 408 pmp in 2016. In 2016, the highest prevalence rates were reported in El Salvador (685 ppm), Mexico (628 ppm), Virgin Islands (627 ppm), and Honduras (416 ppm), with an increase in percentage rate from 1990 to 2016 of 106%, 94%, 122%, and 105.5%, respectively.[43]

An epidemic of DM has characterized the epidemiological transition in Latin America.[44] DM remains the leading cause of ESRD in Latin America, with the highest rates of DM as percentage of all cases of ESRD being in Puerto Rico (65%), Mexico (51%), Venezuela (42%), and Colombia (42%). The lowest rates are in Brazil (26%), Uruguay (22%), Costa Rica (20%), and Paraguay (15%).[45–47]

Several population-targeted approaches have been employed in Latin American nations to explore the prevalence of CKD. A methodology that evaluates population risks when confronted with a disease or injury, called the Global Burden of Disease, showed that in Mexico CKD-associated mortality had increased 108% from 1990 to 2015. DM is one of the main causes of CKD in Mexico and has largely increased mortality from 1990 to 2015, establishing itself as the third most common cause of death in that country.[48] Mexico City has the greatest CKD-related mortality and the greatest number of disability-adjusted life years.[49] A recent large prospective study in Mexico City showed that the greatest absolute excess risk of death associated with DM was from renal disease, primarily CKD.[50]

Glomerulonephritis, in particular secondary to bacterial and parasitic infections, remains a significant cause of ESRD in disadvantaged populations in some regions of Latin America. Herrera et al. showed that the incidence of ESRD in Venezuela's Goajiro Indians was 220 pmp, 1.7 times higher than the estimate for the country.[51] The authors suggested that a combination of high rates of poststreptococcal glomerulonephritis and low nephron number could be responsible.

In Bolivia, Perico et al. found urinary abnormalities in 30% of the subjects according to a screening performed in 14,082 healthy individuals.[52] In Peru, in a cross-sectional study involving 2968 high-risk individuals from 23 centers, the prevalence of microalbuminuria was 53.4%,[53] whereas the prevalence of CKD in the primary care setting was 18%.[54] A crosssectional study from the National Health Survey in Brazil found a prevalence of CKD of 1.4%, of which 7.4% had ESRD.[55] Environmental and socioeconomic factors may play a role in the development of glomerular disease in South America. For example, an outbreak of postinfectious glomerulonephritis in Brazil caused by contaminated nonpasteurized milk, led to the development of progressive nephropathy in some cases.[56]

An epidemic of CKD of unknown origin, named Mesoamerican nephropathy, is present in agricultural communities of the Pacific coast of Central America. This form of CKD is more frequent in young male individuals and has devastating consequences in some communities, in particular in El Salvador and Nicaragua.[57] Clinically and histologically, Mesoamerican nephropathy is a tubulointerstitial disease[57,58] that progresses to ESRD over a variable period of time. A number of possible causes have been proposed, yet it is most likely that it has a multifactorial etiology. Some of the causes that have been explored include recurrent dehydration-associated tubular injury in agricultural workers who labor under exhausting conditions in extremely hot and humid areas where recurrent dehydration and use of nonsteroidal drugs are common, environmental or agrochemical toxicities, and infectious causes, as well as others. A common element in all described cases is a state of economic and social deprivation of those affected.[57–59]

Asia

An epidemiological transition has been observed in the etiology of ESRD in the Middle East, with DM and hypertension as major causes. Together they are responsible for 52% of ESRD in this region. Other forms of glomerulonephritis, inherited nephropathies, and obstructive nephropathy occur, yet less frequently.[60]

In South Asia, chronic glomerulonephritis is the most common cause of CKD in Cambodia, Indonesia, Singapore, and Vietnam. Nephrolithiasis is the most common cause of CKD in Thailand.[61] Data from the Indian CKD registry show that DM is the commonest cause of CKD, followed by unknown cause and chronic glomerulonephritis. In Pakistan, the most common cause of CKD in children is obstructive uropathy (22%).[62]

China, the world's most populous country with more than 1.4 billion population, had a CKD prevalence of 10.8% (238 ppm). Nearly 120 million individuals were affected, according to a national survey from 2009 to 2010. Most CKD cases in this study had albuminuria >30 mg/g. Only 1.7% had an eGFR <60 mL/min/1.73 m^2, suggesting that later stages of CKD will increase in the future. In the general population, CKD was related to DM in 1.2% and glomerulonephritis in 0.9%. Approximately 21% of Chinese people with DM were diagnosed with CKD.[63]

Interracial/ethnic variations in CKD risk factors and prevalence have been evaluated in Singapore.[64] The prevalence of an eGFR <60 mL/min/1.73 m^2 or the presence of micro/macroalbuminuria in 4499 participants of Chinese, Malay, and Indian ethnicity, aged 24–95, that participated in the Singapore Prospective Study Program was determined. The age- and sex-standardized prevalence of CKD was 13% in the whole

population, 11% in Chinese, 19% in Malays, and 18% in Indians. The prevalence of major CKD risk factors such as DM, hypertension, overweight/obesity, and dyslipidemia was also higher in Malays and Indians. A population-based cross-sectional study in 10,033 Chinese, Malay, and Indian subjects found a higher risk of CKD and retinal emboli in Indian persons, independent of age, smoking, hypertension status, and other risk factors.[65] The association of these variables with CKD suggests the need to screen high-risk individuals for early detection and control of modifiable risk factors for CKD.

The prevalence of CKD is alarming in high-risk Asian communities. Among hypertensive individuals in rural Pakistan, rural Bangladesh, and Sri Lanka, CKD prevalence was 58%, 36%, and 17%, respectively.[66] A systematic review of prevalence in South Asia found an overall prevalence of CKD in Pakistan of 21%, in 17% in Bangladesh, in 10% in India, and 10% in Nepal. Nevertheless, the unusually high prevalence in Pakistan might be due to the higher minimum age requirement set as an inclusion criterion in Pakistani studies.[67]

In a cross-sectional screening study performed in Nepal, Mongolia, and China among 11,394 participants, decreased eGFR (less than 60 mL/min/1.73 m^2) was present in 7−14% of participants. Proteinuria (≥1+) on dipstick (2.4−10%), hypertension (26−36%), DM (3−8%), and obesity (>BMI 30 kg/m^2; 2−20%) were all common.[68]

In India, three population-based screening programs reported a low CKD prevalence, between 0.79 and 1.4%.[69,70] However, the Screening and Early Evaluation of Kidney Disease (SEEK) program of India reported a prevalence of 17.4% among 5623 participants. CKD was defined as the presence of proteinuria or abnormal urinary findings for more than 3 months with or without reduced eGFR, which was probably the reason for the high incidence.[71]

Africa

In Africa, the prevalence of CKD is uncertain due to poor methods of evaluation and the quality of data of studies. Prevalence is nevertheless estimated between 2% and 41%, yet in high risk groups, it ranges between 11−90% in patients with DM and 13−51% in patients with hypertension.[72] The overall prevalence of CKD in sub-Saharan Africa, obtained from 21 epidemiologic studies, was between 12% and 16%. No differences were observed between urban and rural areas.[73] The risk factors for CKD in sub-Saharan Africa were hypertension, DM, anemia, and history of tuberculosis or schistosomiasis. A single factor was found in 61% of individuals, two in 14% and 3 or more in 10% of all CKD cases. These findings support the hypothesis of a "double burden" of noncommunicable and communicable diseases as an important cause of CKD in Africa.[74]

HIV infection could be another factor related to the prevalence of CKD in regions of Africa. Patrice et al. found that the prevalence of CKD in HIV-infected patients was 44% in Northern Cameroon. Factors associated with CKD were age >35 years, longer duration of HIV infection, history of hepatitis B virus infection, and CD4 cell <200 cells/mL.[75] In 2017, Africa had the highest CKD prevalence in HIV-infected patients.[8] Rates were highest in West Africa (15%) and lowest in southern Africa (3%), compared with a worldwide prevalence of CKD in HIV-infected patients of 5%.[73]

In North Africa, demographic and epidemiological transitions have led to an increased incidence of DM and hypertension, but glomerulonephritis and interstitial nephropathies remain important causes of ESRD. The overall prevalence of CKD in North Africa was 484 ppm in 2016.[43] The reported annual incidence of ESRD ranges between 74 and 200 cases pmp. The pool of patients undergoing dialysis varies from 150 in Mauritania to more than 35,000 in Egypt. The prevalence of RRT ranges between 47 and 680 cases pmp and is highest in Tunisia and Egypt. Chronic glomerulonephritis represents 41% and 27% of the ESRD cases in Algeria and Sudan, respectively. The role of DM and hypertension is important in Egypt (14% and 37%), Morocco (18% and 10%), and Tunisia (14% and 20%). Interstitial nephritis remains an important cause of ESRD in Egypt and Tunisia, representing 17% and 13% of the burden of ESRD, respectively.[43,68] DM affects 9.4 million people in Africa. The estimated increase in DM in Africa is anticipated to be 12.7 million cases, an increase of 140%, by 2025. It is expected that the prevalence of diabetic nephropathy, currently estimated to be 6−16%, will increase dramatically.[73]

In sub-Saharan Africa, hypertension is a leading cause of CKD. Hypertension is the cause of 25% of the ESRD in Senegal, 30% in Nigeria, 46% in South Africa, and 49% in Ghana, especially in black patients. As in North Africa, glomerular diseases are a major cause of ESRD. With the introduction of the hepatitis B vaccine, the number of cases of membranous nephropathy associated with ESRD has declined, whereas the prevalence of HIV-associated nephropathy has increased.[76]

Australia, New Zealand, and South Pacific Islands

The number of Australian Aboriginal people with early CKD is hard to quantitate, yet risk factors, including hypertension and DM, are widespread in this population. DM is 2−5 times more common and

appears at an earlier age among indigenous people compared with the nonindigenous populations of New Zealand and Australia.[77] For all CKD parameters in Australia, rates among Indigenous people were strikingly correlated with increasing remoteness of residence, socioeconomic disadvantage, and female predominance.[78]

Albuminuria is common among indigenous populations of Oceania. Albuminuria ≥30 mg/mL was found in 41% of Nauruan adults.[79] Albuminuria ≥20 mg/mL was found in 26% of adults in one ethnic group in New Guinea.[80] Rates of microalbuminuria and overt albuminuria were 28−31% and 13−21% in two remote Aboriginal communities in Australia's Northern Territory.[81,82] There are great variations in biopsy rates and findings among Indigenous Australians, with high rates of segmental sclerosis and postinfectious glomerulonephritis. Glomerulomegaly was a prevalent finding in many biopsies.[83,84] The association of lower birth weight with CKD has been described in remote Australian community settings. Glomerulomegaly may represent compensatory hypertrophy in the presence of a low nephron number, related to low birth weight, with variable superimposition of postnatal effects. The increased risk of CKD in Australian Aboriginal adults is not established in childhood.[85]

An interesting finding was the prevalence of proteinuria of >100 mg/L in 63% of people without DM in the Australian Aboriginal community of Woorabinda.[86] This suggests that the dogma that most indigenous renal disease in this region is due to DM is not universally correct.

The incidence and prevalence of indigenous people starting RRT in Australia has significantly increased over the past 25 years, mainly due to diabetic nephropathy.[87] Stewart et al., using data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), explored age- and sex-standardized incidence rates for RRT in four age groups of Maori, Pacific Islanders, and all other New Zealanders as well as Indigenous and nonindigenous Australians, from 1992 to 2001. The incidence of ESRD did not differ in those aged 0−14 years. The excess ESRD in Indigenous Australians was due principally not only to type II DM and glomerulonephritis but also to type I DM, hypertensive renal disease, and analgesic nephropathy. The excess in Maori and Pacific Island people was confined to those with type II DM, hypertensive renal disease, and glomerulonephritis.[77] For about two decades, starting in the 1980s, incidence of ESRD in indigenous people of Australia rose steadily, but by 2016 the incidence of RRT may be decreasing[78]

The age at which people develop ESRD is considerably younger among indigenous peoples in Oceania than among the mostly white nonindigenous people. The mean age at onset of RRT for nonindigenous people is 60 years, whereas Aboriginals are on average 48, Maoris 44, and Mariana Islanders 56 years old.[88]

ACCESS TO RENAL CARE

Ethnic disparities in access to health care and health outcomes are well documented worldwide. Gao et al.[89] identified 106,511 non-Aboriginal and 1182 Aboriginal Canadian patients with CKD (eGFR <60 mL/min/1.73 m^2) in Alberta, Canada. The authors compared outcomes, including preventable hospital admissions with appropriate outpatient care (ambulatory care−sensitive conditions) as well as use of specialist services. Aboriginal people were almost twice as likely as non-Aboriginal people to be hospitalized for an ambulatory care−sensitive condition. Aboriginal people with advanced CKD (eGFR <30 mL/min/1.73 m^2) were 43% less likely to visit a nephrologist. These results suggest potential inequities in care of patients with CKD and raise the possibility that aboriginal populations may have differential access to preventive and primary care, including opportunities to slow the rate of CKD progression.[90]

In Australia and New Zealand, the proportion of people receiving home HD and PD is lower among indigenous people compared with non-indigenous populations. Among those receiving dialysis at the end of 2007 in Australia, 33% of nonindigenous people received a home-based dialysis therapy, in contrast to 18% of Aboriginal people. In New Zealand, 62% of the non-indigenous proportion received home dialysis. The rate was 42% among Maori/Pacific Islanders.[91]

Similarly, the proportion of indigenous people receiving RRT with a functioning kidney transplant is lower among Aboriginal Australians (12% vs. 45% among non-indigenous Australians). Transplantation rates for Maori and Pacific people are approximately 25% of those of people of European origin. This is partly related to a reduced listing rate of about 50% compared with non-indigenous people, and a reduced transplantation rate of about 50% for Maori and Pacific Islanders. The causes of reduced listing are likely to be multifactorial, including increased obesity and co-comorbidities associated with DM, but other factors related to socioeconomic status and access to health care may also play a role.[92]

Caskey summarized the disparities in access to kidney transplantation in the United Kingdom. Compared with Caucasians, South Asians and Blacks were equally likely to reach the transplant waiting list, but significantly less likely to receive a transplant once listed. Living kidney donor transplantation was less likely for

those living in deprived areas and classified as South Asian or Black, respectively.[93]

Disparities in renal care are more evident in developing nations, and access to RRT is dependent mostly on health care expenditures and national economic strength. In Mexico, the fragmentation of the health care system has resulted in unequal access to RRT. Significant differences are observed between the insured and uninsured Mexican populations starting RRT. A prospective cohort study of 850 patients with ESRD in Mexico City found that lack of access to health insurance programs occurs in 88% of patients and was the most important risk factor for death.[94] In a report from the Mexican state of Jalisco,[95] the acceptance and prevalence rates of the insured population were significantly higher (327 pmp and 939 pmp, respectively) than patients without medical insurance (99 pmp and 166 pmp, respectively). The transplant rate also was different, at 72 pmp for those with health insurance and 7.5 pmp for those without insurance. In addition, uninsured Mexican patients with CKD have very advanced disease at the time of first nephrologic evaluation and have exceedingly high rates of mortality after dialysis initiation.[96] In Latin America, RRT prevalence and kidney transplantation rates correlate significantly with gross national income and health expenditures.[45]

In India and Pakistan, where total health care expenditures are 1.5% of the Gross National Income, less than 10% of all ESRD patients have access to RRT.[97] Less than 20% of all long-term dialysis patients receive PD. Among the factors identified as barriers to PD are the costs, risk of peritonitis, late referral, and selection bias for financial reasons.[62] Similar experiences have been reported in Africa,[68,76] the Middle East,[60] and Southeast Asia.[61] Transplantation in India and Pakistan is limited, has inadequate financial support, and lacks an organized deceased donor transplant program. Therefore, in these countries, the vast majority of grafts come from living donors.

The provision of renal care to all patients from developing nations, although a difficult task, is not impossible. A number of strategies have been proposed. These include the implementation of programs for prevention of kidney disease and establishment of measures to slow CKD progression. In addition, it would be desirable to be able to have universal coverage of RRT for all those that require it, with kidney transplantation as the ideal modality in all those who can receive a graft. Use of generic immunosuppressive drugs can make transplantation more affordable. PD has been considered a better choice of dialysis modality, as it may be more affordable and appropriate for patients living in areas where HD is not available.[98]

Access to kidney transplantation is the most serious disparity in ESRD, as it limits duration and quality of life in minority ethnic groups. In the US, the most important factors that drive racial disparities in transplantation for African Americans include poor access to timely donation, poor health insurance and a low rate of living donation, lack of education about kidney transplantation, and a lower rate of referrals, race-based bias, and poor communication, socioeconomic and environmental disparities, and genetic etiology and racial ancestry.[99] Living donation may be impaired by complex reasons related to ethnicity. For example, African Americans have a higher likelihood of ABO or crossmatch incompatibility with their intended recipients, a higher body mass index, and other medical conditions that may preclude donation.[100] Metabolic syndrome, DM, and overweight are frequent causes of rejection for living donation in Mexico.[101] A multinational study using data from Australia, New Zealand, and Canada found low rates of kidney transplantation among Aboriginal Canadians. Datasets were obtained from each country's ESRD registry. By the end of follow-up, 88,173 patients had received a renal transplant and 130,261 had died without receiving a transplant. Compared with white patients, the adjusted likelihood of receiving a transplant for Aboriginal patients was 77% lower in Australia, 66% lower in Canada, and 77% lower in New Zealand.[93] Although in Canada the likelihood of referral for kidney transplantation is similar for both Aboriginal and non-Aboriginal patients, the former are 54% less likely to be active on the transplant waiting list than non-Aboriginal patients and are more likely to be in the process of completing their transplant workup than on "hold" status on the waiting list, indicating that barriers that lead to reduced rates of transplantation appear to occur downstream from the referral step.[102]

Several potential barriers may prevent Aboriginal dialysis patients in Canada from successfully receiving a kidney transplant. These may include patient attitudes and preferences regarding transplantation, physician biases, residence in rural or remote geographic locations, differences in human leukocyte antigen pools, and lower selection from the waiting list. It is important to note that other global social determinants of health, such as poverty and lack of education, may also impact multiple levels of the transplantation process.

Rodrigue et al. proposed a transplant education program based on a house calls approach, designed to reduce racial disparities, which combines patient and group discussions with standardized educational materials.[103] This program increases the likelihood of receipt of a living donor kidney transplant in African-American patients compared with Whites.[104] Health policy can be shaped to immediately reduce ethnic disparities in transplantation. For example, the implementation of a

new American kidney allocation system in 2014 led to a substantial increase in the kidney transplantation rate for African Americans and Hispanics in the months following the policy change.[105]

New strategies to increase transplant evaluations in ethnic minorities have been successful. For example, the Kidney Transplant Fast Track protocol is an evaluation process to complete all pretransplant testing in one day to increase rates of kidney transplantation in vulnerable patients.[106]

End-of-life issues in ESRD patients, including access to palliative care, decisions about advanced life sustaining therapies, and advance care planning, are influenced by ethnicity.[107] African-American and Hispanic patients still remain less likely to discontinue dialysis or utilize hospice care compared with their White peers.[32] Eneanya et al. showed that African-American patients with stages 4 and 5 CKD are less likely to communicate end-of-life preferences and have less knowledge of hospice than their White counterparts, even after adjusting for factors such as age, education, and income. Interestingly, they found no racial differences in distrust of providers, or in spiritual/religious or cultural beliefs.[108] Latinos treated with HD in Denver, Colorado, prefer to avoid medications, favor family group decision-making, and want advance care planning conversations to occur at home with someone who is culturally and linguistically congruent.[109] The implementation of programs in minority ethnic groups to improve preparation for end-of-life decision-making and post-bereavement outcomes could be a successful approach. An advance care planning model of two sessions in HD patients was effective in improving preparation for end-of-life decision-making and post-bereavement outcomes in African Americans but not in Whites[110] The reasons for the ethnic differences reported in these studies are multiple and complex, including cultural differences, yet the observation has important implications for the design of care programs for diverse populations with CKD. Older Latinos with ESRD on dialysis were more trusting of their physicians when deciding on intensive procedures and deferred end-of-life care decision-making to their children compared with other groups.[111] These differences highlight the need for improved patient- and family-centered approaches in minority ethnic groups.

RELATION BETWEEN ETHNICITY AND CKD RISK

Differences in access to health care and other nonmedical factors may not explain worse kidney outcomes in some ethnicities. While there may be differences in health care system–related factors, intrinsic factors related to ethnicity may also play important roles in determining differences. Studies performed in the US have clearly shown that African-Americans progress from earlier stages of CKD to ESRD faster than Caucasians and are at higher risk for developing complications related to CKD such as cardiovascular diseased or reduced cognitive function[112] Van den Beukel et al. investigated whether progression of CKD in particular ethnic groups is also faster in a universal health care system.[113] Data from the PREdialysis PAtient REcord study (a multicenter follow-up study of patients with CKD who started predialysis care in the Netherlands between 1999 and 2011) show the risk of starting RRT within the first 15 months of follow-up was not different between Black and White individuals, whereas from 15 months onward Black populations had double the risk of requiring RRT. Decline of renal function was faster by 0.18 mL/min/1.73 m^2 per month in Blacks compared with Whites.

The higher risk of DM in certain ethnic groups modifies interpretations about ethnicitiy and CKD risk. In analyses from the Chronic Renal Insufficiency Cohort study, Hispanics had significantly higher rates of CKD progression, incident ESRD, and mean annual decline in eGFR compared with non-Hispanic Blacks. Nevertheless, when DM was excluded from the analysis, Hispanic ethnicity was associated with a lower risk of CKD progression and a lower risk of death compared with other ethnic groups.[114]

In Canada, quality of HD care appears to be similar in Aboriginal and non-Aboriginal patients. In a large Canadian population-based study of HD patients, no differences were observed in small solute clearance, anemia management, and use of a permanent access between groups. However, when compared with non-Aboriginal HD patients, Aboriginal patients were significantly less likely to achieve target levels for predialysis systolic blood pressure control and mineral metabolism goals.[115]

Similarly, Udayaraj et al. examined the associations between socieconomic status and ethnicity (White, Black, and South Asian) and the attainment of standards in 14,117 incident dialysis patients in the United Kingdom. Black individuals had lower attainment of appropriate hemoglobin and PTH standards, but better attainment of serum phosphate and calcium targets. South Asians experienced better or comparable outcomes for most standards except serum calcium concentration and PTH.[116] The authors concluded that these differences could be influenced by ethnicity-related biologic factors rather than inequity of care.

People of different ethnicities who become minorities in the country to which they are migrating may have

increased risk factors for CKD, especially after adopting new lifestyles. A population-based case-control study in the Netherlands showed a 22-fold higher risk of ESRD due to type 2 DM in Surinamese Indo-Asian immigrants compared with native Dutch individuals. After adjusting for age, the risk of ESRD was 38 times higher, as Indo-Asians were 14 years younger at onset of type 2 DM. This higher risk is explained by both an 8 times higher prevalence of DM in the Indo-Asian general population in The Hague and by a higher incidence rate of diabetic nephropathy for the Indo-Asian DM population.[117]

Other psychosocial factors related to ethnicity may be related to a higher risk of CKD. Perceived discrimination (general experience of discrimination, ethnicity-related or gender-related discrimination) has been linked to chronic psychosocial stress, to biological changes in neuroendocrine, autonomic and immune systems, and to hopelessness and low self-efficacy affecting the ability to self-manage one's health.[118] A prospective cohort study from 2004 to 2013 found perceived racial and gender discrimination were associated with modestly lower kidney function among African-Americans and white women.[119]

STRATEGIES TO MITIGATE KIDNEY-HEALTH DISPARITIES RELATED TO ETHNICITY

International initiatives, such as the Asian Renal Collaboration, including more than 20 epidemiologic studies from 7 Asian countries, have been proposed to obtain information about CKD prevalence and manifestations.[120] Increasing awareness of the effects of ethnicity may potentially lead to strategies to improve clinical outcomes in minorities with health disparities. Potential interventions to reduce inequities related to ethnicity include providing equal access to medical care and education, increasing access to clinical research in minority populations, instituting CKD awareness programs, improving communication skills of practitioners to modify treatment misconceptions, and identifying critical biomarkers for disease progression and drug responses in heterogeneous populations, as well as others.[121] The eradication of ethnic disparities among kidney disease patients is a highlighted target for Healthy People 2020, the US blueprint for health.[122] The National Institute of Health National Institute on Minority Health and Health Disparities launched a new precision medicine program to promote health equity and to advance the science of minority health and health disparities.[123]

The potential use of health information technologies to target certain ethnic minority groups may reduce inequalities, empower patients, and increase engagement in CKD management. For example, 67% of African Americans obtain health information from smartphones compared with 57% of White Americans.[124] Interventions through the Smartphone Medication Adherence Stops Hypertension program to decrease blood pressure were more effective than standard care in African Americans and Hispanics.[125]

The field of cross-cultural care involves strategies focused on the ability of physicians and organizations to understand and integrate models to provide quality health care to patients from diverse sociocultural backgrounds.[126] New innovative approaches that deliver community-based, culturally grounded interventions to vulnerable and key population ethnic subgroups have been implemented in clinical trials. These new strategies include an emotional health component and are delivered in community settings using a family-based model.[127]

Cultural competence in health care of patients with CKD includes addressing language barriers in the clinical encounter, learning the norms of specific cultures, and provision of care to immigrants, refugees, and other globally mobile populations.[128] From 2014 to 2015, Europe witnessed a huge rise in the number of refugees, increasing from 280,000 to more than a million.[129] Refugees represented 1.5% of the dialysis population according to a 2016 survey in Europe and North Africa.[130] Migration may change epidemiologic patterns in aging developed countries.[131] In the US, based on an estimated adjusted incidence rate of 500 ESRD cases per 100,000 population among all American Latinos, an estimated 11.1 million undocumented immigrants will be at risk of emergent dialysis, frequent hospitalization, blood transfusion, and complications.[132] In the region of Emilia-Romagna in Italy, cardiovascular, pulmonary, renal, and cerebrovascular diseases were significantly less frequent among migrants, a phenomenon that has been defined as the "healthy immigrant effect," although lower access of immigrants to health care may underlie these observations.[133]

A new program of research projects and infrastructure in Canada by the Canadian Institutes of Health Research had the vision that by 2020 every Canadian with or at high risk for CKD will receive the best recommended care, experience optimal outcomes, and have the opportunity to participate in studies with novel therapies, regardless of age, sex, gender, location, or ethnicity.[134] A public health campaign to increase kidney health awareness in Manitoba, Canada, increased overall awareness of the campaign from 7% to 25% and demonstrated that raising awareness of CKD is

possible with a public campaign based on a multifaceted approach.[135]

LIMITATIONS AND CONTROVERSIES

Clinical researchers frequently report race and ethnicity based on self-reporting, which is a major limitation to understanding the importance of sociologic compared with biologic factors.[136] It is important to interpret ethnicity categories as a social-political construct, not scientifically or genetically.[8] Therefore, health outcomes stratified by race and ethnicity are less likely a result of genetic inheritance and are more strongly influenced by socio-ecologic determinants of health such as discrimination, educational and income inequalities, imbalances in access to care, health care resources, and exposure to environmental toxins.[137] A multiplicity of alternatives on attempting to categorize ethnicity have been proposed, including clustering of populations based on genetic markers (single-nucleotide polymorphism or multiallelic microsatellite, for example) or reporting of ancestry instead of self-race by participants. For example, ancestry in African descent people (Africans, Caribbean, and African-American subgroups) is different in terms of the DM risk in complex ways, because Caribbean ancestry seem to have worse glycemic control and a higher rate of renal complications compared with African Americans. Those with direct African ancestry seem to also have a very high risk of DM, independent of body mass index.[138]

The precise mechanisms by which environmental factors interact with genetic determinants to affect CKD susceptibility are still unknown. One genetic approach is to calculate "the proportion of ancestry" of individuals across the genome to elucidate if genetic ancestry has a stronger association than social or environmental factors.[121] The risks and benefits of genetic testing, especially in minority ethnic groups, need to be considered from an individual and societal perspective. All health determinants are potentially stigmatizing, and people may inappropriately judge others as being sick because of "bad genes."[139] For example, APOL1 status may explain 70% of the excess prevalence of nondiabetic CKD in hypertensive people of African ancestry, yet individuals who undergo testing may have concerns about racial stereotyping, medical discrimination, and stigmatization.[140] These risks can be diminished with the use of a transdisciplinary team which includes patients, advocates, and genetic counselors to develop communication strategies and materials that are more appealing, understandable, and inspiring for diverse population.[141]

Despite efforts to achieve greater equity in kidney health, disparities have changed little over the last 20 years. In 2016, Mehrotra et al. showed that African Americans were still 60% less likely to be treated with home HD and 47% less likely to be treated with PD in comparison with Whites.[142]

Genetic variants associated with complex diseases, such as DM or CKD, constitute a major scientific challenge. Jun et al. performed a deep whole-genome analysis of large Mexican-American pedigrees to understand the role of rare-sequence variations in T2DM and concluded that rare expression quantitative trait loci explain a substantial, yet minor, portion of expression heritability.[143]

Ethnic differences may affect risk assessment and therapeutic approaches in clinical care. How clinically meaningful these may be is controversial. For example, normal hemoglobin A1c (Hb_{A1c}) concentrations are different among African Americans, Mexican Americans, and Whites, yet these differences do not influence the power of Hb_{A1c} as a diagnostic or prognostic tool in patients of different ethnic groups.[144] Biomarkers associated with increased risk of all-cause of mortality in ESRD, such as fibroblast growth factor-23, are not significantly modified by ethnicity.[145]

CONCLUSIONS

Factors related to lower socioeconomic status, racial heritage, and ethnicity interact in complex manners to modify the risk of developing CKD, especially in disadvantaged communities. Conditions that predispose to CKD such as hypertension, DM, or obesity can be more prevalent in these communities, due to differences in predisposing genetic background, prenatal and perinatal care, and experiences, including low birth weight, inadequate diets, infectious diseases, or exposure to toxins. ESRD incidence tends to rise in communities with social deprivation, and provision of RRT depends mostly on health care expenditures and national economic strength.

Strategies to provide renal care for all, such as prevention of kidney disease, early referral, timely dialysis initiation, and equalizing opportunities for kidney transplantation can be achieved through a concerted effort between nephrologists, governments, patients, charitable organizations, and industry.

References

1. Garcia-Garcia G, Jha V, Tao Li PK, Garcia-Garcia G, Couser WG, Erk T, et al. Chronic kidney disease (CKD) in disadvantaged populations. *Clin Kidney J* 2015;**8**(1):3–6.
2. Omran AR. The epidemiologic transition: a key of the epidemiology of population change. *Milbank Mem Fund Q* 1971;**49**:509–38.
3. Daw J. Contribution of four comorbid conditions to racial/ethnic disparities in mortality risk. *Am J Prev Med* 2017;**52**(1S1):S95–102.
4. Shenk MK, Kaplan HS, Hooper PL. Status competition, inequality, and fertility: implications for the demographic transition. *Philos Trans R Soc Lond B Biol Sci* 2016;**371**(1692):20150150.
5. Reddy KS, Yusuf S. Emerging epidemic of cardiovascular disease in developing countries. *Circulation* 1998;**97**:596–601.
6. Pearson TA, Jamison DT, Tergo-Gauderies J. Cardiovascular disease. In: Jamison DT, Mosley WH, editors. *Disease control priorities in developing countries*. New York, NY: Oxford University Press; 1993.
7. Brace CL. *"Race" is a four-letter word: the genesis of the concept*. New York: Oxford University Press; 2005. p. 326.
8. Hunt LM, Megyesi MS. The ambiguous meanings of the racial/ethnic categories routinely used in human genetics research. *Soc Sci Med* 2008;**66**(2):349–61.
9. Senior P, Bhopal R. Ethnicity as a variable in epidemiological research. *Br Med J* 1994;**309**:327–8.
10. Burchard EG, Ziv E, Coyle N, Gomez SL, Tang H, Karter AJ, et al. The importance of race and ethnic background in biomedical research and clinical practice. *N Engl J Med* 2003;**348**(12):1170–5.
11. Patzer RE, McClellan WM. Influence of race, ethnicity and socioeconomic status on kidney disease. *Nat Rev Nephrol* 2012;**8**(9):533–41.
12. Vart P, van Zon SKR, Gansevoort RT, Bültmann U, Reijneveld SA. SES, chronic kidney disease, and race in the U.S.: a systematic review and meta-analysis. *Am J Prev Med* 2017;**53**(5):730–9.
13. Crews DC, McClellan WM, Shoham DA, Gao L, Warnock DG, Judd S, et al. Low income and albuminuria among REGARDS (reasons for geographic and racial differences in stroke) study participants. *Am J Kidney Dis* 2012;**60**(5):779–86.
14. Raffensperger S, Kuczmarski MF, Hotchkiss L, Cotugna N, Evans MK, Zonderman AB. Effect of race and predictors of socioeconomic status on diet quality in the HANDLS Study sample. *J Natl Med Assoc* 2010;**102**(10):923–30.
15. Fouque D, Laville M. Low protein diets for chronic kidney disease in non diabetic adults. *Cochrane Database Syst Rev* 2009;**8**(3):CD001892.
16. Boone-Heinonen J, Gordon-Larsen P, Kiefe CI, Shikany JM, Lewis CE, Popkin BM. Fast food restaurants and food stores: longitudinal associations with diet in young to middle-aged adults: the CARDIA study. *Arch Intern Med* 2011;**171**(13):1162–70.
17. Jones-Burton C, Mishra SI, Fink JC, Brown J, Gossa W, Bakris GL, et al. An in-depth review of the evidence linking dietary salt intake and progression of chronic kidney disease. *Am J Nephrol* 2006;**26**(3):268–75.
18. Malhotra R, Cavanaugh KL, Blot WJ, Ikizler TA, Lipworth L, Kabagambe EK. Higher protein intake is associated with increased risk for incident end-stage renal disease among blacks with diabetes in the Southern Community Cohort Study. *Nutr Metabol Cardiovasc Dis* 2016;**26**(12):1079–87.
19. Adjei DN, Stronks K, Adu D, Snijder MB, Modesti PA, Peters RJG, et al. Relationship between educational and occupational levels, and chronic kidney disease in a multi-ethnic sample – the HELIUS study. *PLoS One* 2017;**12**(11):e0186460.
20. De Luca A, Hankard R, Borys JM, Sinnett D, Marcil V, Levy E. Nutriepigenomics and malnutrition. *Epigenomics* 2017;**9**(6):893–917.
21. Dennison E, Fall C, Cooper C, Barker D. Prenatal factors influencing long-term outcome. *Horm Res* 1997;**48**(S1):25–9.
22. Nistala R, Hayden MR, Demarco VG, Henriksen EJ, Lackland DT, Sowers JR. Prenatal programming and epigenetics in the genesis of the cardiorenal syndrome. *Cardiorenal Med* 2011;**1**(4):243–54.
23. Raphael D. Poverty in childhood and adverse health outcomes in adulthood. *Maturitas* 2011;**69**(1):22–6.
24. Böger CA, Heid IM. Chronic kidney disease: novel insights from genome-wide association studies. *Kidney Blood Press Res* 2011;**34**(4):225–34.
25. Hamet P, Haloui M, Harvey F, Marois-Blanchet FC, Sylvestre MP, Tahir MR, et al. PROX1 gene CC genotype as a major determinant of early onset of type 2 diabetes in slavic study participants from action in diabetes and vascular disease: preterax and diamicron MR controlled evaluation study. *J Hypertens* 2017;**35**(S1):S24–32.
26. Everett CJ, Thompson OM, Dismuke CE. Exposure to DDT and diabetic nephropathy among Mexican Americans in the 1999-2004 National Health and Nutrition Examination Survey. *Environ Pollut* 2017;**222**:132–7.
27. Franceschini N, Deng Y, Flessner MF, Eckfeldt JH, Kramer HJ, Lash JP, et al. Smoking patterns and chronic kidney disease in US Hispanics: Hispanic community Health Study/Study of Latinos. *Nephrol Dial Transplant* 2016;**31**(10):1670–6.
28. Barsoum R. In: Schriei RW, et al., editors. *Diseases of the kidney and urinary tract*. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 2013–55.
29. Lewis MJ, Jawad AS. The effect of ethnicity and genetic ancestry on the epidemiology, clinical features and outcome of systemic lupus erythematosus. *Rheumatology* 2017;**56**(S1):i67–77.
30. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. *Lancet* 2013;**382**(9888):260–72.
31. Barsoum RS. Chronic kidney disease in the developing world. *N Engl J Med* 2006;**354**(10):997–9.
32. United States Renal Data System. *USRDS 2015 annual data report: epidemiology of kidney disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2015.
33. Li PK, Chow KM, Van de Luijtgaarden MW, Johnson DW, Jager KJ, Mehrotra R, et al. Changes in the worldwide epidemiology of peritoneal dialysis. *Nat Rev Nephrol* 2017;**13**(2):90–103.
34. Komenda P, Lavallee B, Ferguson TW, Tangri N, Chartrand C, McLeod L, et al. The prevalence of CKD in rural Canadian indigenous peoples: results from the First Nations Community Based Screening to Improve Kidney Health and Prevent Dialysis (FINISHED) screen, triage, and treat program. *Am J Kidney Dis* 2016;**68**(4):582–90.
35. Dart A, Lavallee B, Chartrand C, McLeod L, Ferguson TW, Tangri N, et al. Screening for kidney disease in Indigenous Canadian children: the FINISHED screen, triage and treat program. *Paediatr Child Health* 2018;**23**(7):e134–42.
36. Gao S, Manns BJ, Culleton BF, Tonelli M, Quan H, Crowshoe L, et al. Prevalence of chronic kidney disease and survival among Aboriginal people. *J Am Soc Nephrol* 2007;**18**:2953–9.
37. Zacharias JM, Young TK, Riediger ND, Roulette J, Bruce SG. Prevalence, risk factors and awareness of albuminuria on a Canadian First Nation: a community-based screening study. *BMC Public Health* 2012;**12**:290.
38. Conley J, Tonelli M, Quan H, Manns BJ, Palacios-Derflingher L, Bresee LC, et al. Association between GFR, proteinuria, and adverse outcomes among White, Chinese, and South Asian individuals in Canada. *Am J Kidney Dis* 2012;**59**:390–9.

39. Samuel SM, Foster BJ, Hemmelgarn BR, Nettel-Aguirre A, Crowshoe L, Alexander RT, et al. Pediatric Renal Outcomes Canada Group. Incidence and causes of end-stage renal disease among Aboriginal children and young adults. *CMAJ* 2012; **184**(14):E758–64.
40. Dyck RF. Mechanisms of renal disease in indigenous populations: influences at work in Canadian indigenous peoples. *Nephrology* 2001;**6**:3–7.
41. Tonelli M, Hemmelgarn B, Kim AK, Bertazzon S, Klarenbach S, Manns B, et al. Association between residence location and likelihood of kidney transplantation in Aboriginal patients treated with dialysis in Canada. *Kidney Int* 2006;**70**:826–8.
42. Tonelli M, Hemmelgarn B, Manns B, Davison S, Bohm C, Gourishankar S, et al. Use and outcomes of peritoneal dialysis among Aboriginal people in Canada. *J Am Soc Nephrol* 2005;**16**: 482–8.
43. Xie Y, Bowe B, Mokdad AH, Xian H, Yan Y, Li T, et al. Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. *Kidney Int* 2018;**94**(3):567–81.
44. Correa-Rotter R. Renal replacement therapy in the developing world: are we on the right track, or should there be a new paradigm? *J Am Soc Nephrol* 2007;**18**(6):1635–6.
45. Cusumano AM, Garcia-Garcia G, Gonzalez-Bedat MC, Marinovich S, Lugon J, Poblete-Badal H, et al. Latin American Dialysis and Transplant Registry: 2008 prevalence and incidence of end-stage renal disease and correlation with socioeconomic indexes. *Kidney Int Suppl* 2013;**3**:153–6.
46. Cerdas M. Chronic kidney disease in Costa Rica. *Kidney Int* 2005; **68**(Suppl. 97):S31–3.
47. Santa Cruz F, Cabrera W, Barreto B, Mayor MM, Baez D. Kidney disease in Paraguay. *Kidney Int* 2005;**68**(S97):S120–5.
48. Gómez-Dantés H, Fullman N, Lamadrid-Figueroa H, Cahuana-Hurtado L, Darney B, Avila-Burgos L, et al. Dissonant health transition in the states of Mexico, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2016;**388**(10058): 2386–402.
49. Torres-Toledano M, Granados-García V, López-Ocaña LR. Global burden of disease of chronic kidney disease in Mexico. *Rev Med Inst Mex Seguro Soc* 2017;**55**(Suppl. 2):S118–23.
50. Alegre-Díaz J, Herrington W, López-Cervantes M, Gnatiuc L, Ramirez R, Hill M, et al. Diabetes and cause-specific mortality in Mexico city. *N Engl J Med* 2016;**375**(20):1961–71.
51. Herrera J, Rodríguez-Iturbe B. End-stage renal disease and acute glomerulonephritis in Goajiro Indians. *Kidney Int Suppl* 2003;**83**: S22–6.
52. Perico N, Plata R, Anabaya A, Codreanu I, Schieppati A, Ruggenenti P, et al. Strategies for national health care systems in emerging countries: the case of screening and prevention of renal disease progression in Bolivia. *Kidney Int Suppl* 2005;**97**:S87–94.
53. National Campaign of World Kidney Day 2010, Peruvian Society of Nephrology. Microalbuminuria in adult outpatients not receiving nephrological care and with risk factors for chronic kidney disease in Peruvian nephrology departments. *Nefrologia* 2012; **32**(2):180–6.
54. Herrera-Añazco P, Taype-Rondan A, Lazo-Porras M, Alberto Quintanilla E, Ortiz-Soriano VM, Hernandez AV. Prevalence of chronic kidney disease in Peruvian primary care setting. *BMC Nephrol* 2017;**18**(1):2469.
55. De Moura L, Andrade SS, Malta DC, Pereira CA, Passos JE. Prevalence of self-reported chronic kidney disease in Brazil: National Health Survey of 2013. *Rev Bras Epidemiol* 2015;**18**(Suppl. 2): 181–91.
56. Pinto SW, Sesso R, Vasconcelos E, Watanabe YJ, Pansute AM. Follow-up of patients with epidemic poststreptococcal glomerulonephritis. *Am J Kidney Dis* 2001;**38**(2):249–55.
57. Correa-Rotter R, Wesseling C, Johnson RJ. CKD of unknown origin in Central America: the case for a Mesoamerican nephropathy. *Am J Kidney Dis* 2014;**63**(3):506–20.
58. Johnson RJ, Sánchez-Lozada LG. Chronic kidney disease: Mesoamerican nephropathy–new clues to the cause. *Nat Rev Nephrol* 2013;**9**(10):560–1.
59. Madero M, García-Arroyo FE, Sánchez-Lozada LG. Pathophysiologic insight into MesoAmerican nephropathy. *Curr Opin Nephrol Hypertens* 2017;**26**(4):296–302.
60. Shaheen FAM, Souqiyyeh MZ. Kidney health in the Middle East. *Clin Nephrol* 2010;**74**(S1):S85–8.
61. Sitprija V. Nephrology in South East Asia: fact and concept. *Kidney Int* 2003;**63**(S83):S128–30.
62. Jha V. Current status of end-stage renal disease care in India and Pakistan. *Kidney Int Suppl* 2013;**3**:157–60.
63. Zhang L, Long J, Jiang W, Shi Y, He X, Zhou Z, et al. Trends in chronic kidney disease in China. *N Engl J Med* 2016;**375**:905–6.
64. Sabanayagam C, Lim SC, Wong TY, Lee J, Shankar A, Tai ES. Ethnic disparities in prevalence and impact of risk factors of chronic kidney disease. *Nephrol Dial Transplant* 2010;**25**: 2564–70.
65. Cheung N, Teo K, Zhao W, Wang JJ, Neelam K, Tan NYQ, et al. Prevalence and associations of retinal emboli with ethnicity, stroke, and renal disease in a multiethnic Asian Population. The Singapore epidemiology of eye disease study. *JAMA Ophthalmol* 2017;**135**(10):1023–8.
66. Feng L, de Silva HA, Jehan I, Naheed A, Kasturiratne A, Himani G, et al. Regional variation in chronic kidney disease and associated factors in hypertensive individuals in rural South Asia: findings from control of blood pressure and risk attenuation-Bangladesh, Pakistan and Sri Lanka. *Nephrol Dial Transplant* 2018. [in press]. https://doi.org/10.1093/ndt/gfy184.
67. Hasan M, Sutradhar I, Gupta RD, Sarker M. Prevalence of chronic kidney diseasein South Asia: a systematic review. *BMC Nephrol* 2018;**19**(1):291.
68. Gharbi MB. Renal replacement therapies for end-stage renal disease in North Africa. *Clin Nephrol* 2010;**74**(S1):S17–9.
69. Mani MK. Experience with a program for prevention of chronic renal failure in India. *Kidney Int* 2005;**67**(S94):75–8.
70. Agarwal SK, Dash SC, Irshad M, Raju S, Singh R, Pandey RM. Prevalence of chronic renal failure in adults in Delhi, India. *Nephrol Dial Transplant* 2005;**20**(8):1638–42.
71. Rajapurkar M, Dabhi M. Burden of disease – prevalence and incidence of renal disease in India. *Clin Nephrol* 2010;**74**(S1): S9–12.
72. Abd ElHafeez S, Bolignano D, D'Arrigo G, Dounousi E, Tripepi G, Zoccali C. Prevalence and burden of chronic kidney disease among the general population and high-risk groups in Africa: a systematic review. *BMJ Open* 2018;**8**(1):e015069.
73. Stanifer JW, Jing B, Tolan S, Helmke N, Mukerjee R, Naicker S, Patel U. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Glob Health* 2014;**2**(3):e174–81.
74. Hodel NC, Hamad A, Praehauser C, Mwangoka G, Kasella IM, Reither K, et al. The epidemiology of chronic kidney disease and the association with non-communicable and communicable disorders in a population of sub-Saharan Africa. *PLoS One* 2018; **13**(10):e0205326.
75. Marie Patrice H, Moussa O, Francois K, Yacouba M, Hugo M, Henry L. Prevalence and associated factors of chronic kidney

disease among patients infected with human immunodeficiency virus in Cameroon. *Iran J Kidney Dis* 2018;**12**(5):268–74.
76. Naicker S. End-stage renal disease in sub-Saharan Africa. *Kidney Int Suppl* 2013;**3**:161–3.
77. Stewart JH, McCredie MR, McDonald SP. The incidence of treated end-stage renal disease in New Zealand Maori and Pacific Island People and in indigenous Australians. *Nephrol Dial Transplant* 2004;**19**(3):678–85.
78. Hoy WE, Mott SA, Mc Donald SP. An expanded nationwide view of chronic kidney disease in Aboriginal Australians. *Nephrology* 2018;**23**(1):98.
79. Collins VR, Dowse GK, Finch CF, Zimmet PZ, Linnane AW. Prevalence and risk factors for micro-macroalbuminuria in diabetic subjects and entire population of Nauru. *Diabetes* 1989;**38**: 1602–10.
80. Hodge AM, Dowse GK, Zimmet PZ. Microalbuminuria, cardiovascular risk factors, and insulin resistance in two populations with a high risk of type 2 diabetes mellitus. *Diabet Med* 1996;**13**: 441–9.
81. Hoy W, McDonald SP. Albuminuria: marker or target in indigenous populations. *Kidney Int* 2004;**66**(S92):S25–31.
82. McDonald SP, Maguire GP, Hoy WE. Renal function and cardiovascular risk markers in a remote Australian Aboriginal community. *Nephrol Dial Transplant* 2003;**18**:1555–61.
83. Hoy WE, Samuel T, Mott SA, Kincaid-Smith PS, Fogo AB, Dowling JP, et al. Renal biopsy findings among Indigenous Australians: a nationwide review. *Kidney Int* 2012;**82**:1321–31.
84. Hoy WE, Hughson MD, Zimanyi M, Samuel T, Douglas-Denton R, Holden L, et al. Distribution of volumes of individual glomeruli in kidneys at autopsy: association with age, nephron number, birth weight and body mass index. *Clin Nephrol* 2010; **74**(S1):S105–12.
85. Haysom L, Williams R, Hodson E, Lopez-Vargas P, Roy LP, Lyle D, et al. Risk of CKD in Australian indigenous and nonindigenous children: a population-based cohort study. *Am J Kidney Dis* 2009; **53**:229–37.
86. Hazel TJ, Hill PS. Renal disease in the aboriginal community of Woorabinda. *Aust J Rural Health* 2006;**14**(1):20–3.
87. McDonald S. Incidence and treatment of ESRD among indigenous peoples of Australasia. *Clin Nephrol* 2010;**74**(S1):S28–31.
88. Weil EJ, Nelson RG. Kidney disease among the indigenous peoples of Oceania. *Ethn Dis* 2006;**16**(S2):S24–30.
89. Gao S, Manns BJ, Culleton BF, Tonelli M, Quan H, Crowshoe L, et al. Access to health care among status Aboriginal people with chronic kidney disease. *CMAJ* 2008;**179**:1007–12.
90. Yeates K, Tonelli M. Chronic kidney disease among Aboriginal people living in Canada. *Clin Nephrol* 2010;**74**(S1):S57–60.
91. McDonald SP, Russ GR. Burden of end-stage renal disease among indigenous peoples in Australia and New Zealand. *Kidney Int* 2003;**63**(S83):S123–7.
92. Collins JF. Kidney disease in Maori and Pacific people in New Zealand. *Clin Nephrol* 2010;**74**(S1):S61–5.
93. Caskey FJ. Renal replacement therapy: can we separate the effects of social deprivation and ethnicity? *Kidney Int Suppl* 2013;**3**:246–9.
94. Valdez-Ortiz R, Navarro-Reynoso F, Olvera-Soto MG, Martin-Alemañy G, Rodríguez-Matías A, Hernández-Arciniega CR, et al. Mortality in patients with chronic renal disease without health insurance in Mexico: opportunities for a National Renal Health policy. *Kidney Int Rep* 2018;**3**(5):1171–82.
95. Garcia-Garcia G, Monteon-Ramos JF, Garcia-Bejarano H, Gomez-Navarro B, Hernandez-Reyes I, Lomeli AM, et al. Renal replacement therapy among disadvantaged populations in Mexico: a report from the Jalisco Dialysis and Transplant Registry (REDTJAL). *Kidney Int* 2005;**68**(S97):S58–61.
96. Garcia-Garcia G, Briseño-Renteria G, Luquin-Arellano VH, Gao Z, Gill J, Tonelli M. Survival among patients with kidney failure in Jalisco, Mexico. *J Am Soc Nephrol* 2007;**18**:1922–7.
97. Sakhuja V, Sud K. End-stage renal disease in India and Pakistan: burden of disease and management issues. *Kidney Int* 2003; **63**(S83):S115–8.
98. Aviles-Gomez R, Luquin-Arellano VH, Garcia-Garcia G, Ibarra-Hernandez M, Briseño-Renteria G. Is renal replacement therapy for all possible in developing countries? *Ethn Dis* 2006;**16**(S2): S2–70.
99. Harding K, Mersha TB, Pham PT, Waterman AD, Webb FA, Vassalotti JA, et al. Health disparities in kidney transplantation for African Americans. *Am J Nephrol* 2017;**46**(2):165–75.
100. Lunsford SL, Simpson KS, Chavin KD, Menching KJ, Miles LG, Shilling LM, et al. Racial disparities in living kidney donation: is there a lack of willing donors or an excess of medically unsuitable candidates? *Transplantation* 2006;**82**:876–81.
101. Mejía-Vilet JM, Córdova-Sánchez BM, Arreola-Guerra JM, Alberú J, Morales-Buenrostro LE. Facing the metabolic syndrome epidemic in living kidney donor programs. *Ann Transplant* 2016; **21**:456–62.
102. Tonelli M, Chou S, Gourishankar S, Jhangri GS, Bradley J, Hemmelgarn B. Wait-listing for kidney transplantation among Aboriginal hemodialysis patients. *Am J Kidney Dis* 2005;**46**: 1117–23.
103. Rodrigue JR, Pavlakis M, Egbuna O, Paek M, Waterman AD, Mandelbrot DA. The "house calls" trial: a randomized controlled trial to reduce racial disparities in live donor kidney transplantation: rationale and design. *Contemp Clin Trials* 2012; **33**:811–8.
104. Rodrigue JR, Cornell DL, Kaplan B, Howard RJ. A randomized trial of a home-based educational approach to increase live donor kidney transplantation: effects in blacks and whites. *Am J Kidney Dis* 2008;**51**:663–70.
105. Melanson TA, Hockenberry JM, Plantinga L, Basu M, Pastan S, Mohan S, et al. New kidney allocation system associated with increased rates of transplants among Black and Hispanic patients. *Health Aff* 2017;**36**(6):1078–85.
106. Bornemann K, Croswell E, Abaye M, Bryce CL, Chang CH, Good DS, et al. Protocol of the KTFT-TALK study to reduce racial disparities in kidney transplant evaluation and living donor kidney transplantation. *Contemp Clin Trials* 2017;**53**:52–9.
107. Norris KC, Nicholas SB. Racial disparities in end-of-life issues in patients with chronic kidney disease. *Am J Nephrol* 2016;**44**:81–3.
108. Eneanya ND, Wenger JB, Waite K, Crittenden S, Hazar DB, Volandes A, et al. Racial disparities in end-of-life communication and preferences among chronic kidney disease patients. *Am J Nephrol* 2016;**44**(1):46–53.
109. Cervantes L, Jones J, Linas S, Fischer S. Qualitative Interviews exploring palliative care perspectives of Latinos on dialysis. *Clin J Am Soc Nephrol* 2017;**12**(5):788–98.
110. Song MK, Ward SE, Lin FC, Hamilton JB, Hanson LC, Hladik GA, et al. Racial differences in outcomes of an advance care planning intervention for dialysis patients and their surrogates. *J Palliat Med* 2016;**19**(2):134–42.
111. Gonzalez K, Ulloa JG, Moreno G, Echeverría O, Norris K, Talamantes E. Intensive procedure preferences at the end of life (EOL) in older Latino adults with end stage renal disease (ESRD) on dialysis. *BMC Nephrol* 2017;**18**(1):319.
112. Freedman BI, Sink KM, Hugenschmidt CE, Hughes TM, Williamson JD, Whitlow CT, et al. Associations of early kidney disease with brain magnetic resonance imaging and cognitive function in African Americans with type 2 diabetes mellitus. *Am J Kidney Dis* 2017;**70**(5):627–37.

113. Van den Beukel TO, de Goeij MC, Dekker FW, Siegert CE, Halbesma N, PREPARE Study Group. Differences in progression to ESRD between black and white patients receiving predialysis care in a universal health care system. *Clin J Am Soc Nephrol* 2013;**8**(9):1540–7.
114. Fischer MJ, Hsu JY, Lora CM, Ricardo AC, Anderson AH, Bazzano L, et al. CKD progression and mortality among Hispanics and non-Hispanics. *J Am Soc Nephrol* 2016;**27**(11):3488–97.
115. Chou SH, Tonelli M, Bradley JS, Gourishankar S, Hemmelgarn BR, Alberta Kidney Disease Network. Quality of care among Aboriginal hemodialysis patients. *Clin J Am Soc Nephrol* 2006;**1**(1):58–63.
116. Udayaraj UP, Ben-Shlomo Y, Roderick P, Steenkamp R, Ansell D, Tomson CRV, et al. Ethnicity, socioeconomic status, and attainment of clinical practice guideline standards in dialysis patients in the United Kingdom. *Clin J Am Soc Nephrol* 2009;**4**:979–87.
117. Chandie Shaw PK, Vandenbroucke JP, Tjandra YI, Rosendaal FR, Rosman JB, Geerlings W, et al. Increased end-stage diabetic nephropathy in Indo-Asian immigrants living in The Netherlands. *Diabetologia* 2002;**45**:337–41.
118. Ahmed AT, Mohammed SA, Williams DR. Racial discrimination & health: pathways & evidence. *Indian J Med Res* 2007;**126**:318–27.
119. Beydoun MA, Poggi-Burke A, Zonderman AB, Rostant OS, Evans MK, Crews DC. Perceived discrimination and longitudinal change in kidney function among urban adults. *Psychosom Med* 2017;**79**(7):824–34.
120. Fukagawa M, Komaba H. Chronic kidney disease-mineral and bone disorder in Asia. *Kidney Dis* 2017;**3**(1):1–7.
121. Harding K, Mersha TB, Vassalotti JA, Webb FA, Nicholas SB. Current state and future trends to optimize the care of chronic kidney disease in African Americans. *Am J Nephrol* 2017;**46**(2):176–86.
122. https://www.healthypeople.gov/2020/topics-objectives/topic/chronic-kidney-disease.
123. https://www.nih.gov/news-events/news-releases/nih-funds-precision-medicine-research-focus-health-disparities.
124. Ong SW, Jassal SV, Miller JA, Porter EC, Cafazzo JA, Seto E, et al. Integrating a smartphone-based self-management system into usual care of advanced CKD. *Clin J Am Soc Nephrol* 2016;**11**:1054–62.
125. Davidson TM, McGillicuddy J, Mueller M, Brunner-Jackson B, Favella A, Anderson A, et al. Evaluation of an mHealth medication regimen self-management program for African American and Hispanic uncontrolled hypertensives. *J Personalized Med* 2015;**5**:389–405.
126. Horvat L, Horey D, Romios P, Kis-Rigo J. Cultural competence education for health professionals. *Cochrane Database Syst Rev* 2014;**5**: CD009405.
127. Soltero EG, Konopken YP, Olson ML, Keller CS, Castro FG, Williams AN, et al. Preventing diabetes in obese Latino youth with prediabetes: a study protocol for a randomized controlled trial. *BMC Public Health* 2017;**17**(1):261.
128. Sekkarie MA, Abdel-Rahman EM. Cultural challenges in the care of refugees with end-stage renal disease: what western nephrologists should know. *Nephron* 2017;**137**(2):85–90.
129. Scholz N. The public health dimension of the European migrant crisis. http://www.pewglobal.org/2016/08/02/.
130. Van Biesen W, Vanholder R, Vanderhaegen B, Lameire N, Wanner C, Wiecek A, et al. Renal replacement therapy for refugees with end-stage kidney disease: an international survey of the nephrological community. *Kidney Int Suppl* 2016;**6**:35–41.
131. Buja A, Gini R, Visca M, Damiani G, Federico B, Francesconi P, et al. Prevalence of chronic diseases by immigrant status and disparities in chronic disease management in immigrants: a population-based cohort study, Valore Project. *BMC Public Health* 2013;**13**:504.
132. Madden EF, Qeadan F. Dialysis hospitalization inequities by Hispanic ethnicity and immigration status. *J Health Care Poor Underserved* 2017;**28**(4):1509–21.
133. Lenzi J, Avaldi VM, Rucci P, Pieri G, Fantini MP. Burden of multimorbidity in relation to age, gender and immigrant status: a cross-sectional study based on administrative data. *BMJ Open* 2016; **6**(12):e012812.
134. Levin A, Adams E, Barrett BJ, Beanlands H, Burns KD, Chiu HH, et al. Canadians seeking solutions and innovations to overcome chronic kidney disease (Can-SOLVE CKD): form and function. *Can J Kidney Health Dis* 2018;**5**. https://doi.org/10.1177/2054358117749530.
135. Ryz K, Tangri N, Verrelli M, Schneider J, Lesyk A, Eng A, et al. A before and after cross-sectional analysis of a public health campaign to increase kidney health awareness in a Canadian province. *BMC Res Notes* 2015;**8**:695.
136. Gutierrez OM, Isakova T, Smith K, Epstein M, Patel N, Wolf M. Racial differences in postprandial mineral ion handling in health and in chronic kidney disease. *Nephrol Dial Transplant* 2010;**25**: 3970–7.
137. Norris KC, Williams SF, Rhee CM, Nicholas SB, Kovesdy CP, Kalantar-Zadeh K, et al. Hemodialysis disparities in African Americans: the deeply integrated concept of race in the social fabric of our society. *Semin Dial* 2017;**30**(3):213–23.
138. Utumatwishima JN, Chung ST, Bentley AR, Udahogora M, Sumner AE. Reversing the tide - diagnosis and prevention of T2DM in populations of African descent. *Nat Rev Endocrinol* 2018;**14**(1):45–56.
139. Boulware LE, Cooper LA, Ratner LE, LaVeist TA, Powe NR. Race and trust in the health care system. *Publ Health Rep* 2003;**118**(4): 358–65.
140. Ito K, Bick AG, Flannick J, Friedman DJ, Genovese G, Parfenov MG, et al. Increased burden of cardiovascular disease in carriers of APOL1 genetic variants. *Circ Res* 2014;**114**(5): 845–50.
141. Horowitz CR, Ferryman K, Negron R, Sabin T, Rodriguez M, Zinberg RF, et al. Race, genomics and chronic disease: what patients with African ancestry have to say. *J Health Care Poor Underserved* 2017;**28**(1):248–60.
142. Mehrotra R, Soohoo M, Rivara MB, Himmelfarb J, Cheung AK, Arah OA, et al. Racial and ethnic disparities in use of and outcomes with home dialysis in the United States. *J Am Soc Nephrol* 2016;**27**(7):2123–34.
143. Jun G, Manning A, Almeida M, Zawistowski M, Wood AR, Teslovich TM, et al. Evaluating the contribution of rare variants to type 2 diabetes and related traits using pedigrees. *Proc Natl Acad Sci USA* 2018;**115**(2):379–84.
144. Selvin E. Are there clinical implications of racial differences in HbA1c? A difference, to be a difference, must make a difference. *Diabetes Care* 2016;**39**(8):1462–7.
145. Souma N, Isakova T, Lipiszko D, Sacco RL, Elkind MS, DeRosa JT, et al. Fibroblast growth factor 23 and cause-specific mortality in the general population: the Northern Manhattan study. *J Clin Endocrinol Metab* 2016;**101**(10):3779–86.

QUESTIONS AND ANSWERS

Question 1

Which one of the following statements about the definition of ethnicity is most accepted?

A. Ethnicity is defined as the genetic, biologic, or epigenetic factors related to inheritance, which are not modified by environmental or cultural factors
B. Ethnicity is a system of categories based on physical characteristics such as skin color or hair type
C. Ethnicity is a category of people who identify with each other according to their country of birth
D. Ethnicity, or race, is an old term based on biological terms without scientific basis and must not be used anymore
E. Ethnicity is a group of people who share subjective identification, cultural tradition, common population history, physical appearance, religion, and language

Answer: E

Contemporary definitions of race and ethnicity are controversial, and occasionally indistinguishable, as they may be viewed as a genetic inheritance or as a social construct. The most accepted term of ethnicity emphasizes the social definition of the term. **The correct answer is E**, given that ethnicity is commonly accepted as a community whose shared heritage offers important characteristics in common between the members of a group, including physical appearance (the old concept of "race"), subjective identification, cultural tradition, common population history, religion, and language. The answers A and B are incorrect, given that these old definitions based on the biological terms of race are no longer recommended.

Question 2

A 29-year-old Latino man is referred to your clinic for evaluation of asymptomatic kidney disease which has been detected by routine laboratory examination. He noticed occasional intermittent weakness and muscle cramps, which he relates to his previous work, yet he has been asymptomatic for several months. On physical examination, height is 161 cm, weight is 57 kg, body mass index is 22 kg/m^2, blood pressure is 110/80 mm Hg, and pulse is 71 beats per minute. The remainder of his examination is unremarkable. The following laboratory values are obtained:

Serum electrolytes:
Hemoglobin 13 g/dL
S[Cr] 3.2 mg/dL (24.8 mL/min/1.73 m^2 by CKD-EPI); previous S[Cr] 3.2 mg/dL (3 months ago) and 3.1 mg/dL (5 months ago).
BUN 58 mg/dL
Serum electrolytes: S[Na] 138 mEq/L, S[K] 3.8 mEq/L,S[Cl] 97 mEq/L, S[HCO_3] 19 mEq/L
Urine protein:creatine ratio: 0.32 g/g Cr. Urinalysis: SG 1.010, negative leukocyte esterase negative, hemoglobin negative, protein 30 mg/dL.
Glycated hemoglobin 5.5%
Hepatitis panel and HIV negative.
Ultrasound examination of kidneys shows small kidneys with decreased cortical thickness. A kidney biopsy is deferred.

Which one of the following clinical data is the most valuable to guide a diagnosis of kidney disease in this case?

A. The patient's mother has a diagnosis of diabetic nephropathy and his father has hypertension
B. The patient smoked five cigarettes per day, for 3 years, and consumed 20 g of alcohol every weekend for 2 years
C. The patient worked as sugarcane cutter in Nicaragua for 9 years
D. Antinuclear antibody titer is 1:80 (nucleolar pattern); normal C3 and C4
E. Tuberculin skin test 15 mm, positive interferon-gamma release

Answer: C

The clinical presentation is of a healthy young man who has asymptomatic, moderately advanced CKD. The ultrasonographic characteristics of kidneys preclude performance of a biopsy. **The correct answer is C** as the history of agricultural work in Central America, in the absence of any clear etiology, suggests a high probability of Mesoamerican nephropathy. Tubular atrophy and fibrosis coupled with widespread chronic glomerular changes are changes observed on biopsies. The diagnosis is suspected in Central American agricultural workers who perform physically demanding work for long hours in conditions of heat exposure. Even though family history of diabetes and hypertension increases the risk for these conditions in first degree relatives, especially in ethnic groups living in the same environment, these clinical data are of less relevance compared with the past work exposure (option A is incorrect). Likewise, the patient has latent tuberculosis (option E) and tobacco exposure (option B), yet these are insufficient elements to suspect or diagnose CKD. Symptoms of intermittent weakness and muscle cramps are nonspecific and not consistent with a diagnosis of lupus, especially with negative serology (option D).

Question 3

Which of the following statements about the relationship between ethnicity and kidney disease is true?

A. Ethnicity assessment is based on genetic markers more than self-reporting in the majority of clinical studies
B. One of the main objectives of ethnicity studies is to find harmful genes for different races to stratify diagnostic and prognostic clinical tools
C. In general, biochemical values such as electrolytes, glycosylated hemoglobin, parathyroid hormone, or hemoglobin values are radically different among populations of different ethnic origins
D. Health outcomes related to ethnicity are more influenced by socio-ecologic determinants than by genetic inheritance
E. To achieve better clinical outcomes taking into account ethnicity, assessment of race (for example, Black, White, Latino, and Asian) by clinical observers is more useful compared with other alternatives, for example, reporting of ancestry

Answer: D

There are a multiplicity of limitations and controversies regarding the relationship between ethnicity and health. **The correct answer is D**, as health outcomes stratified by ethnicity are less likely a result of genetic inheritance and are strongly influenced by socio-ecologic determinants of health, such as discrimination, educational and income inequalities, imbalances in access to care, availability of health care resources, and exposure to environmental toxins. Answer A is incorrect, as the majority of ethnicity assessments in clinical studies are based on self-report by participants and genetic markers are not well validated. One of the risks of genetic testing, especially in minority ethnic groups, is inappropriately judging a group of people as being sick due to "bad genes." Genetic variants associated with complex diseases explain only a minority of risk factors associated with CKD, most of which are more completely explained by social and environmental exposures, making Answer B incorrect. Answer C is incorrect, considering the majority of biochemical laboratories are not significantly modified by ethnicity, although there are exceptions such as the value of S[Cr] or hemoglobin. Answer E is incorrect, given that ethnicity classification according to physical features, such as skin color and hair texture, is subject to biases and discrimination. A multiplicity of alternatives attempting to categorize ethnicity have been proposed, such as self-questionnaires, clustering patients on genetic marker, or reporting ancestry, yet it is not clear which is best to achieve better clinical outcomes.

Question 4

An 84-year-old Latino man with type 2 DM, with ESRD treated with HD, undergoes follow-up evaluation following a recent diagnosis of metastatic pancreatic cancer. Three months after the diagnosis of cancer, the patient has been hospitalized three times due to episodes of heart failure, venous thromboembolism, and disabling pain. Decisions about suspending HD will be discussed with the patient.

Which one of the following should be taken in account before a decision is made?

A. In general, Latinos prefer to avoid family group decision-making as they make their decisions individually
B. End-of-life attitudes and expectations are similar between white patients and minority ethnic groups
C. Whenever possible, it would be desirable to choose a doctor who is culturally and linguistically similar
D. Latinos treated with HD are less likely to communicate and trust their doctors differently, compared with members of other minority groups
E. Latino groups are more likely to stop HD based on religious beliefs

Answer: C

Understanding and integrating cultural values and preferences into supportive or palliative care improves quality patient-centered care. A one-size-fits-all approach to palliative care perpetuates disparities. **The correct answer is C**, given that Latinos treated with HD favor family group decision-making and want advance care planning conversations to occur at home with someone who is culturally and linguistically congruent. Latinos describe unique cultural preferences, such as avoidance of medications for symptom alleviation and a preference to have family group decision-making and communication of advance care planning, making Answer A incorrect.[109] Option B is incorrect, given that end-of-life issues in HD patients, including decisions about stopping HD, are greatly influenced by ethnicity. New evidence highlights that older Latinos treated with HD are more trusting of their physicians and defer end-of-life care decision-making to their children.

Question 5

Which of the following statements about risk factors related to ethnicity is true?

A. In most of the world, high socioeconomic status is associated with more obesity, hypertension, diabetes, and CKD, compared with low socioeconomic status

B. Tropical countries have at least twice the risk for glomerular diseases in comparison with developed countries
C. Around the world, the most prevalent mode of renal therapy replacement therapy is PD
D. Severe caloric restriction during pregnancy and low birth weight in offspring of ethnic minorities are associated with hematuria or nephritic syndrome in adulthood
E. In the next decades, the potential number of patients with ESRD in developing countries will decrease as a consequence of control and prevention of infectious diseases

Answer: B

Tropical regions, the regions of the Earth flanking the equator, comprise mostly of emerging nations with similarities in terms of risks of kidney diseases. Tropical infections increase the risk of AKI and diverse glomerulonephridites. It has been estimated that there is an increased risk for glomerulonephritis in emerging compared with developed regions of the world. **Answer B is correct**. The interplay between socioeconomic status and CKD is complex, yet evidence suggests that low socioeconomic status is linked to the risk of CKD in multiple cohorts, probably associated with inadequate diet, lesser access to education and health services, and epigenetic interactions related to environmental adversity, so option A is incorrect. Although PD is prevalent in some countries such as China or Mexico, the most prevalent mode of renal therapy replacement around the world is HD; option C is incorrect. Severe caloric restriction during pregnancy and low birth weight are risk factors associated with low nephron mass, microalbuminuria, and low eGFR, yet unassociated with hematuria or nephritic syndrome in adulthood, so option D is incorrect. The projected worldwide population changes suggest that the number of cases of ESRD will increase disproportionately in developing countries, explained by an increase in elderly people. This effect will be enhanced further if the trends of increasing hypertension and DM prevalence persist, competing causes of death such as stroke and CVDs are reduced, and access to treatment improves.

Question 6

Which of the following statements is true?

A. Type 2 DM is the leading cause of ESRD in Latin America
B. Canadian First Nations experience ESRD related to hepatitis B virus and glomerulonephritis more frequently compared with non-First Nations
C. In South Asia, DM is the most common cause of CKD
D. In North Africa, HIV infection is the most common cause of CKD compared with other regions
E. In Oceania, Indigenous people develop ESRD late compared with nonindigenous people

Answer: A

An epidemic of DM has characterized the epidemiological transition in Latin America. DM remains the leading cause of ESRD in Latin America, with the highest rates of DM as percentage of all cases of ESRD being in Puerto Rico (65%), Mexico (51%), Venezuela (42%), and Colombia (42%). **Answer A is correct**. Canadian First Nations experience ESRD 2.5 to 4 times more frequently compared with their non-First Nations counterparts, and those with DM have seven times the rate of diabetic ESRD. Therefore, Answer B is incorrect. Option C is incorrect, given that chronic glomerulonephritis is the most common cause of CKD in South Asia (Cambodia, Indonesia, Singapore, and Vietnam), except in Thailand, where nephrolithiasis is the most common cause of CKD. Although Africa had the highest CKD prevalence in HIV-infected patients, rates are highest in West and sub-Saharan Africa. Therefore, option D is incorrect. The age at which people develop ESRD is considerably younger among indigenous peoples in Oceania than among the mostly white nonindigenous people. Therefore, Answer E is not correct.

CHAPTER

10

Ethnicity and Chronic Kidney Disease in Japan

Hiroko Kanno[a], *Yoshihiko Kanno*[b]

[a]Tokyo Women's Medical University, Tokyo, Japan; [b]Tokyo Medical University, Tokyo, Japan

Abstract

Japan is one of the higher-income countries in Asia, composed of people of almost a single race. Chronic kidney disease prevalence is about 12% in the general population, similar to that seen in other Asian countries. The most common primary kidney disease is immunoglobulin A nephropathy (IgAN). High rates of participation in health checks in school, the workplace, and in the community might increase disease detection of incidental findings of hematuria/proteinuria, rather than due to specific genetic factors. In Japan, tonsillectomy with corticosteroid therapy has become a major choice in treatment of IgAN. Over 90% of end-stage renal disease patients are treated with hemodialysis, with a high survival rate. However, aging is a major factor in dialysis outcomes, due to many aging complications such as sarcopenia, frailty, dementia, and social isolation.

INTRODUCTION

The population of Japan is approximately 125 million, including mostly people of Japanese ethnicity. There are about 70,000 Ryukyuan and 16,000 Ainu members of minority groups. The physical characteristics of the people in Japan are similar to those of other Asians, but the genetic characteristics may differ and polymorphisms related to kidney disease have not been determined.[1,2] Lifestyles and personalities also differ somewhat from those of other Asians.

The common characteristics that reflect the so-called Japanese personality and character include choosing obligations to the community over individual rights, exhibiting politeness and respect in interpersonal relationships, belief in order and stability, tidiness, a strong work ethic, punctuality, attention to keeping promises, and avoidance of religious conflict and terrorism. The effects of these characteristics on health care in Japan are uncertain. Race and beliefs are more related to the prognosis of cardiac failure in low-income patients, compared with economic conditions.[3] In chronic kidney disease (CKD), for which long-term management is important, Japanese lifestyle and character may be critical in disease management.

The Japanese diet is referred to as Washoku (Figure 10.1). "Washoku; traditional dietary cultures of the Japanese" was registered on the Intangible Cultural Heritage UNESCO list in 2013. Although Washoku has not been defined, traditional Japanese dietary patterns include many foods from vegetable sources (fruits, vegetables, grains, corn, beans, and seeds), low to moderate intake of fish and meat, and low intake of lean meat.

FIGURE 10.1 Traditional Japanese food "Washoku." Daily menu for lunch or dinner. Simmered black cod and konjac starch noodle with soy sauce (bottom); simmered daikon radish and boiled shrimp with sweet miso sauce (right); white rice (left); and small salad of corn and asparagus (top). *Photograph is transferred with permission from Kanno Y, editor.* Safety meal for patients receiving renal replacement therapy. *Tokyo: Kagawa Nutrition University Publishing Division; 2016.*

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00010-3

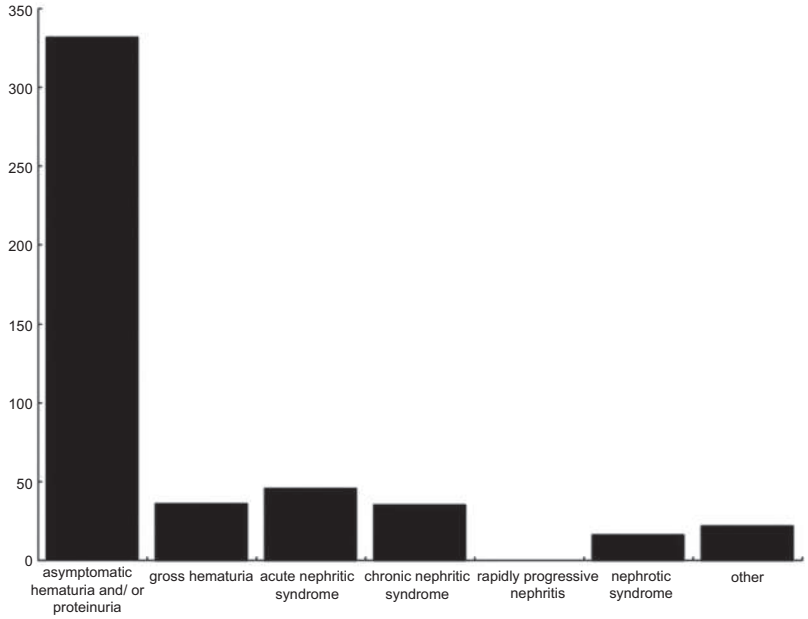


FIGURE 10.2 Clinical manifestation of immunoglobulin A nephropathy (IgAN) among 487 patients. Approximately 68.2% of the patients with IgAN were discovered by asymptomatic proteinuria and/or hematuria by a urinalysis screening program held in Japan. *From reference 6.*

Therefore, the diet can be thought of as an "oriental" Mediterranean diet.

The large amount of salt used as a preservative and for seasoning (in miso and shoyu) is a problem. In a study performed in the 1950s, salt intake was found to be 27 g/day, contributing to a high incidence of stroke.[4] This has now been decreased to about 10 g/day through a public awareness campaign and improvement of food conservation techniques without use of salt. Washoku has a beneficial lipid profile[5] and has traditional protein restriction. Thus, the diet may have long-term renal protective effects if salt use is reduced.

There are racial differences in primary renal diseases that lead to end-stage renal disease (ESRD) and in the incidence and prevalence of cardiovascular disease (CVD). To reduce the number of patients with ESRD and CVD, an effective screening method for CKD is required. In Japan, screening with the urine dipstick test for proteinuria has been used since 1972 for every child and worker, and since 1983 for every resident over 40 years old. Japanese kidney disease management is performed in the context of the Japanese people overall having a strong interest in health, easy access to medical facilities, and relatively low medical expenses. Housewives and the elderly account for about 50% of the population, and dipstick urinalysis is performed for all of them at health checks, contributing to early detection of kidney disease.

There are several reasons for continuing the CKD screening program. First, the rate of proteinuria is high in the Japanese population, and especially in those with neither hypertension nor diabetes. Most of these subjects are asymptomatic, and the only sign of renal disease is urinary abnormalities. Second, the prevalence and incidence of glomerulonephritis, especially immunoglobulin A nephropathy (IgAN), are high in Japanese and Asian people, and urinalysis is the only method for early detection of chronic glomerulonephritis. Third, the 10-year survival of patients with ESRD due to glomerulonephritis is approximately twice that of those with ESRD due to diabetes and nephrosclerosis. Proteinuria is the best predictor of reduced renal function, and the urine dipstick test for proteinuria is less expensive than other tests (Figure 10.2). Therefore, universal screening with this test may be an effective strategy for detecting hematuria and proteinuria and reducing the prevalence of ESRD in Japanese and Asian populations.[6]

EPIDEMIOLOGY

The prevalence of CKD in the adult Japanese population is higher than that in other high-income East Asian countries, such as Hong Kong and Taiwan[7] (Table 10.1). A study by the Japanese Society of Nephrology (JSN) in 2005 estimated that 19.1 million patients had stage 3 CKD in the Japanese adult population of 103.2 million in 2004, with prevalences of 1.4%, 3.6%, 10.8%, 15.9%, 31.8%, 44.0%, and 59.1% at ages 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80–89 years, respectively. About 200,000 patients were predicted to have CKD stages 4 and 5. The prevalence of hypertension, diabetes,

TABLE 10.1 Chronic Kidney Disease Epidemics in North and East Asia

Parameters	Chinese Mainland	Japan	Mongolia	South Korea	Taiwan
Prevalence of CKD,[1] %	10.80	12.90	13.90	13.7[a]	11.90
PREVALENCE OF CKD STAGES,[1,6] %					
1	5.70	0.60	–	2.00	1.02
2	3.40	1.70	–	6.70	3.79
3 (a and b)	1.60	10.40	8.40	4.80	6.81
4	0.10	0.20	1.10	0.20	0.22
5	0.03	0.20	0.20	0.04	0.10
Incidence of treated ESRD[3]	15.4 pmp/yr[b]	284.6 pmp	226.6 pmp	256.0 pmp	455.0 pmp
Prevalence of ESRD[3]	237.3 pmp[c]	2504.8 pmp	–	1571.5 pmp	3219.4 pmp
Prevalence of diabetes,[3] %	9.40	7.70	5	6.30	–
Prevalence of hypertension,[3] %	38.20	43.90	45	30.60	–
Prevalence of nephrologists,[9] %	5.1–10 pmp	>15 pmp	>15 pmp	>15 pmp	>15 pmp

CKD, chronic kidney disease; *ESRD*, end-stage renal disease; *pmp*, per million population.
[a]*The data were based on survey of urban population.*
[b]*The incidence of treated ESRD of China is much higher in big cities (e.g. 107.3 pmp/yr in Beijing and 82.9 pmp/yr in Shanghai).*
[c]*The prevalence of ESRD of China is much higher in big cities (e.g. 524.6 pmp in Beijing and 544.7 pmp in Shanghai).*

and proteinuria increased as the estimated GFR (eGFR) decreased. The prevalence of concurrent CKD was significantly higher in patients with hypertension and diabetes than in the general population, when CKD was defined as an eGFR of <40 mL/min/1.73 m^2 instead of <60 mL/min/1.73 m^2.[8]

There are several theories regarding the high prevalence of CKD in the Japanese population. Greater than 20% of the Japanese population is aged $\geq$60 years. This percentage is much higher than in other countries. With increased average age, the prevalence of CKD becomes higher. Second, Asian populations, including Japanese people, may have a lower normal GFR than Caucasian populations in the US. The average kidney size of Japanese people is smaller (longest axis of 10 cm) than in Caucasians (11 cm). Inulin clearance in healthy Japanese controls in their 20s is about 83 ± 9 mL/min/1.73 m^2 while fasting and 121 ± 16 mL/min/1.73 m^2 after excess protein intake.[9] The average GFR is similar, at 81.4 ± 19.4 mL/min/1.73 m^2, in healthy organ donors in India ($n = 610$, average age 35 years).[10] In contrast, Davis and Shock[11] found that the US population has a higher average GFR of 122.8 ± 16.4 mL/min/1.73 m^2. In another report in a Caucasian population, GFRs were 130 and 120 mL/min/1.73 m^2 in young men and women, respectively. The difference in kidney size may affect the normal GFR in different ethnic groups, but the reason for the differences in normal GFR levels between Asian and Caucasian ethnic groups is not well understood.

The prevalence of diabetic nephropathy is increasing in Japan concurrent with the change from a traditional Japanese to a western lifestyle. The prevalence of overweight subjects increased from 30.3% in 1983 to 36.1% in 1993, while the prevalence of hypertension significantly decreased.[12] The impact of obesity and complications of diabetes mellitus (DM) may be different among races and ethnicities.[13] Public information on the risk of DM and its complications is especially important in Asian countries, because Asians have more fat than non-Asians, even with the same BMI.[14] Knowledge of predictors of DM/ESRD is crucial as a first step toward prevention, and international initiatives on the management of CKD and ESRD have recently been organized to address this issue.[12]

In the town of Hisayama-cho in Kyushu, all residents have undergone screening since the 1960s. All health data from Hisayama-cho have been collected and analyzed at Kyushu University as the Hisayama study, which is a community-based cohort study with the goal of evaluating the effects of lifestyle changes on CVDs in Japan.[15–17] In the series of reports on the Hisayama study, Nagata et al. assessed trends in the prevalence of CKD and risk factors over the last three decades.[18] The prevalence of CKD increased significantly over time in men (13.8% [95% confidence interval (95% CI), 11.4–16.2%] in 1974, 15.9% [95% CI, 13.6–18.2%] in 1988, and 22.1% [95% CI, 19.6–24.6%] in 2002; $p < 0.001$ for trend), but not in women (14.3% [95% CI, 12.2–16.4%], 12.6% [95% CI, 10.9–14.3%], and

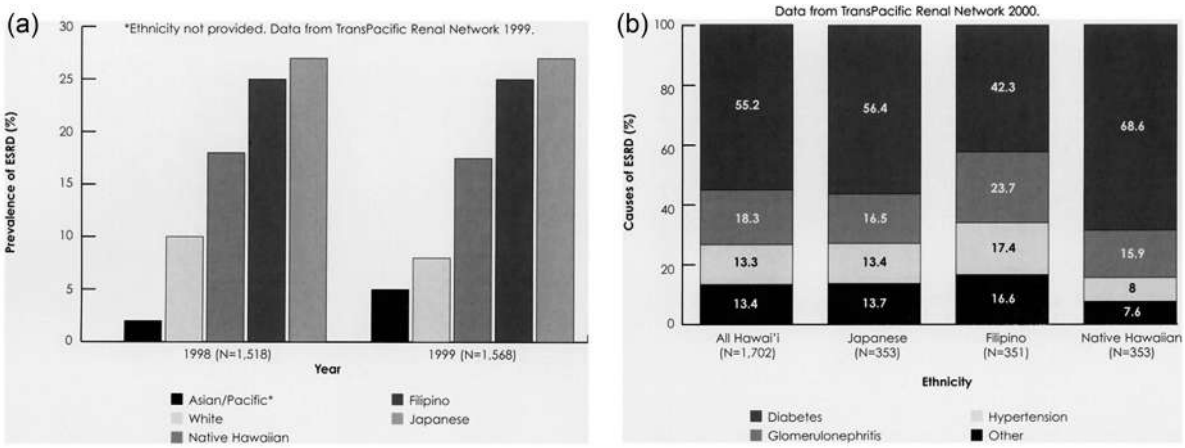


FIGURE 10.3 (a) Prevalence of end-stage renal disease (ESRD) in Hawaii in 1998 and 1999. Japanese show the highest prevalence among five ethnic groups. (b) Causes of ESRD in Hawaii in 2000 by ethnicity. The prevalence of glomerulonephritis in Japanese is lower than other ethnic groups. *From reference 20.*

15.3% [95% CI, 13.4–17.2%]; $p = 0.97$ for trend). The prevalence of CKD stages 3–5 (eGFR <60 mL/min/1.73 m^2) increased over the three decades in both sexes. Despite the widespread use of antihypertensive agents, only 27.0% of men and 47.5% of women with CKD had blood pressure <130/80 mm Hg. The prevalence of metabolic disorders including DM, hypercholesterolemia, and obesity increased over the three decades in both sexes. In the general Japanese population, the prevalence of CKD has also increased significantly in men, but not in women, over the last three decades, but there are regional variations. Thus, the demographics of participants differed in the 1993 and 2003 general screenings in Okinawa, but the prevalence of CKD seemed to be similar or at least did not increase substantially from 1993 to 2003.[19]

Mau et al. compared the prevalence of CKD in Japanese people living in Hawaii with other races.[20] As shown in Figure 10.3, of 1568 patients in Hawaii diagnosed with ESRD in 1999, 88.2% of those on dialysis were of Asian or Pacific Islander ancestry, with the major ethnic groups being Japanese (26.7%), Filipino (24.7%), and Native Hawaiian (17.0%).

In addition to common Japanese views on disease and society, additional ideas that influenced health and well-being were identified: the importance and hierarchy of the family; bachi, which means "curse"; and shikata ga nai, which means "it cannot be helped." Thus, several common themes prevail in the health beliefs and attitudes of Hawaii's ethnically diverse populations. For example, both Asian and Pacific Islander populations have strong ties to family and community, and wellness is achieved through balance or harmony of physical being and nature. They seem to share a sense of fatalism toward their health status, and they value interpersonal relationships, including the patient–physician relationship.

Role of the Japanese Society of Nephrology

The JSN was established in 1959, and now has over 10,000 members. The JSN conducts a range of activities to promote the practice and study of nephrology. These include holding regular meetings as a forum for diffusion of information, publishing journals (Clinical and Experimental Nephrology, CEN Case Reports, Japanese Journal of Nephrology), coordinating clinical research, developing national guidelines, establishing systems for CKD management, and promoting cooperation with related national and international societies. In 2007, the Committee for Standardization of Renal Pathological Diagnosis and the Working Group for the Renal Biopsy Database of the JSN started the first nationwide, web-based, and prospective registry system, the Japan Renal Biopsy Registry (J-RBR), to record pathological, clinical, and laboratory data for renal biopsies. The J-RBR contains data regarding more than 20,000 patients, including age, gender, laboratory data, and clinical and pathological diagnoses, recorded until the end of 2013.

The JSN analyzed clinical and pathological data collected from 818 patients at 18 centers in 2007 and from 1582 patients at 23 centers in 2008. In 2007, the most common clinical diagnosis was chronic nephritic syndrome (47.4%), followed by nephrotic syndrome (16.8%), and renal transplantation (11.2%). Similar rates were found in 2008. For native kidneys, the most common pathological diagnosis was IgAN in 2007 (32.9%) and 2008 (30.2%). Among primary glomerular diseases (except IgAN), membranous nephropathy (MN) was most common in 2007 (31.4%) and 2008 (25.7%).[21]

Ethnic differences in the eGFR equation may affect the epidemiological prevalence of CKD. An equation from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) provides a more accurate eGFR than that from the Modification of Diet in Renal Disease (MDRD) Study, although both include a two-level variable for race (Black and White, and other). Because creatinine generation differs among ethnic groups, a multilevel ethnic variable should allow more accurate estimates across all groups. Stevens et al. developed an equation to calculate eGFR that includes a four-level race variable (Black; Asian; Native American and Hispanic; White and other) using a database of 8254 patients pooled from 10 studies. This equation was then validated in 4014 patients using 17 additional studies from the US and Europe (validation database), and in 1022 patients from China (675), Japan (248), and South Africa (99). In the validation database, the two-level race equation had minimal bias in the Black, Native American and Hispanic, and White and other cohorts. The four-level ethnicity equation significantly improved bias in Asians in the validation dataset and in Chinese, but both equations had a large bias in Japanese and South African patients. Thus, heterogeneity in performance among ethnic and geographic groups precludes use of the four-level race equation.

The CKD-EPI two-level race equation can be used in the US and Europe across a wide range of ethnicities.[22] Because there was a significant discrepancy between measured inulin clearance and eGFR using the 1.0 × MDRD and the Cockcroft Gault equations, it has been suggested that an original eGFR equation is required for Japanese patients.

The MDRD equation modified with the Japanese coefficient (0.881 × MDRD) determined for Japanese CKD patients yielded a lower mean difference and higher accuracy for GFR estimation. In particular, in patients with inulin clearance of 30−59 mL/min/1.73 m^2, the mean difference was significantly smaller with the 0.881 × MDRD equation than with the 1.0 × MDRD equation (1.9 vs. 7.9 mL/min/1.73 m^2; $p < 0.01$). The accuracy was significantly higher, with 60% vs. 39% of the points deviating within 15%, and 97% vs. 87% of points within 50% (both $p < 0.01$). Validation with a different dataset showed that the correlation between eGFR and inulin clearance was better with the 0.881 × MDRD equation than with the 1.0 × MDRD equation. In participants with inulin clearance <60 mL/min/1.73 m^2, the accuracy was significantly higher, with 85% vs. 69% of the points deviating within 50% ($p < 0.01$). The mean difference was also significantly smaller ($p < 0.01$). However, GFR values calculated by the 0.881 × MDRD equation still underestimated inulin clearance in the range >60 mL/min/1.73 m^2.[23]

The final equation for Japanese patients was developed based on a national study directed by the JSN. This was a diagnostic test study using a prospective cross-sectional design, with new equations developed in 413 participants and validated in an additional 350 participants. eGFR was determined with the modified isotope dilution mass spectrometry (IDMS)-traceable four-variable MDRD equation, using the previous Japanese Society of Nephrology Chronic Kidney Disease Initiative (JSN-CKDI) coefficient of 0.741 (equation 1), the previous JSN-CKDI equation (equation 2), and new equations derived in the development dataset: a modified MDRD equation using a new Japanese coefficient (equation 3), and a three-variable Japanese equation (equation 4). Performance of equations was assessed based on bias (eGFR—mGFR), accuracy (percentage of estimates within 15% or 30% of mGFR), root mean squared error, and correlation coefficient. In the development dataset, the new Japanese coefficient was 0.808 (95% CI, 0.728−0.829) for the IDMS-MDRD equation (equation 3), and the three-variable Japanese equation (equation 4) was eGFR (mL/min/1.73 m^2) = 194 × S [Cr]$^{-1.094}$ × Age$^{-0.287}$ × 0.739 (if female). In the validation dataset, bias was −1.3 ± 19.4 vs. −5.9 ± 19.0 mL/min/1.73 m^2 ($p = 0.002$), and accuracy within 30% of mGFR was 73% vs. 72% ($p = 0.6$) for equation 3 vs. equation 1 and −2.1 ± 19.0 vs. −7.9 ± 18.7 mL/min/1.73 m^2 ($p < 0.001$) and 75% vs. 73% ($p = 0.06$) for equation 4 vs. equation 2 ($p = 0.06$). Therefore, equation 4 is more accurate for the Japanese population than the previous equation and is now used as the standard.[24]

CKD PROGRESSION

Umesawa et al. examined 135,007 participants who completed an annual health checkup in 1993−1996 in Ibaraki Prefecture, Japan, and were initially free of CKD (defined as stage 3, 4, or 5 CKD or proteinuria [2+ or 3+] by dipstick evaluation). During follow-up, 7500 and 8964 cases of CKD developed in the northern and southern regions, respectively. Older age, proteinuria (1+), higher systolic blood pressure, medication for hypertension, and current smoking were associated with increased risk for CKD in both sexes. Higher eGFR and daily alcohol intake were associated with lower risk.[25] Despite Japan being a relatively small country, regional variation in CKD progression was found. The incidence of ESRD increased by about 3 times in Japan during the study period, from 81.3 per million (1 m) in 1982 to 237.6/m in 1998. Significant regional differences have been found in the mean (SEM) annual ESRD incidence ($p < 0.01$) and in the rate of increase of ESRD ($p<0.01$) across Japan. Koshinetsu (140 ± 11

per 1 million and 9.1 ± 0.6 per 1 million/year) and Hokuriku (141 ± 12 per 1 million and 9.7 ± 0.5/million/year) were the areas with the lowest incidence and rate of increase. Okinawa (188 ± 17/million/year and 13.4 ± 0.6/million/year) and Kyushu (179 ± 15/million/year and 12.0 ± 0.6/million/year) had the highest incidence and rate of increase.[26]

IGA NEPHROPATHY AND TONSILLECTOMY

O'Shaughnessy reported a large-scale study comparing glomerular disease frequencies across regions and race/ethnicity, using 42,603 diagnosed cases of glomerular disease (median age 47 years, 52% male, 57% White) from 29 laboratories in four continents. Those in Asia were from Japan and Thailand. IgAN (39.5%) and lupus nephritis (16.8%) predominated in Asia (mostly Japan), more than in other regions (22.1% in Europe, 11.8% in US/Canada, and 6.1% in Latin America).[27] In the national renal biopsy database, IgAN was also the most frequent pathological diagnosis.[28] Effects of expression and inhibition of salivary secretory IgA on negative emotions, health, and mood states have been examined in Japanese undergraduates with mild depression.[29] For this frequent glomerulopathy, the JSN has disease-specific original guidelines.[30] In Japan, the major treatment modalities for adult IgAN are renin–angiotensin–aldosterone system (RAAS) blockers, corticosteroids, nonsteroidal immunosuppressive agents, antiplatelet agents, n-3 fatty acids (fish oil), and tonsillectomy with corticosteroid pulse therapy (TSP).

Use of tonsillectomy differs from the international consensus and has a low recommendation grade (C1) in the JSN guidelines: "Tonsillectomy (with corticosteroids) may improve urinary findings in patients with IgAN and slow the progression of renal dysfunction. This may also be considered as a treatment option." Several studies are described in the guidelines as evidence for this treatment. In a retrospective cohort study, Hotta et al. found that TSP normalized urinary findings, which are predictors of renal failure.[31] Additionally, in a nonrandomized comparative study, Komatsu et al. found a higher normalization rate of urinary findings with TSP compared with steroid pulse (SP) therapy alone.[32] However, the level of evidence is regarded as insufficient because these studies were not designed as RCTs. However, at a JSN meeting in 2011, the Ministry of Health, Labor and Welfare Progressive Renal Dysfunction Research Group stated that TSP was more effective than SP therapy alone in reducing urinary protein in RCTs.[33]

After this announcement, Hoshino et al. followed 1127 biopsy-proven IgAN patients with CKD who were treated with TSP (n = 209), SP therapy (n = 103), oral corticosteroids (OS) only (n = 300), or RAAS inhibitors (RAASis) alone (n = 515). The hazard ratios (HRs) for ESRD or death, renal survival, and proteinuria level were analyzed. With TSP as the reference, the overall HRs for SP therapy, OS, and RAASi were 1.33 (0.44–4.04), 3.56 (1.45–8.71), and 3.64 (1.48–8.96), respectively. The respective HRs were 2.99 (0.71–12.54), 5.04 (1.44–17.67), and 7.23 (1.98–26.40) for patients with proteinuria ≥1.0 g/gCr and 0.42 (0.04–4.89), 3.24 (0.79–13.30), and 2.05 (0.52–8.05) for those with proteinuria <1.0 g/gCr. They concluded that TSP may decrease the risk of ESRD more than other therapies for IgAN patients with CKD with eGFR ≥60 mL/min/1.73 m^2 and proteinuria ≥1.0 g/gCr, while outcomes are similar to SP therapy in those with CKD stage 3 or proteinuria <1.0 g/gCr.[34]

In a network meta-analysis of IgAN with proteinuria >1 g/day, a total of 21 RCTs with 1822 participants were included for comparison of seven interventions. The rank of the most effective treatments to induce clinical remission was RAASi plus urokinase, TSP, and RAASi plus steroids, with the surface under the cumulative ranking area (SUCRA) of 0.912, 0.710, and 0.583, respectively. For prevention of ESRD or doubling of S[Cr], RAASi plus steroids (SUCRA 0.012) were most effective, followed by RAASi alone (SUCRA 0.282) and steroids alone (SUCRA 0.494), leaving mycophenolate mofetil as the least effective (SUCRA 0.644).[35] To establish more substantial evidence, the superiority of TSP requires further investigation.

RENAL REPLACEMENT THERAPY IN JAPAN

The annual survey of the Japanese Society for Dialysis Therapy Renal Data Registry was conducted for 4380 dialysis facilities at the end of 2015. 4321 facilities (98.7%) responded. This survey has been carried out since 1968. Initially, the purpose was to ensure the presence of dialysis units nationwide, and not for research. In 1968, there were only 215 patients and 48 consoles. The number of chronic dialysis patients in Japan continues to increase every year and reached 324,986 at the end of 2015 (Figure 10.4). The mean age of these patients was 67.9 years. At the end of 2015, the prevalence was 2592 patients/m population.

Diabetic nephropathy was the most common primary disease among prevalent dialysis patients (38.4%), followed by chronic glomerulonephritis (29.8%) and nephrosclerosis (9.5%). The rates of diabetic nephropathy and nephrosclerosis have been increasing yearly, while chronic glomerulonephritis has been declining. The number of incident dialysis patients in 2015 was

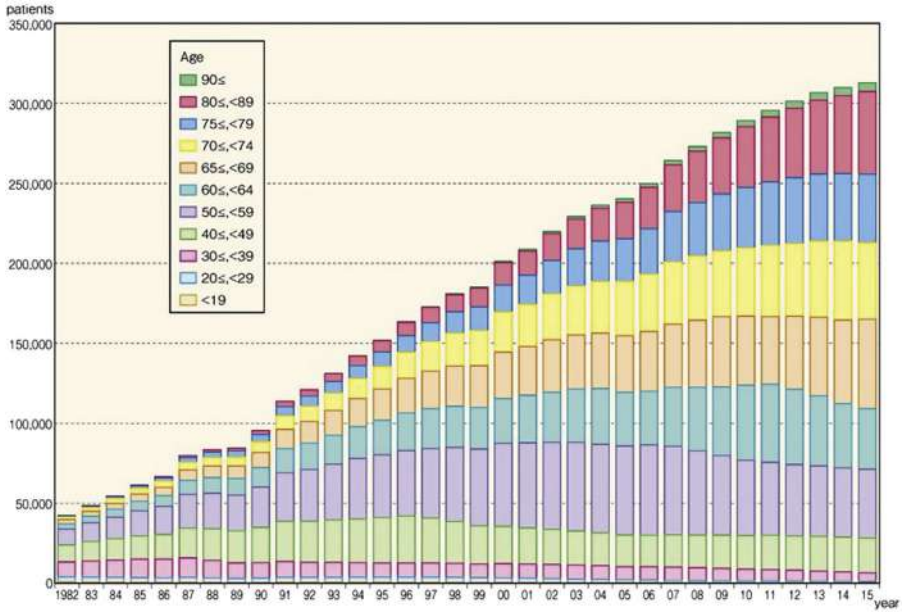


FIGURE 10.4 Prevalent dialysis patient distribution by age, 1982–2015. *From reference 36.*

39,462. This number has remained stable since 2008. The average age was 69.2 years, and diabetic nephropathy (43.7%) was the most common cause of incident dialysis. Cases caused by diabetes have not changed in number for the last several years. A total of 31,608 dialysis patients died in 2015, yielding a crude mortality of 9.6%. The number of peritoneal dialysis (PD) patients was 9322 in 2015, with a slight increase from 2014.[36]

In 2015, there were 71,270 dialysis patients aged <60 years, 141,634 aged 60–74, and 100,308 aged ≥75 years. Males were more frequent in all age categories, but as age increased, the percentage of females also increased. Women accounted for 40.8% of elderly dialysis patients. Elderly patients had the shortest dialysis period of 5.71 years, with 54.8% having received dialysis for <5 years and 80.3% for <10 years. Nephrosclerosis (16.6%) was the more common primary kidney disease among elderly dialysis patients than in other age groups. The rates of diabetic nephropathy (34.3%) and chronic glomerulonephritis (26.5%) were lower than in other age groups. The rates of myocardial infarction, cerebral infarction, and proximal femur fracture were high in the medical histories of elderly dialysis patients. No differences were found for cerebral hemorrhage or limb amputation.

Figure 10.5 shows the overall survival of hemodialysis patients. Despite progress in technology and medicine, the 5-year survival rate remains about 60%. This may partly be because patients who originally had expected survival of less than 5 years (i.e. those aged >90 years or with multiple complications) have started dialysis recently.

Itoh et al. established a scoring system for prediction of 15-year survival in 622 Japanese dialysis patients. In this system, age ≥65 years, diabetic nephropathy, hypotension, pre-HD cardiothoracic ratio ≥50%, pre-HD BNP ≥250 pg/mL, and pre-HD abnormal findings on electrocardiograms were prognostic risk factors.[37]

On March 11, 2011, the Great East Japan Earthquake highlighted the vulnerability of chronic dialysis patients to disasters. Of 4205 facilities, 314 could not offer daily dialysis sessions for various reasons that depended on seismic intensity (Figure 10.6). To minimize negative effects on patients treated with chronic maintenance dialysis in future large-scale disasters, it will be important to promote self-help for dialysis facilities and to develop mutual assistance systems within local communities. The effects of the 2011 earthquake showed that each facility requires comprehensive disaster management, including vibration control of large machinery, use of flexible tubes, securing patient beds, and flexible use of bedside consoles. Local governments should plan for support of chronic dialysis therapy in their areas and assign roles among themselves for dealing with a large number of patients with acute kidney injury during long-term disruption of lifelines, including electricity, water supply, and fuel.[38]

A characteristic of Renal Replacement Therapy in Japan is the variation in therapy selection. About 300,000 of 320,000 ESRD patients receive HD, while

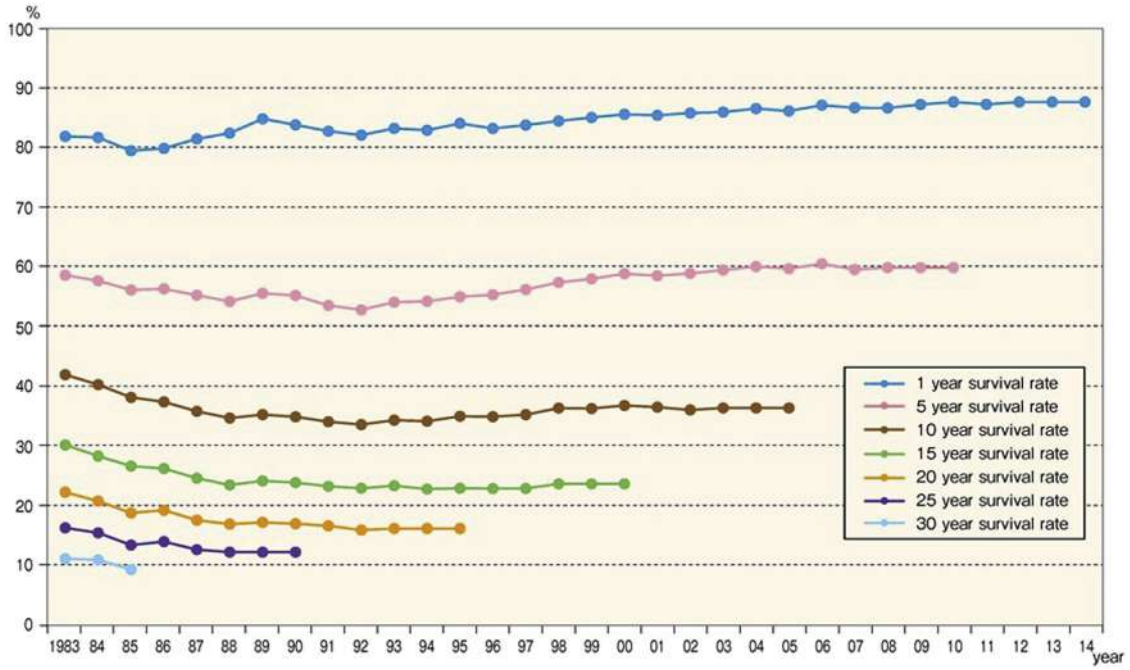


FIGURE 10.5 1-, 5-, 10-, 15-, 20-, 25-, and 30-year survival rate in Japanese dialysis patients from 1983 to 2014. *From reference 36.*

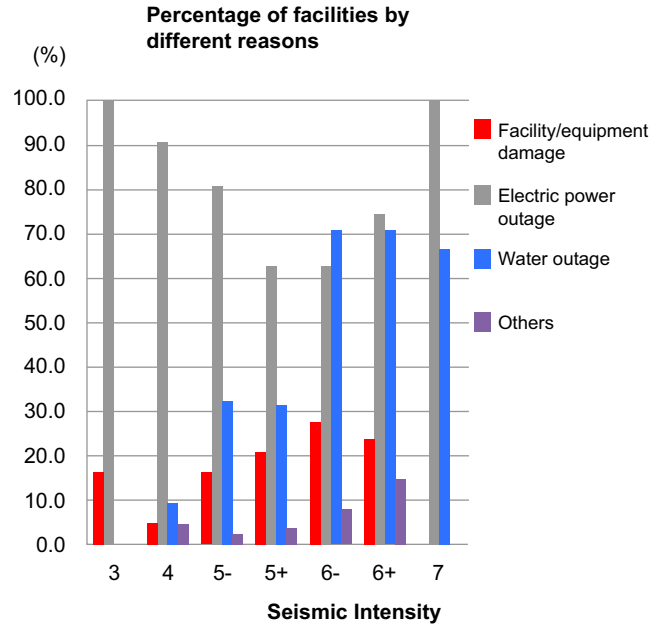


FIGURE 10.6 Reasons for interruption of dialysis services related to seismic intensity showing the percentage of different reasons. The most common reason for interruption was power outage. Some facilities that were hit by an earthquake of moderate intensity (3 or 4) also experienced interruption due to facility damage. *From reference 38.*

fewer patients receive PD and renal transplantation. The first deceased and living donor kidney transplants were performed in Japan in 1956 and 1964, respectively. More transplants were performed after the introduction of cyclosporine in 1983, and the number has gradually increased, with 1661 transplants performed in 2015. In addition, outcomes have improved year by year. The indications for transplantation have also expanded in various ways, including recipient and donor age, primary diseases, ABO-incompatible and highly sensitized cases, and preemptive transplantation.[39]

CONCLUSION

As observed in other countries, CKD has become one of the most important diseases in Japan over the last decade. Countermeasures have been started through the combined efforts of the government and the JSN. Etiological causes of ESRD used to be chronic glomerulonephritis, mainly IgAN, but have now been replaced by diabetic nephropathy. Nephrosclerosis associated with aging is expected to increase in the future. As these diseases lack fundamental treatment, patients, families and physicians need to manage the lifestyle implications of CKD and ESRD.

References

1. Horibe H, Fujimaki T, Oguri M, et al. Association of a polymorphism of the interleukin 6 receptor gene with chronic kidney disease in Japanese individuals. *Nephrology* 2015;**20**:273–8.
2. Yoshida T, Kato K, Fujimaki T, et al. Association of genetic variants with chronic kidney disease in Japanese individuals. *Clin J Am Soc Nephrol* 2009;**4**:883–90.

3. Zhang Y, Baik SH. Race/Ethnicity, disability, and medication adherence among medicare beneficiaries with heart failure. *J Gen Intern Med* 2014;**29**:602−7.
4. Takahashi E, Sasaki N, Takeda J, et al. The geographic distribution of cerebral hemorrhage and hypertension in Japan. *Hum Biol* 1957; **29**:139−66.
5. Shijo Y, Maruyama C, Nakamura E, et al. Japan diet intake changes serum phospholipid fatty acid compositions in middle-aged men: a pilot study. *J Atheroscler Thromb* 2018;**26**:3−13.
6. Yamagata K, Iseki K, Nitta K, et al. Chronic kidney disease perspectives in Japan and the importance of urinalysis screening. *Clin Exp Nephrol* 2008;**12**:1−8.
7. Wang J, Zhang L, Tang SC, et al. Disease burden and challenges of chronic kidney disease in North and East Asia. *Kidney Int* 2018;**94**: 22−5.
8. Imai E, Horio M, Iseki K, et al. Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. *Clin Exp Nephrol* 2007; **11**:156−63.
9. Orita Y, Okada M, Harada S, et al. Skim soy protein enhances GFR as much as beefsteak protein in healthy human subjects. *Clin Exp Nephrol* 2004;**8**:103−8.
10. Barai S, Bandopadhayaya GP, Patel CD, et al. Do healthy potential kidney donors in India have an average glomerular filtration rate of 81.4 ml/min? *Nephron Physiol* 2005;**101**:p21−26.
11. Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J Clin Investig* 1950;**29**:496−507.
12. Iseki K. Predictors of diabetic end-stage renal disease in Japan. *Nephrology* 2005;**10**(Suppl. l):S2−6.
13. Lee KU, Park JY, Kim SW, et al. Prevalence and associated features of albuminuria in Koreans with NIDDM. *Diabetes Care* 1995;**18**: 793−9.
14. Mandavilli A, Cyranoski D. Asia's big problem. *Nat Med* 2004;**10**: 325−7.
15. Fujishima M, Kiyohara Y, Kato I, et al. Diabetes and cardiovascular disease in a prospective population survey in Japan: the Hisayama Study. *Diabetes* 1996;**45**(Suppl. 3):S14−16.
16. Katsuki S. Epidemiological and clinicopathological study on cerebrovascular disease in Japan. *Prog Brain Res* 1966;**21**:64−89.
17. Kikumura T, Omae T, Ueda K, et al. Long-term changes in blood pressure prior to the development of cerebral infarction–the Hisayama study. *J Chronic Dis* 1981;**34**:239−48.
18. Nagata M, Ninomiya T, Doi Y, et al. Trends in the prevalence of chronic kidney disease and its risk factors in a general Japanese population: the Hisayama Study. *Nephrol Dial Transplant* 2010;**25**: 2557−64.
19. Iseki K, Kohagura K, Sakima A, et al. Changes in the demographics and prevalence of chronic kidney disease in Okinawa, Japan (1993 to 2003). *Hypertens Res* 2007;**30**:55−62.
20. Mau MK, West M, Sugihara J, et al. Renal disease disparities in Asian and Pacific-based populations in Hawai'i. *J Natl Med Assoc* 2003;**95**:955−63.
21. Sugiyama H, Yokoyama H, Sato H, et al. Japan Renal Biopsy Registry: the first nationwide, web-based, and prospective registry system of renal biopsies in Japan. *Clin Exp Nephrol* 2011;**15**: 493−503.
22. Stevens LA, Claybon MA, Schmid CH, et al. Evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating the glomerular filtration rate in multiple ethnicities. *Kidney Int* 2011;**79**:555−62.
23. Imai E, Horio M, Nitta K, et al. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol* 2007;**11**:41−50.
24. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;**53**: 982−92.
25. Umesawa M, Sairenchi T, Haruyama Y, et al. Validity of a risk prediction equation for CKD after 10 years of follow-up in a Japanese population: the Ibaraki prefectural health study. *Am J Kidney Dis* 2018;**71**:842−50.
26. Usami T, Koyama K, Takeuchi O, et al. Regional variations in the incidence of end-stage renal failure in Japan. *J Am Med Assoc* 2000;**284**:2622−4.
27. O'Shaughnessy MM, Hogan SL, Thompson BD, et al. Glomerular disease frequencies by race, sex and region: results from the International Kidney Biopsy Survey. *Nephrol Dial Transplant* 2018;**33**:661−9.
28. Sugiyama H, Yokoyama H, Sato H, et al. Japan renal biopsy registry and Japan kidney disease registry: committee report for 2009 and 2010. *Clin Exp Nephrol* 2013;**17**:155−73.
29. Takagi S, Ohira H. Effects of expression and inhibition of negative emotions on health, mood states, and salivary secretory immunoglobulin A in Japanese mildly depressed undergraduates. *Percept Mot Skills* 2004;**98**:1187−98.
30. Yuzawa Y, Yamamoto R, Takahashi K, et al. Evidence-based clinical practice guidelines for IgA nephropathy 2014. *Clin Exp Nephrol* 2016;**20**:511−35.
31. Hotta O, Miyazaki M, Furuta T, et al. Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy. *Am J Kidney Dis* 2001;**38**:736−43.
32. Komatsu H, Fujimoto S, Hara S, et al. Effect of tonsillectomy plus steroid pulse therapy on clinical remission of IgA nephropathy: a controlled study. *Clin J Am Soc Nephrol* 2008;**3**:1301−7.
33. Kawamura T, Yoshimura M, Miyazaki Y, et al. A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy. *Nephrol Dial Transplant* 2014;**29**:1546−53.
34. Hoshino J, Fujii T, Usui J, et al. Renal outcome after tonsillectomy plus corticosteroid pulse therapy in patients with immunoglobulin A nephropathy: results of a multicenter cohort study. *Clin Exp Nephrol* 2016;**20**:618−27.
35. Yang P, Zou H, Xiao B, et al. Comparative efficacy and safety of therapies in IgA nephropathy: a network meta-analysis of randomized controlled trials. *Kidney Int Rep* 2018;**3**:794−803.
36. Masakane I, Taniguchi M, Nakai S, et al. Annual dialysis data report 2015, JSDT renal data registry. *Ren Replace Ther* 2018;**4**:19.
37. Itoh H, Kawaguchi H, Tabata Y, et al. A new risk scoring system for prediction of long-term mortality in patients on maintenance hemodialysis. *Ren Replace Ther* 2016;**2**:49.
38. Masakane I, Akatsuka T, Yamakawa T, et al. Survey of dialysis therapy during the Great East Japan Earthquake Disaster and recommendations for dialysis therapy preparation in case of future disasters. *Ren Replace Ther* 2016;**2**:48.
39. Yagisawa T, Mieno M, Yoshimura N, et al. Current status of kidney transplantation in Japan in 2015: the data of the kidney transplant registry committee, Japanese society for clinical renal transplantation and the Japan society for transplantation. *Ren Replace Ther* 2016;**2**:68.

QUESTIONS AND ANSWERS

Question 1

Which nations have a lower CKD prevalence compared with Japan?

A. South Korea
B. Mexico
C. US
D. China
E. Germany

Answer: D

As shown in Table 10.1, CKD prevalence in China (10.8%) is lower than in Japan (12.9%). The prevalence of CKD is higher in the US, Mexico, and Germany.

Question 2

Which is the most frequent primary glomerulonephritis in Japan?

A. MN
B. Lupus nephritis
C. IgAN
D. FSGS
E. Minimal change disease

Answer: C

As in other Asian countries, IgAN is the most common primary glomerulonephritis in Japan. However, as a cause of ESRD, diabetic kidney disease and hypertensive glomerulosclerosis are more common than primary glomerulonephritis.

Question 3

Which element is heavily used in Washoku?

A. Oil
B. Salt
C. Sugar
D. Protein
E. Dairy products

Answer: B

Washoku is approved as low-protein, low oil healthy food worldwide, but its problem is salt-rich seasoning. Salt is a major factor in the high prevalence of stroke in Japan, prompting the Japanese Ministry of Health, Labour and Welfare to work on lowering the worked salt intake of Japanese people.

Question 4

What is the mean age of patients receiving dialysis therapy in Japan?

A. 48 years old
B. 56 years old
C. 62 years old
D. 68 years old
E. 72 years old

Answer: D

The number of chronic dialysis patients in Japan reached 324,986 at the end of 2015. The mean age of these patients was 67.9 years and for incident patients 69.2 years. Both of these ages have increased yearly.

Question 5

What did Japanese dialysis facilities learn about disaster management from the 2011 earthquake?

A. Vibration control of large machinery
B. Flexible use of bedside consoles
C. Securing patient beds
D. Use of flexible tubes
E. All of the above

Answer: E

Of 4205 facilities in Japan, 314 could not offer daily dialysis sessions mainly because of electric power and water shortages. In each facility, vibration control of large machinery, use of flexible tubes, securing patient beds, and flexible use of bedside consoles have been improved since the earthquake.

CHAPTER

11

Ethnicity and Chronic Kidney Disease in Africa

Dwomoa Adu[a], *Akinlolu O. Ojo*[b]

[a]Honorary Senior Research Fellow and Consultant Nephrologist, School of Medicine and Dentistry, University of Ghana, Accra, Ghana; [b]Associate Vice President for Clinical Research and Global Health Initiatives, University of Arizona Health Sciences, Tucson, AZ, United States

Abstract

The estimated prevalence of chronic kidney disease (CKD) in adults in sub-Saharan Africa (SSA) is 13.9%. The major causes of CKD in Africa are hypertension, diabetes mellitus, glomerulonephritis, and HIV infection. These diseases occur on a background of a high prevalence of Apolipoprotein L1 (*APOL1*) gene variants G1 and G2, which are common in Africans, presumably having evolved to provide protection against Trypanosomiasis some 10,000 years ago. The prevalence of CKD in individuals in Africa with hypertension ranges from 15 to 48%, in individuals with diabetes mellitus from 14.1 to 32.6% and in individuals with HIV infection from 5.6 to 27.3%. Up to 33% of patients with end-stage renal disease (ESRD) in Africa have glomerulonephritis. Other major causes of CKD in Africa are *Schistosoma mansoni* (*S. mansoni*) and *Schistosoma haematobium* (*S. haematobium*) infection and sickle cell disease. The major causes of CKD in children in Africa are glomerulonephritis and congenital abnormalities of the kidneys and urinary tract. In SSA there is a startling gap between the estimated incidence of ESRD due to diabetes and hypertension of 239 per million population and patients receiving renal replacement therapy of 1.5%.

INTRODUCTION

Africa is geographically and ethnically diverse and has a population of over one billion people. Africans face a growing burden of chronic kidney disease (CKD), which is driven by several factors. First, there is a demographic transition in which populations in Africa are aging with a corresponding increase in the prevalence of obesity, diabetes, and hypertension. Second, this is occurring in populations in which infections such as human immunodeficiency virus (HIV) and schistosomiasis, which increase the risk of CKD, are common. Third, many African populations have a genetic susceptibility to CKD driven by allelic variants in the gene encoding Apolipoprotein L1 (*APOL1*), which evolved to provide protection against Trypanosomiasis some 10,000 years ago.[1,2] These APOL1 variants are also associated with an increased risk of HIV-associated nephropathy (HIVAN), hypertensive CKD, focal and segmental glomerulosclerosis (FSGS), sickle cell nephropathy, and lupus.[3–5] The prevalence of CKD in sub-Saharan Africa (SSA) is estimated to be 13.9%.[6] The Global Burden of Disease study reported that individuals in low sociodemographic index countries (SDI) such as SSA had a greater percentage of subjects with CKD at an earlier age (adolescents and young adulthood) compared with high SDI countries.[7] Our data from SSA confirm this, as Africans succumb to end-stage renal disease (ESRD) 20–30 years earlier than the median age of onset of ESRD among Europeans.[8] The major causes of CKD in Africa are HIV infection, hypertension, glomerulonephritis, and diabetes mellitus. Renal replacement therapy (RRT) is either unavailable or unaffordable, making the development of ESRD a death sentence for many. In addition predialysis CKD extracts an enormous toll in premature mortality, cardiovascular comorbidities, and health care expenditures.[9] CKD imposes severe human suffering on the African continent as well as a huge economic burden.

PREVALENCE OF CKD IN SSA

Africa has a population of 1.2 billion people with 969.2 million in SSA and 225.1 million in Northern Africa.[10] Africa is facing a double burden of disease in which infections such as HIV, schistosomiasis, and hepatitis B (HBV) and C (HCV) viruses are still common. At the same time, Africa is facing an increasing burden of noncommunicable diseases (NCD) such as obesity, hypertension, and diabetes, all of which are risk factors

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00011-5

for CKD. CKD appears to be common in SSA, but until recently there were very little data on prevalence. A recent systematic review and meta-analysis of 21 medium- and high-quality studies reported that the prevalence of CKD in SSA was 13.9% (95% CI: 12.2–15.7)[6] (Table 11.1). Other systematic reviews, pooled analyses, and meta-analyses from Africa have come to broadly similar conclusions. In the meta-analysis of Kaze et al.[11] the overall prevalence of CKD (stages 1–5) was 15.8% (95% CI: 12.1–19.9). For CKD stages 3–5 it was 4.6% (95% CI: 3.3–6.1). These rates of CKD are comparable to that of 13.1% (95% CI 12.0–14.1%) in the US.[12] The study of Abd El-Hafeez et al. reported the pooled prevalence of CKD to be a little lower than in the studies described above at 10.1% (95% CI: 9.8–10.5%).[13] The prevalence of CKD was also higher in West/Central Africa at 16.5% than in North Africa where the prevalence was lower.[13] The study of Kaze et al. provided similar conclusions.[11] All the studies report significant heterogeneity in the prevalence of CKD in Africa. This is to be expected as African populations differ at many levels, including genetic ancestry and the prevalence of hypertension, diabetes mellitus, and HIV infection. In a study in Ghana we reported that the prevalence of CKD in 2424 individuals aged 25–70 years was 13.3% (95% CI 11.6–13.4).[14] By contrast in a study from Tanzania the prevalence of CKD was 7.0% (95% CI 3.8–12.3).[15] There may be a genetic cause for this difference, because in Tanzania the APOL1 renal risk variant frequency of 11–17%[16] is less than half of that of the 41% found in Ghana.[2,17] CKD is thus a major NCD in Africa. Patients with CKD are at increased risk of developing ESRD, as well as cardiovascular disease and death.[18]

CAUSES OF CKD IN AFRICA

The major causes of CKD in Africa are hypertension, diabetes mellitus, glomerulonephritis, and HIV infection, and these occur on a background of a high prevalence of *APOL1* variants, which increase the risk of CKD.

Apolipoprotein L1 Nephropathy in Sub-Saharan Africa

Studies showing variable susceptibilities in African populations to HIVAN had postulated the existence of an "African renal susceptibility gene" prior to the established association between risk variants on chromosome 22 and CKD in people of African ancestry.[19] APOL1 G1 and G2 variants have been identified as potentially causative and progression factors in people of African descent, and possible mechanisms by which these renal risk variants lead to the development and progression of CKD of various etiologies are beginning to be defined.[1,2] The variability in the population frequencies in the heterozygous, homozygous, and compound homozygous states of *APOL1* G1 and G2 alleles in various African populations are shown in Figure 11.1 and Table 11.2. The highest frequencies of the G1 and G2 variants have been observed among the Yoruba and Igbo tribes in Southern Nigeria, with East Africans generally having the lowest frequencies.[17] The heterozygote *APOL1* G1 and G2 variant proteins are most effective as trypanolytic factors for the *Trypanosoma brucei rhodesiense* (*T. b. rhodesiense*).[1] A recent study showed the *APOL1* G2 variant leads to strong protection against *T. b. rhodesiense* infection in Uganda, while the G1 variant did not.[20] The association between *APOL1* variants and *Trypanosoma brucei gambiense* (*T. b. gambiense*) infection is also complex, in that individuals carrying the G1 and G2 variant were not protected from developing *T. b. gambiense* infections. However individuals carrying the G1 variant were more likely to have asymptomatic latent infections, whereas individuals with the G2 variant had severe active infection.[20] This study provides some explanation for why the highest allele frequencies of G1 variants are found in West Africa, where the *T. b. gambiense* is endemic, but do not explain why the highest frequencies of the G2 variants are also found in West Africa. The discrepancy in the trypanosomal distributions and the G1 and G2 variants allele frequencies may be due to more recent evolution of the G2 variant and possible evolution of the G1 variant in response to other intracellular or extracellular pathogens. Studies are ongoing to determine more precisely the explanations for the discrepancies between the patterns of trypanosomal species endemicity and the *APOL1* risk variants geographic allele distributions.

Genetic epidemiologic studies of *APOL1* nephropathy have been undertaken in only a few thousand individuals in African populations, in contrast to large numbers of studies in people of African descent in the US, Brazil, and Western Europe.[21] Most studies consistently show that (1) the presence of *APOL1* renal risk variants (G1/G1, G2/G2, or G1/G2) confers highest susceptibility to HIVAN with odds ratio as high as 89;[5] (2) in addition to HIVAN, *APOL1* risk variants increase susceptibility to CKD due to sickle cell disease,[22] systemic lupus erythematosus,[23] FSGS,[24] and hypertension-associated kidney disease[1], but not to diabetic nephropathy; and (3) homozygous or compound homozygous *APOL1* renal risk variants may be progression factors for most forms of CKD that have been studied, including diabetic nephropathy.[25] The Human Heredity and Health in Africa (H3Africa) Consortium funded by the National Institutes of Health (NIH) and the Wellcome Trust are conducting studies in large populations in

TABLE 11.1 Prevalence of Chronic Kidney Disease (CKD) in Africa

	Sumaili EK et al.[134] Democratic Republic of Congo	**Stanifer JW et al.[6] Meta-analysis**	**Seck SM et al.[135] Senegal**	**Hill NR et al.[136] Meta-analysis**	**Kaze AD et al.[11] Meta-analysis**	**Abd ElHafeez S et al.[13] Systematic Review**	**Stanifer JW et al.[15] Tanzania**	**Adjei DN et al.[14] Ghana**	**Coresh J et al.[12] NHANES (1999−2004) US**
CKD1	2%								1.78% (1.35−2.25)
CKD2	2.4%								3.24% (2.61−3.88)
CKD 3	7.8%								7.69% (7.02−8.36)
CKD 4	0%								0.35% (0.25−0.45)
CKD 5	0.2%								
CKD Overall	12.4% (95% CI: 11.0−15.1)	13.9% (95% CI: 12.2−15.7)	6.1% (95% CI: 4.7−7.6)	8.66% (95% CI: 1.31, 16.01)	15.8% (95% CI: 12.1−19.9)	10.1%; 95% CI: (9.8−10.5)	7.0% (95% CI 3.8−12.3)	13.1% (95% CI: 11.6−14.4)	13.1% (95% CI: 12.0−14.1)
CKD 3−5				7.6 (95% CI: 6.10−8.10)	4.6% (95% CI: 3.3−6.1)				

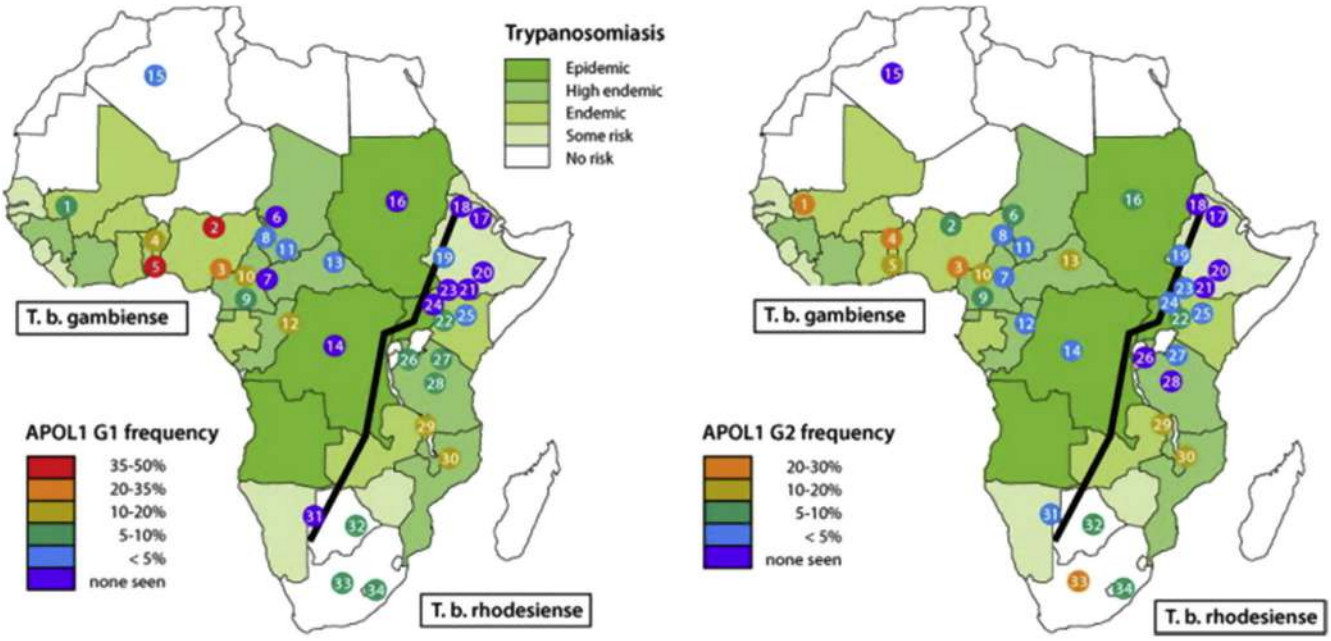


FIGURE 11.1 Map of Africa showing the geographic prevalence of *APOL1* G1 and G2 Variants and *Trypanosoma* infections. *Reprinted with permission from reference 17. Copyright © 2014 Elsevier.*

SSA to more precisely characterize the variability in susceptibility to CKD among geographic and ethnic populations and elucidate the etiologies of the CKD for which the *APOL1* risk variants confer increased risk of causality and progression.[8,26]

The prevalence of *APOL1* risk alleles in West Africa is twice as high as in African Americans, and this would be expected to be associated with an increased prevalence of CKD. Although this appears to be the case, confirmatory studies are required. The high prevalence of CKD in East and South Africa that have a lower frequency of *APOL1* risk alleles suggests the presence of other "African susceptibility genes" and/or other environmental factors contributing to the high burden of CKD in SSA.[27]

In African Americans, an estimated 11% of individuals with two *APOL1* risk alleles have a lifetime risk of developing CKD, but studies in SSA have yet to determine what fraction of the population with *APOL1* risk alleles will develop kidney disease. The higher overall prevalence of CKD in SSA would also suggest that the attributable risk of *APOL1* renal risk variants would be much higher than that in African Americans. The average age of onset of CKD in SSA (where measurable, as only 1–2% have access to maintenance dialysis or kidney transplantation) is about one and one-half decade earlier than the average age of onset of ESRD in African Americans (45 years vs. 61 years).[8] Whether CKD is initiated at an earlier age in general, or whether ApoL1 risk renal variants independently confer more accelerated progression, or interact with other progression factors to accelerate the progression of CKD in SSA, have not be determined. These questions are being addressed in ongoing cohort studies of ApoL1 nephropathy in SSA.

Specific Causes of CKD in Africa

Hypertension

Across the World Health Organization (WHO) regions, the highest prevalence of hypertension is found in Africa, with an age-adjusted prevalence in individuals over 18 years of 27.4% (95% CI: 24.5–30.4).[28] The prevalence rates of hypertension differ substantially across Africa. Rates in the AWI-Gen study ranged from 15.1% in Burkina Faso to 54.1% in South Africa.[29] A meta-analysis of hypertension studies from Africa came to broadly similar conclusions, with the prevalence of hypertension rising from 16% at the age of 30 years–44% at 60 years.[30] This high prevalence of hypertension was confirmed in a recent systematic review.[31]

Hypertension is a recognized risk factor leading to CKD. In Africa, the prevalence of CKD in people with hypertension was reported as 18.8% (medium-quality studies) and 14.8% (high-quality studies).[6] (Table 11.3) In the study of Kaze et al.[11] the prevalence of CKD in people with hypertension in Africa was 35.6% (95% CI: 27.9–43.7). In a pooled study the prevalence of CKD in patients with hypertension was similar at 34.5% (95% CI: 34.04–36.0).[13] In a study of 712 adults from Ghana with hypertension, the median age was 59 years (range 19–90), the median duration of hypertension was

TABLE 11.2 Prevalence of *APOL1* G1 and G2 Variants in African Populations

Population/Ethnic Group	Country	*APOL1* Allele G1 %	*APOL1* Allele G2 %
WEST AFRICA			
Mandenka	Senegal	5	21
Yoruba	Nigeria	45	17
Igbo	Nigeria	30	25
Bulsa	Ghana	11	21
Asante	Ghana	41	13
WEST CENTRAL AFRICA			
Fulani	Cameroon	0	8
Lemande	Cameroon	0	3
Mada	Cameroon	3	3
Bakola	Cameroon	5	5
Somie	Cameroon	16	12
COG	Democratic Republic of Congo	11	5
CENTRAL AFRICA			
Biaka	Central African Republic	4	10
NORTH AFRICA			
Mozabite	Algeria	2	0
Kordofan	Sudan	2	5
Amhara	Ethiopia	0	0
Annuak	Ethiopia	2	3
Maale	Ethiopia	0	0
Oromo	Ethiopia	0	0
EAST AFRICA			
Luhya	Kenya	5	7
Borana	Kenya	0	3
Sengwer	Kenya	0	3
Banyu-NE	Kenya	5	5
Hadza	Tanzania	5	0
Iraqw	Tanzania	5	3
Sadawe	Tanzania	5	0
SOUTHEASTERN AFRICA			
MWI	Malawi	12	12
Sena	Mozambique	12	11
SOUTHERN AFRICA			
San	Namibia	0	1
Motswana	Botswana	6	6
Bantu-SA	Republic South Africa	7	21
Zulu	Republic South Africa	5	6

Adapted from Limou S.[17]

4 years, and the prevalence of CKD was 46.9% (95% CI: 43.2–50.7).[32] Hypertension is thus common in Africa and contributes substantially to the risk of CKD.

Diabetes Mellitus

The prevalence of diabetes mellitus has increased from 3.1% in 1980 to 7.1% in 2014 in the African region of the WHO.[33] Over 90% of people with diabetes in SSA, as elsewhere, have type 2 diabetes mellitus.[34,35] The true burden of CKD in people with diabetes is unknown, as there are few reliable data at the population level, and the definitions of CKD have been variable and imprecise. The increased prevalence of type 2 diabetes in SSA will be a major driver of CKD. Studies of the prevalence of proteinuria and CKD in patients with diabetes in Africa are hampered by small sample sizes, variable quality, and a wide variation in prevalence rates. Several meta-analyses and pooled studies have reported the prevalence of diabetic nephropathy in people with CKD (Table 11.3). In the study of Stanifer et al.[6] the prevalence of CKD in people with diabetes mellitus was 14.1% (in medium-quality studies) and 19.8% (high-quality studies). Kaze et al.[11] reported a prevalence of CKD in diabetes of 32.6% (95% CI: 0.3–82.3%). Abd El-Hafeez et al.[13] found a prevalence of CKD in diabetes of 24.7% (95% CI: 23.6–25.7) in their pooled study. A further systematic review of 32 studies from Africa reported that 34.7% of people with diabetes mellitus had ESRD after 5 years and that 18.4% died at 20 years.[36] Despite the variability of these studies, they all report a high prevalence of CKD in people with diabetes. Studies are needed to define the prevalence of CKD in people with diabetes mellitus in Africa and to establish optimal methods of reducing this, including using blockers of the renin angiotensin aldosterone system.

TABLE 11.3 Prevalence of CKD by Disease Specific Population

Prevalence by Disease Specific Population	% CKD (Stages 1–5) Stanifer, JW et al.[6]	Kaze AD et al.[11]	Abd ElHafeez et al.[13]	Erikpo et al.[39]
HIV	11.9% (medium-quality studies)	27.3% (95% CI: 17.0–38.9)	5.6% (95% CI: 5.4–5.8)	7.0% (95% CI: 2.8–12.9)
Hypertension	18.8% (medium-quality studies) 14.8% (high quality studies)	35.6% (95% CI: 27.9–43.7%)	34.5% (95% CI: 34–36)	
Diabetes	14.1% (medium-quality studies) 19.8 (high-quality studies)	32.6% (95% CI: 0.3–82.3%)	24.7% (95% CI: 23.6–25.7)	

HIV and CKD

Prevalence of HIV in Africa

Over 25 million people in SSA have HIV infection,[37] and this is associated with a high prevalence of CKD. The highest prevalence of HIV-associated renal disease is found in SSA. The adult (age 15–49 years) prevalence of HIV infection ranges from 1.9% in West and Central Africa, to 6.8% in East and Southern Africa, to 18.8% in South Africa and 22.8% in Botswana.[37] The reasons for this are due first to the high prevalence of HIV infection. Secondly, populations in SSA have a genetic predisposition to HIVAN. South Africans with two copies of the risk alleles (G1 and G2) of *APOL1* have a significantly higher risk of developing HIVAN (OR: 89.1; 95% CI: 17.8–811.72) compared to individuals without these risk variants.[5] This is higher than in African Americans (OR of 29.2; 95% CI: 13.1–68.5).[24] By contrast, Ethiopians with HIV infection who lack *APOL1* risk variants do not develop HIVAN.[38] The HIV epidemic in SSA may soon lead to an additional epidemic of CKD as a significant cause of morbidity and mortality.

Prevalence of CKD in HIV

The prevalence of CKD in people with HIV infection ranges widely, from 5.6 (95% CI: 5.4–5.8),[13] to 7.0% (95% CI 2.8–12.9%),[39] and 11.9% (medium-quality studies)[6] and 27.3% (95% CI: 17.0–38.9).[11] In Ethiopia the absence of HIVAN in subjects with HIV can be explained by the lack of APOL1 variants in this population (Table 11.3).[38]

HIV Renal Disease in Africa (Table 11.4)

The causes of kidney disease in people with HIV infection include HIVAN, FSGS, immune complex kidney disease, and kidney injury from nephrotoxicity from antiretroviral drugs and coexistent HBV or HCV infection.[40,41] The two major histological lesions in HIV-infected individuals in Africa are HIVAN and HIV immune complex kidney disease (HIVICK) (Table 11.4). Han et al.[42] studied 615 patients with HIV infection in South Africa. Of these 38 (6%) had proteinuria. Thirty of their patients had a renal biopsy. Twenty-five (83%) showed HIVAN with collapsing FSGS (Figure 11.2). Two had membranoproliferative glomerulonephritis (7%), three interstitial nephritis (10%), and four patients had coexistent HIVAN and membranous nephropathy. Of these four patients, two had HBV surface antigenaemia.

In another study from South Africa, Gerntholtz et al.[43] reported that of 99 patients with HIV infection who had a renal biopsy, 27 (27%) had HIVAN with an FSGS pattern of glomerular damage with or without a collapsing pattern, and 21 (21%) had HIVICK. They also described subepithelial deposits with a basement membrane reaction giving a "ball in cup" appearance in the HIVICK biopsies. Other lesions seen were membranous nephropathy, postinfectious glomerulonephritis, mesangial proliferative glomerulonephritis, and IgA nephropathy. In a large study of 192 renal biopsies in patients with HIV infection from South Africa, of whom 172 (89.6%) were of black African ancestry, Wearne et al.[44] reported that the most common histological feature was HIVAN in 110 biopsies (57.3%), followed by a mixed HIVAN and HIVICK pattern in 42 (21.9%) biopsies, and HIVICK alone in 16 (8.4%) biopsies. They also reported a "fetal" variant of FSGS that showed a dense mesangial core with absent capillary loops.

Studies in South African children also showed a prevalence of HIVAN of 26.5% and HIVICK of 10.2%.[45] Other studies from Africa have reported smaller numbers of HIV-infected patients who have had a renal biopsy. In a report from the Democratic Republic of the Congo, 6 out of 32 renal biopsies (19%) showed HIVAN.[46] By contrast two studies from Nigeria showed that 70% of patients with HIV infection who had a renal biopsy had HIVAN.[47,48] Finally a report from Kenya showed a striking absence of HIVAN in the renal biopsies in 27 combined antiretroviral treatment (cART) naïve subjects with HIV infection and persistent microalbuminuria.[49] The most common histological lesion was acute interstitial nephritis in 41% of the patients. It is difficult to explain the absence of HIVAN in this Kenyan study.

In patients with HIV-associated renal disease, adverse prognostic factors were proteinuria, the presence of microcysts (Figure 11.3), the fetal variant, and

TABLE 11.4 HIV Renal Disease in Africa

	Assounga[46]	Han et al.[42]	Gerntholtz et al.[43]	Emem et al.[47]	Wearne et al.[44]	Ramsuran et al.[45] Children	Odonmeta et al.[48]
Country	Democratic Republic of Congo	South Africa	South Africa	Nigeria	South Africa	South Africa-children	Nigeria
Number of subjects biopsied	32	30	99	10	192	49	17
HIVAN	6 (19%)	25 (83%) (4 also had coexistent membranous nephropathy	27 (27%)	7 (70%)	110 (57.3%)	13 (26.5%)	12 (70.6%)
HIVAN +Immune complex glomerulonephritis					42 (21.9%)		
HIV Immune complex glomerulonephritis			21 (21%)		16 (8.35)	5 (10.2%)	
FSGS						19 (38.8%)	
Other					24 (12.5%)		2 (11.8%)
Other glomeulonephritides			9 (9%)				
Membranoproliferative glomerulonephritis		2 (7%)					
Membranous			13 (13%)				1 (5.9%)
Post infectious glomerulonephritis			8 (8%)				
Mesangial proliferative			6 (6%)				
Mesangial hyperplasia						8 (15.7%)	
IgA nephropathy			5 (5%)				
Other renal diseases			10 (10%)				
Minimal change disease						4 (8.2%)	2 (11.8%)
Interstitial nephritis		3 (10%)					
Normal glomeruli				3 (30%)			

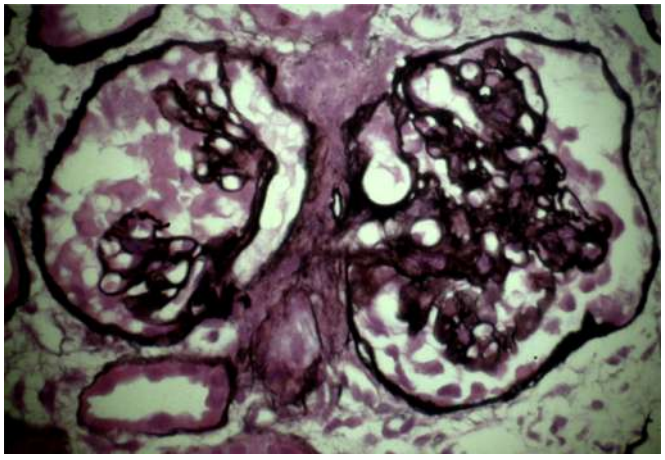


FIGURE 11.2 Collapsing glomerulopathy in HIV infection. *Courtesy Professor A.J. Howie.*

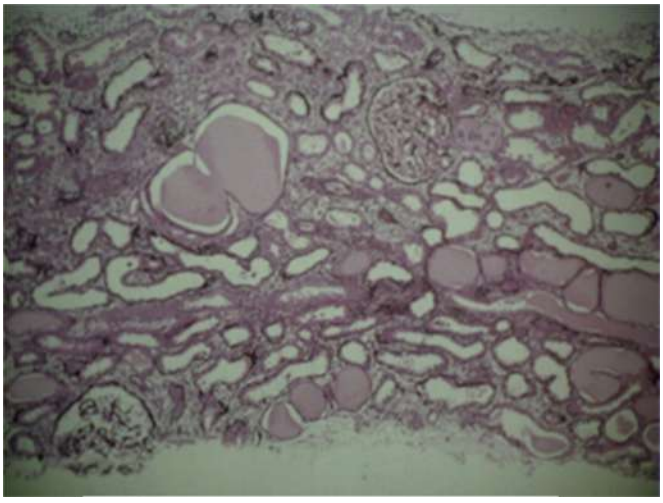


FIGURE 11.3 Microcystic tubular dilatation with casts in HIV-associated renal disease. *Courtesy Professor A.J. Howie.*

interstitial fibrosis. The prognosis is poor in untreated patients with HIVAN. In the study of Wearne et al. the 50% survival without treatment was 4.47 months.[44] The prognosis improved as did renal survival with cART. In addition to an improvement in renal function, the use of cART was accompanied by improvement in renal histology.[50]

Tenofovir Nephrotoxicity

Tenofovir disoproxil fumarate (TDF) is a nucleotide analogue reverse transcriptase inhibitor, which is effective in the treatment of HIV and HBV infections. TDF enters proximal tubular cells through basolateral organic anion transporters and is excreted into the lumen through multidrug resistance associated protein (MRP4) but not MRP2. TDF is associated with the development of proximal tubular injury, occasionally leading to Fanconi syndrome characterized by phosphaturia, glycosuria, amino aciduria, proteinuria, and bicarbonate wasting and rarely to acute kidney injury.[51] In addition, TDF is associated with increased risk of developing CKD, although the size of this effect is unclear. A systematic review and meta-analysis reported that patients treated with TDF showed a small but significant difference in glomerular filtration rate (GFR) of 3.9 mL/min (95% CI: 2.1−5.7) using the Cockroft-Gault formula compared with patients not on TDF.[52] None of the studies analyzed were from Africa, although most included black participants. In a large study from Zambia, of 62,230 adults with HIV infection, 38,716 were started on cART containing TDF. Patients with normal or mild renal impairment at the start of TDF were more likely to develop moderate (OR: 3.11 95% CI: 2.52−3.87) or severe (OR: 2.43 95% CI: 1.8−3.28) decrease in eGFR compared with patients not on TDF. Among patients with moderate or severe renal dysfunction, however, renal function improved regardless of the type of cART therapy.[53] One study in Nigeria of 5273 patients with HIV infection found the risk of CKD (eGFR <60 mL/min/1.73 m^2) at 48 weeks in patients on TDF was 4.6%, compared to 2.3% in the TDF unexposed group (OR: 2.0; 95% CI: 1.58−2.89).[54] The study of De Waal et al. from South Africa reported a small decline in eGFR (-2.3 mL/min/1.73 m^2 (95% CI: -2.5 to -2.1)) in participants on TDF who had a CKD-EPI eGFR >90 mL/min/1.73 m^2 but improvement in patients with initial renal impairment.[55] A study from Uganda showed no differences in renal function of participants whether or not they were on TDF.[56] Our anecdotal experience is that TDF is an important cause of CKD and that this effect merits further study. Recently an analogue of TDF, tenofovir alafenamide has been introduced, which is reported to be less nephrotoxic.[57]

CKD in Children

The major causes of CKD in children in Africa are glomerulonephritis and congenital abnormalities of the kidneys and urinary tract (CAKUT) (Table 11.5). Studies from West and South Africa showed a higher prevalence of glomerulonephritis (53−77%)[58−60] than studies from Sudan[61] and Egypt,[62] where the prevalence ranged from 15.3 to 25.4%. CAKUT were the next most common cause of CKD in children in Africa, ranging from 9.8 to 28.9%.

Low Birth Weight and CKD

Low birth weight (LBW) is common in SSA with an incidence of around 15%.[63] LBW is associated with an increased risk of adult hypertension, impaired glucose tolerance, and CKD compared to those with normal birth weight.[64,65] LBW is thus likely to be an important contributor to hypertension and CKD in later life in SSA. Future studies should focus on translational research that combines investigation with measures to reduce the impact of LBW on public health.

Glomerulonephritis

Glomerulonephritis is an important cause of ESRD in Africa.[66,67] In most cases the diagnosis of glomerulonephritis is presumed in patients who present with late-stage renal failure with kidneys that are too small to biopsy safely. In an autopsy study we showed histologically proven glomerular disease, mostly FSGS, in 33 of 78 (42.3%) patients with ESRD.[66] A recent systematic review of renal biopsy studies from Africa showed a high prevalence of glomerular diseases that may lead to CKD (such as FSGS, mesangiocapillary glomerulonephritis, HBV-associated glomerulonephritis, and lupus nephritis).[68] Because of selection issues, the prevalence of HIV-associated glomerular disease was low in the study, but this has been reported to be increasing in South Africa.[69] Similarly in children in Africa, FSGS (26.3%), membranoproliferative glomerulonephritis (16.8%), proliferative glomerulonephritis (27.0%), and membranous nephropathy (4.5%) are now major causes of the nephrotic syndrome in childhood, as are HBV, HIV infection, and sickle cell disease, and these may lead to CKD.[70] One striking feature of contemporary renal histology from African children is the lack of *Plasmodium malariae*−associated nephropathy (Quartan malarial nephropathy),[71] which was a prominent cause of the nephrotic syndrome in the 1950s and 1960s.[72,73]

Schistosomiasis

Schistosoma haematobium (*S. haematobium*) and *Schistosoma mansoni* (*S. mansoni*) are parasitic flukes that are found in tropical areas where there are large areas of water. Both are common in Africa and may lead to CKD.

TABLE 11.5 Causes of Chronic Kidney Disease (CKD) in Children in Africa

Study	Country	No. of Subjects	M:F	Age	Glomerulo-nephritis	CAKUT	Obstructive Uropathy	Urolithiasis	Other	Unknown
Anochie I.[58]	Nigeria	45	28:17	9.1 years (range 6 months −16 years	23 (53.3%)	13 (28.9%)			10 (hemolytic uremic syndrome (2), Sickle cell (2), malignant hypertension (3), pyelonephritis (1), malignancy (1), bladder rhabdomyosarcoma (1))	
Bhimma R.[59]	South Africa	126	65.9% M	Age<5: n:55 (43.7%) Age>5: n:71 (56.3%)	66 (53.4%)	27 (21.4%)			Hemolytic uremic syndrome; 8 (6.4%), others: 23 (18.3%)	
Ali el.[61]	Sudan	205	60.5% M	9.8 (range 3 months −17 years	52 (25.4%)	36 (17.55)		19 (9.3%)	Hereditary nephropathy 14 (6.8%), multisystem disease 4 (2%) Unknown 80 (39.1%)	
Asinobi A.[60]	Nigeria	53	56.6% M	11 (interquartile range 8.5−12)	41 (77.4%)	11 (21.2%)				
Safouh H.[62]	Egypt	1018	56.7% M		15.3%	9.8%	21.7%		Reflux/urinary tract infections (14.6%), familial/metabolic diseases (6.8%)	20.6%

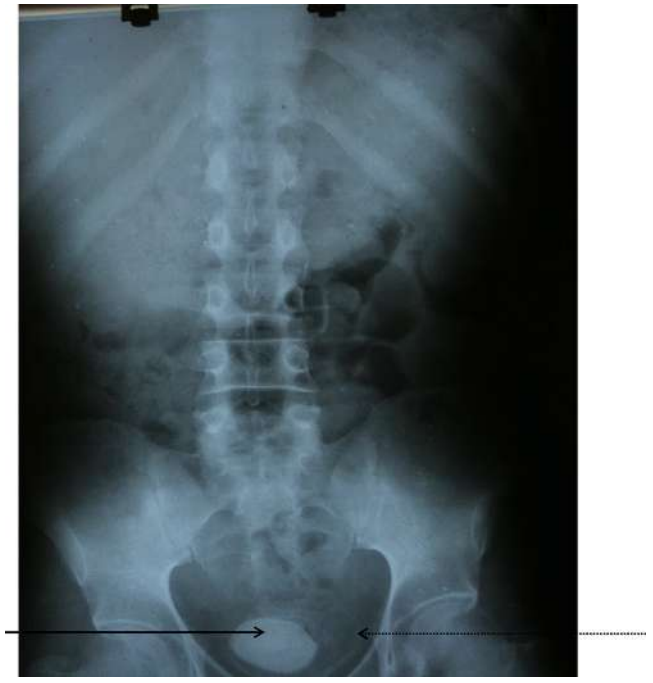


FIGURE 11.4 Bladder calculus and bladder wall calcification in a patient with *Schistosoma haematobium* infection. Bladder calculus ——→. Calcified bladder wall ·····→.

Schistosoma haematobium

S. haematobium is common in many African countries, with a prevalence of 22.4 ± 9.8% in 43 countries.[74] The disease is caused by parasite eggs that are deposited in the blood vessels surrounding the genitourinary tract, leading to inflammation and scarring. The clinical presentation is hematuria and dysuria. The inflammatory reaction to severe urogenital schistosomiasis leads to chronic fibrosis of the urinary tract with hydroureter and hydronephrosis.[75–77] Other features include bladder calcification and stones (Figure 11.4). These urological complications lead to CKD in a significant proportion of patients. The WHO estimates 112 million individuals in SSA have *S. haematobium* infection and that an estimated 150,000 infected individuals die from kidney failure each year.[78] This makes *S. haematobium* infection a major and as yet poorly studied cause of CKD in Africa. In the long-term, chronic infection can lead to squamous cell carcinoma of the bladder.[75,79]

Schistosoma mansoni

S. mansoni infects an estimated 54 million people in Africa.[78] The disease is caused by parasite eggs that are deposited in the blood vessels of the gastrointestinal tract, leading to inflammation and scarring. Some people with *S. mansoni* infection develop hepatosplenic disease with periportal fibrosis. *S. mansoni*–associated glomerular disease is found in 5–6% of infected patients. It more commonly occurs in 10–15% of patients with hepatosplenic disease.[80] The clinical presentation varies from asymptomatic proteinuria to ESRD. Common histological glomerular lesions are mesangioproliferative glomerulonephritis, diffuse proliferative glomerulonephritis, mesangiocapillary glomerulonephritis, FSGS, and amyloidosis.[80] Treatment of both *S. mansoni* and *S. haematobium* is with praziquantel or oxamniquine.

Sickle Cell Nephropathy

Sickle cell disease is a major public health burden in SSA. It is estimated that in 2010, 200,000–300,000 children were born with this disorder.[81] Early renal manifestations of sickle cell disease are hyposthenuria, renal tubular acidosis, and defects in potassium excretion.[82] For those children who survive, renal disease is a common complication, which starts in childhood with hyperfiltration and microalbuminuria, and can progress in adult life to CKD. In a study of 2582 patients with sickle cell disease from four SSA countries (Cameroon, Cote d'Ivoire, Mali, and Senegal) albuminuria was reported in 33.7% (95% CI: 31.6–35.8) of patients with Hb SS and $S\beta^0$ and 16.4% (95% CI: 13.6–19.2) of patients with Hb SC and $S\beta^+$ phenotypes.[83] The prevalence of albuminuria increased with age (27% for children aged less than 10 years and 48% for patients aged over 40 years). Hyperfiltration was more common in younger individuals and individuals with Hb SS and $S\beta^0$ compared with Hb SC and $S\beta^+$ phenotypes. Risk factors for albuminuria were age, female sex, and high lactic dehydrogenase and low hemoglobin (negative correlation). Other studies from SSA show rates of microalbuminuria of 18.5–28.0%,[84–86] which increases with age.[87,88] In addition eGFR decreases with age.[87,88] The renal lesions seen on biopsy in patients with sickle cell disease are FSGS, membranoproliferative glomerulonephritis, and glomerular hypertrophy with or without mesangial hypercellularity and thrombotic microangiopathy.[89] Biopsy studies from Africa also report membranoproliferative glomerulonephritis and FSGS.[71,90] Albuminuria in sickle cell disease reduces with treatment with angiotensin-converting inhibitors or angiotensin II-receptor blockade. It is possible that these agents, by reducing intraglomerular pressures, might reduce the rate at which renal function declines.[91,92]

CKD and Sickle Cell Disease

There are relatively few data on the prevalence of CKD in adults in SSA. This is in part because of the high childhood mortality in children with sickle cell disease in Africa, where an estimated 50–80% die before adulthood. In a study of 413 sickle cell disease patients

from Cameroon, *APOL1* renal risk variants were significantly associated with microalbuminuria, and there was a borderline association with GFR,[93] as had been reported from the US[22,94] and Europe.[95]

Sickle Cell Trait and CKD

Sickle cell trait is associated with hyposthenuria, hematuria, and renal papillary necrosis.[96] There is contradictory evidence regarding whether sickle cell trait (Hb AS) is associated with a risk of developing CKD. Three US studies reported an increased risk of ESRD[97,98] or CKD[98,99] in people with sickle cell trait. In another study from the US, however, there was no association between sickle cell trait and diabetic or nondiabetic ESRD.[100] Studies from Africa did not show an increased risk of CKD in people with sickle cell trait. In a study of 359 people from the Democratic Republic of Congo, sickle cell trait was found in 21% of subjects with CKD and 18% of those without CKD ($p > 0.05$).[101] In an unpublished study from Ghana of 244 subjects, 17.1% of healthy controls had sickle cell trait compared with 14.0% of cases with CKD ($p = 0.24$).[102] Further studies are required to determine the risk of CKD in people with sickle cell trait.

Traditional Herbal Remedies and CKD

There are temporal associations between the use of traditional herbal remedies and the development of AKI that make a causative association plausible. In one prospective study in South Africa, 76% of 103 patients who had taken herbal remedies had renal dysfunction.[103] Although many of our patients with CKD have taken herbal remedies, it is harder to implicate these agents as a cause of CKD.[104] Most users of traditional herbal remedies do not disclose this to their medical attendants.[105] The best known example of herbal remedies causing CKD is the use of Chinese herbal remedies containing aristolochic acid, which are associated with the development of urothelial cancers. Aristolochic acid has also been implicated as the cause of Balkan endemic nephropathy.[106]

Chronic Kidney Disease of Uncertain Aetiology

Chronic kidney disease of uncertain etiology (CKDu) describes a disorder in which CKD is not due to disorders such as diabetes, hypertension, glomerulonephritis, or HIV infection. CKDu is found in tropical countries (mostly in Central America and Sri Lanka) and is more common in young men in agricultural communities working in high ambient temperatures and with exposure to agrochemicals.[107,108] There are only a few reports of CKDu from Africa. A study from El-Minya in Egypt reported that 27% of patients with ESRD had CKDu.[109] In a follow-up case control study from the same area, patients with CKDu were significantly more likely to be living in rural areas, drinking unsafe water, exposed to pesticides, and more likely to use herbal remedies and have a family history of CKD compared with controls.[110] A study from Tunisia reported an association between exposure to ochratoxin and CKD, but the kidney disease was not well characterized.[111] A study of sugarcane plantation workers in Cameroon found a low prevalence of CKD of 2.4%.[112] Further studies are required to determine the prevalence of CKDu in Africa.

Lupus Nephritis

Lupus nephritis remains an important cause of renal failure and death in Africa. Most reports come from Northern African countries. The clinical presentation and treatment differs little from that elsewhere, except most patients are likely to be treated with prednisolone and cyclophosphamide.[113]

Hepatitis B

There is high prevalence of HBV infection in Africa, averaging 8.8%.[114] The association between HBV infection and glomerular disease has been widely reported from Africa.[115] It is perhaps less widely appreciated that HBV infection is associated with a small but significant increase in the rate of CKD, with a hazard rate of 1.13 (95% CI: 1.03–1.21) in Korea.[116] However other meta-analyses have reported contradictory results, showing no association between HBV infection and CKD,[117] while another study showed an association.[118] There are no comparable studies from Africa. Appropriately designed studies would determine whether HBV infection leads to the development of CKD. The widespread HBV vaccination programmes in Africa should lead to a reduction in kidney disease from this cause.

Hepatitis C

Meta-analysis shows that HCV seropositivity is associated with an increased risk of CKD, with a hazard ratio of 1.54 (95% CI: 1.26–1.87).[119] Although the prevalence of HCV is high in parts of Africa, there are no studies to assess the effect on development of CKD.

Tuberculosis

Renal disease is an important extrapulmonary complication of tuberculosis and one that is likely to become more prominent with the increase in the prevalence of tuberculosis in Africa as a consequence of HIV infection. Tuberculosis can involve the renal parenchyma with caseating and cavitation lesions, leading in an advanced stage to autonephrectomy. The ureters and bladder are also often affected with ulcerating lesions leading to scarring and obstruction.[120] Other lesions include interstitial nephritis (sometimes with granulomatous inflammation) and renal amyloid as a

TABLE 11.6 Causes of End-Stage Renal Disease in Africa

	Ulasi II and Ijoma CK[125]	Nigeria[126]	Egypt[109]	North Africa 2013[127]	Sudan[128]	South African Renal Registry 2016[122]	Ghana Renal Registry 2019[130]
Hypertensive renal disease %	17.2	31.1	21	10–35	34.6	34.7	42.7
Cause unknown %	51.6	12	27		10.7	32.4	31.5
Diabetic nephropathy %	11.8	3.7	13	11–18	12.8	15.2	10.1
Glomerulonephritis%	14.8	43.7	10	9–20	17.6	9.9	8.8
Cystic kidney disease %		0.7		2–3	4.7	3.0	0.8
Obstruction and reflux %		6.7	11		9.6	1.7	1.1
Chronic interstitial nephritis		2.2		7–17			
Others	4.6		18		10.0		5.1

consequence of extrarenal tuberculosis. Coexistence of tuberculosis and interstitial nephritis with HIVAN has been reported.[44] In one study from Tanzania, a history of tuberculosis was associated with an increased risk of CKD, OR 3.75 (95% CI: 1.66–8.18; p = 0.001).[121]

Incident Renal Disease in ESRD

Because of a lack of renal registries there are few data on the prevalence, causes, and treatment of ESRD in Africa.[122] The clinical impression that ESRD is common is in keeping with reports that the proportion of medical admissions in Ghana with CKD has risen from 5% in 1999[123] to 17% in 2016.[8] In Ghana an autopsy study of 94,309 deaths reported that the mortality rate from renal disease doubled from 5.0% in 1994–2009 to 10.8% in 2010–2013.[124] The reasons for the apparent increase in the prevalence and mortality rate from renal disease are not known. The major causes of ESRD show regional differences in Africa, but in all regions the major causes of ESRD are hypertension (10–42.7%), glomerulonephritis (9–43.7%), and diabetes mellitus (3.7–15.25%)[109,125–130] (Table 11.6).

Treatment of ESRD

In SSA there is a startling gap between the estimated incidence of ESRD due to diabetes and hypertension of 239 per million population and patients receiving RRT of 1.5%.[131] A systematic review reported that 84% of patients in SSA who needed dialysis did not receive this therapy.[132] In a pooled study 96% and 95% of adults and children, respectively, who needed but could not access dialysis did not survive.[133] Of those who had dialysis, 84% of adults discontinued dialysis and died.

CONCLUSION

CKD is a leading public health problem in Africa with an estimated prevalence of 13.9%. The major causes of CKD in Africa are hypertension and diabetes, which are both increasing in prevalence. Other causes of CKD in Africa include glomerulonephritis, infections with HIV, *S. mansoni*, *S. haematobium*, and possibly HBV. In addition sickle cell anemia, which is common in SSA, increases the risk of CKD. These etiological causes of CKD occur in a population with a high prevalence of *APOL1* G1 and G2 variants, which also increase the risk of CKD. Less than 1.5% of patients projected to develop ESRD in SSA have access to RRT, meaning that most patients die untreated.

References

1. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al. Association of trypanolytic ApoL1 variants with kidney disease in African-Americans. *Science* 2010;**329**:841–5.
2. Tzur S, Rosset S, Shemer R, Yudkovsky G, Selig S, Tarekegn A, et al. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. *Hum Genet* 2010;**128**(3):345–50.
3. Tayo BO, Kramer H, Salako BL, Gottesman O, McKenzie CA, Ogunniyi A, et al. Genetic variation in APOL1 and MYH9 genes is associated with chronic kidney disease among Nigerians. *Int Urol Nephrol* 2013;**45**(2):485–94.
4. Ulasi II, Tzur S, Wasser WG, Shemer R, Kruzel E, Feigin E, et al. High population frequencies of APOL1 risk variants are associated with increased prevalence of non-diabetic chronic kidney disease in the Igbo people from South-Eastern Nigeria. *Nephron Clin Pract* 2013;**123**(1–2):123–8.
5. Kasembeli AN, Duarte R, Ramsay M, Mosiane P, Dickens C, Dix-Peek T, et al. APOL1 risk variants are strongly associated with HIV-associated nephropathy in black South Africans. *J Am Soc Nephrol* 2015;**26**(11):2882–90.
6. Stanifer JW, Jing B, Tolan S, Helmke N, Mukerjee R, Naicker S, et al. The epidemiology of chronic kidney disease in sub-

Saharan Africa: a systematic review and meta-analysis. *Lancet Global Health* 2014;**2**(3):e174–81.
7. Xie Y, Bowe B, Mokdad AH, Xian H, Yan Y, Li T, et al. Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. *Kidney Int* 2018;**94**(3):567–81.
8. Osafo C, Raji YR, Olanrewaju T, Mamven M, Arogundade F, Ajayi S, et al. Genomic approaches to the burden of kidney disease in sub-saharan Africa: the human heredity and health in Africa (H3Africa) kidney disease research network. *Kidney Int* 2016; **90**(1):2–5.
9. Bello AK, Levin A, Tonelli M, Okpechi IG, Feehally J, Harris D, et al. Assessment of global kidney health care status. *J Am Med Assoc* 2017;**317**(18):1864–81.
10. Division UNDP. *World population prospects 2017*. 2017 [Available from: https://population.un.org/wpp/Download/Standard/Population/.
11. Kaze AD, Ilori T, Jaar BG, Echouffo-Tcheugui JB. Burden of chronic kidney disease on the African continent: a systematic review and meta-analysis. *BMC Nephrol* 2018;**19**(1):125.
12. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. *J Am Med Assoc* 2007;**298**(17):2038–47.
13. Abd ElHafeez S, Bolignano D, D'Arrigo G, Dounousi E, Tripepi G, Zoccali C. Prevalence and burden of chronic kidney disease among the general population and high-risk groups in Africa: a systematic review. *BMJ Open* 2018;**8**(1):e015069.
14. Adjei DN, Stronks K, Adu D, Beune E, Meeks K, Smeeth L, et al. Chronic kidney disease burden among African migrants in three European countries and in urban and rural Ghana: the RODAM cross-sectional study. *Nephrol Dial Transplant* 2018;**33**(10):1812–22.
15. Stanifer JW, Maro V, Egger J, Karia F, Thielman N, Turner EL, et al. The epidemiology of chronic kidney disease in Northern Tanzania: a population-based survey. *PLoS One* 2015;**10**(4): e0124506.
16. Stanifer JW, Karia F, Maro V, Kilonzo K, Qin X, Patel UD, et al. APOL1 risk alleles among individuals with CKD in Northern Tanzania: a pilot study. *PLoS One* 2017;**12**(7):e0181811.
17. Limou S, Nelson GW, Kopp JB, Winkler CA. APOL1 kidney risk alleles: population genetics and disease associations. *Adv Chron Kidney Dis* 2014;**21**(5):426–33.
18. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**(13):1296–305.
19. Behar DM, Rosset S, Tzur S, Selig S, Yudkovsky G, Bercovici S, et al. African ancestry allelic variation at the MYH9 gene contributes to increased susceptibility to non-diabetic end-stage kidney disease in Hispanic Americans. *Hum Mol Genet* 2010;**19**(9): 1816–27.
20. Cooper A, Ilboudo H, Alibu VP, Ravel S, Enyaru J, Weir W, et al. APOL1 renal risk variants have contrasting resistance and susceptibility associations with African trypanosomiasis. *eLife* 2017;**6**.
21. Freedman BI, Limou S, Ma L, Kopp JB. APOL1-associated nephropathy: a key contributor to racial disparities in CKD. *Am J Kidney Dis* 2018;**72**(5s1):S8–s16.
22. Ashley-Koch AE, Okocha EC, Garrett ME, Soldano K, De Castro LM, Jonassaint JC, et al. MYH9 and APOL1 are both associated with sickle cell disease nephropathy. *Br J Haematol* 2011; **155**(3):386–94.
23. Larsen CP, Beggs ML, Saeed M, Walker PD. Apolipoprotein L1 risk variants associate with systemic lupus erythematosus-associated collapsing glomerulopathy. *J Am Soc Nephrol* 2013; **24**(5):722–5.
24. Kopp JB, Nelson GW, Sampath K, Johnson RC, Genovese G, An P, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol* 2011;**22**(11):2129–37.
25. Parsa A, Kao WH, Xie D, Astor BC, Li M, Hsu CY, et al. APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med* 2013;**369**(23):2183–96.
26. Osafo C, Raji YR, Burke D, Tayo BO, Tiffin N, Moxey-Mims MM, et al. Human Heredity and Health (H3) in Africa kidney disease research network: a focus on methods in sub-saharan Africa. *Clin J Am Soc Nephrol* 2015;**10**(12):2279–87.
27. George C, Yako YY, Okpechi IG, Matsha TE, Kaze Folefack FJ, Kengne AP. An African perspective on the genetic risk of chronic kidney disease: a systematic review. *BMC Med Genet* 2018;**19**(1): 187.
28. *WHO global health observatory data repository*. 2017.
29. Gomez-Olive FX, Ali SA, Made F, Kyobutungi C, Nonterah E, Micklesfield L, et al. Regional and sex differences in the prevalence and awareness of hypertension: an H3Africa AWI-Gen study across 6 sites in sub-Saharan Africa. *Glob Heart* 2017;**12**(2): 81–90.
30. Ataklte F, Erqou S, Kaptoge S, Taye B, Echouffo-Tcheugui JB, Kengne AP. Burden of undiagnosed hypertension in sub-saharan Africa: a systematic review and meta-analysis. *Hypertension* 2015;**65**(2):291–8.
31. Addo J, Smeeth L, Leon DA. Hypertension in sub-saharan Africa: a systematic review. *Hypertension* 2007;**50**(6):1012–8.
32. Osafo C, Mate-Kole M, Affram K, Adu D. Prevalence of chronic kidney disease in hypertensive patients in Ghana. *Ren Fail* 2011; **33**(4):388–92.
33. Atun R, Davies JI, Gale EAM, Barnighausen T, Beran D, Kengne AP, et al. Diabetes in sub-Saharan Africa: from clinical care to health policy. *Lancet Diabetes Endocrinol* 2017;**5**(8):622–67.
34. Levitt NS. Diabetes in Africa: epidemiology, management and healthcare challenges. *Heart* 2008;**94**(11):1376–82.
35. Hall V, Thomsen RW, Henriksen O, Lohse N. Diabetes in Sub Saharan Africa 1999-2011: epidemiology and public health implications. A systematic review. *BMC Public Health* 2011;**11**:564.
36. Noubiap JJ, Naidoo J, Kengne AP. Diabetic nephropathy in Africa: a systematic review. *World J Diabetes* 2015;**6**(5):759–73.
37. Avert. *Global information and education on HIV and Aids*. 2017. Available from: https://www.avert.org/global-hiv-and-aids-statistics.
38. Behar DM, Kedem E, Rosset S, Haileselassie Y, Tzur S, Kra-Oz Z, et al. Absence of APOL1 risk variants protects against HIV-associated nephropathy in the Ethiopian population. *Am J Nephrol* 2011;**34**(5):452–9.
39. Ekrikpo UE, Kengne AP, Bello AK, Effa EE, Noubiap JJ, Salako BL, et al. Chronic kidney disease in the global adult HIV-infected population: a systematic review and meta-analysis. *PLoS One* 2018; **13**(4):e0195443.
40. Cohen SD, Kopp JB, Kimmel PL. Kidney diseases associated with human immunodeficiency virus infection. *N Engl J Med* 2017; **377**(24):2363–74.
41. Swanepoel CR, Atta MG, D'Agati VD, Estrella MM, Fogo AB, Naicker S, et al. Kidney disease in the setting of HIV infection: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. *Kidney Int* 2018; **93**(3):545–59.
42. Han TM, Naicker S, Ramdial PK, Assounga AGH. A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa. *Kidney Int* 2006;**69**.
43. Gerntholtz TE, Goetsch SJ, Katz I. HIV-related nephropathy: a South African perspective. *Kidney Int* 2006;**69**(10):1885–91.
44. Wearne N, Swanepoel CR, Boulle A, Duffield MS, Rayner BL. The spectrum of renal histologies seen in HIV with outcomes, prognostic indicators and clinical correlations. *Nephrol Dial Transplant* 2012;**27**(11):4109–18.

45. Ramsuran D, Bhimma R, Ramdial PK, Naicker E, Adhikari M, Deonarain J, et al. The spectrum of HIV-related nephropathy in children. *Pediatr Nephrol* 2012;**27**(5):821–7.
46. Assounga AG, Yala F, Mongo Y, Assambo C, Mpio I. HIV and nephropathy in Congo: a comparative study of HIV-positive vs HIV-negative patients. *Saudi J Kidney Dis Transplant* 1996;**7**:S30–2.
47. Emem CP, Arogundade F, Sanusi A, Adelusola K, Wokoma F, Akinsola A. Renal disease in HIV-seropositive patients in Nigeria: an assessment of prevalence, clinical features and risk factors. *Nephrol Dial Transplant* 2008;**23**(2):741–6.
48. Odonmeta AB, Oviasu E, Ojogwu LI. Renal histopathological study of human immunodeficiency virus - positive patients with clinical evidence of renal disease in Benin City, Nigeria. *Saudi J Kidney Dis Transpl* 2014;**25**(2):425–7.
49. Koech MK, Owiti MOG, Owino-Ong'or WD, Koskei AK, Karoney MJ, D'Agati VD, et al. Absence of HIV-associated nephropathy among antiretroviral naive adults with persistent albuminuria in Western Kenya. *Kidney Int Rep* 2017;**2**(2):159–64.
50. Fabian J, Naicker S, Goetsch S, Venter WD. The clinical and histological response of HIV-associated kidney disease to antiretroviral therapy in South Africans. *Nephrol Dial Transplant* 2013;**28**(6):1543–54.
51. Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. *Am J Kidney Dis* 2011;**57**(5):773–80.
52. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis* 2010;**51**(5):496–505.
53. Mulenga L, Musonda P, Mwango A, Vinikoor MJ, Davies MA, Mweemba A. Effect of baseline renal function on tenofovir-containing antiretroviral therapy outcomes in Zambia. *Clin Infect Dis* 2014;**58**(10):1473–80.
54. Ojeh BV, Abah IO, Ugoagwu P, Agaba PA, Agbaji OO, Gyang SS. Incidence and predictors of tenofovir disoproxil fumarate-induced renal impairment in HIV infected Nigerian patients. *Germs* 2018;**8**(2):67–76.
55. De Waal R, Cohen K, Fox MP, Stinson K, Maartens G, Boulle A, et al. Changes in estimated glomerular filtration rate over time in South African HIV-1-infected patients receiving tenofovir: a retrospective cohort study. *J Int AIDS Soc* 2017;**20**(1):21317.
56. Salome T, Kasamba I, Mayanja BN, Kazooba P, Were J, Kaleebu P, et al. The effect of Tenofovir on renal function among Ugandan adults on long-term antiretroviral therapy: a cross-sectional enrolment analysis. *AIDS Res Ther* 2016;**13**(1):28.
57. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet* 2015;**385**(9987):2606–15.
58. Anochie I, Eke F. Chronic renal failure in children: a report from Port Harcourt, Nigeria (1985-2000). *Pediatr Nephrol* 2003;**18**(7):692–5.
59. Bhimma R, Adhikari M, Asharam K, Connolly C. The spectrum of chronic kidney disease (stages 2-5) in KwaZulu-Natal, South Africa. *Pediatr Nephrol* 2008;**23**(10):1841–6.
60. Asinobi AO, Ademola AD, Ogunkunle OO, Mott SA. Paediatric end-stage renal disease in a tertiary hospital in South West Nigeria. *BMC Nephrol* 2014;**15**:25.
61. Ali el TM, Abdelraheem MB, Mohamed RM, Hassan EG, Watson AR. Chronic renal failure in Sudanese children: aetiology and outcomes. *Pediatr Nephrol* 2009;**24**(2):349–53.
62. Safouh H, Fadel F, Essam R, Salah A, Bekhet A. Causes of chronic kidney disease in Egyptian children. *Saudi J Kidney Dis Transpl* 2015;**26**(4):806–9.
63. UNICEF. *Low birthweight: country, regional and global estimates*. 2004. Available from: https://www.unicef.org/publications/index_24840.html.
64. White SL, Perkovic V, Cass A, Chang CL, Poulter NR, Spector T, et al. Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. *Am J Kidney Dis* 2009;**54**(2):248–61.
65. Luyckx VA, Brenner BM. Birth weight, malnutrition and kidney-associated outcomes–a global concern. *Nat Rev Nephrol* 2015;**11**(3):135–49.
66. Matekole M, Affram K, Lee SJ, Howie AJ, Michael J, Adu D. Hypertension and end-stage renal failure in tropical Africa. *J Hum Hypertens* 1993;**7**(5):443–6.
67. Maoujoud O, Aatif T, Bahadi A, Zajjari Y, Benyahya M, Ahid S, et al. Regional disparities in etiology of end-stage renal disease in Africa. *Saudi J Kidney Dis Transpl* 2013;**24**(3):594–5.
68. Okpechi IG, Ameh OI, Bello AK, Ronco P, Swanepoel CR, Kengne AP. Epidemiology of histologically proven glomerulonephritis in Africa: a systematic review and meta-analysis. *PLoS One* 2016;**11**(3):e0152203.
69. Okpechi I, Swanepoel C, Duffield M, Mahala B, Wearne N, Alagbe S, et al. Patterns of renal disease in Cape Town South Africa: a 10-year review of a single-centre renal biopsy database. *Nephrol Dial Transplant* 2011:26.
70. Olowu WA, Ademola A, Ajite AB, Saad YM. Childhood nephrotic syndrome in tropical Africa: then and now. *Paediatr Int Child Health* 2017;**37**(4):259–68.
71. Olowu WA, Adelusola KA, Adefehinti O, Oyetunji TG. Quartan malaria-associated childhood nephrotic syndrome: now a rare clinical entity in malaria endemic Nigeria. *Nephrol Dial Transplant* 2010;**25**(3):794–801.
72. Wing AJ, Hutt MS, Kibukamusoke JW. Progression and remission in the nehprotic syndrome associated with quartan malaria in Uganda. *Q J Med* 1972;**41**(163):273–89.
73. Hendrickse RG, Adeniyi A. Quartan malarial nephrotic syndrome in children. *Kidney Int* 1979;**16**(1):64–74.
74. Mbah MLN, Poolman EM, Drain PK, Coffee MP, van der Werf MJ, Galvani AP. HIV and *Schistosoma haematobium* prevalences correlate in sub-Saharan Africa. *Trop Med Int Health* 2013;**18**(10):1174–9.
75. Khalaf I, Shokeir A, Shalaby M. Urologic complications of genitourinary schistosomiasis. *World J Urol* 2012;**30**(1):31–8.
76. Colley DG, Bustinduy AL, Secor WE, King CH. Human schistosomiasis. *Lancet* 2014;**383**(9936):2253–64.
77. Antwi S, Aboah KE, Sarpong CK. The unacknowledged impact of urinary schistosomiasis in children: 5 cases from Kumasi, Ghana. *Ghana Med J* 2014;**48**(4):228–33.
78. WHO. *Current estimated total number of individuals with morbidity and mortality due to* Schistosomiasis haematobium *and* S. mansoni *infection in sub-Saharan Africa*. 2010. Available from: https://www.who.int/schistosomiasis/epidemiology/table/en/.
79. Schwartz DA. Helminths in the induction of cancer II. *Schistosoma haematobium* and bladder cancer. *Trop Geogr Med* 1981;**33**(1):1–7.
80. Barsoum R. The changing face of schistosomal glomerulopathy. *Kidney Int* 2004;**66**(6):2472–84.
81. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010-2050: modelling based on demographics, excess mortality, and interventions. *PLoS Med* 2013;**10**(7):e1001484.
82. de Jong PE, Statius van Eps LW. Sickle cell nephropathy: new insights into its pathophysiology. *Kidney Int* 1985;**27**(5):711–7.
83. Ranque B, Menet A, Diop IB, Thiam MM, Diallo D, Diop S, et al. Early renal damage in patients with sickle cell disease in sub-Saharan Africa: a multinational, prospective, cross-sectional study. *Lancet Haematol* 2014;**1**(2):e64–73.

84. Eke CB, Okafor HU, Ibe BC. Prevalence and correlates of microalbuminuria in children with sickle cell anaemia: experience in a tertiary health facility in Enugu, Nigeria. *Int J Nephrol* 2012;**2012**: 240173.
85. Iwalokun BA, Iwalokun SO, Hodonu SO, Aina OA, Agomo PU. Evaluation of microalbuminuria in relation to asymptomatic bacteruria in Nigerian patients with sickle cell anemia. *Saudi J Kidney Dis Transpl* 2012;**23**(6):1320–30.
86. Mawanda M, Ssenkusu JM, Odiit A, Kiguli S, Muyingo A, Ndugwa C. Micro-albuminuria in Ugandan children with sickle cell anaemia: a cross-sectional study. *Ann Trop Paediatr* 2011; **31**(2):115–21.
87. Arogundade FA, Sanusi AA, Hassan MO, Salawu L, Durosinmi MA, Akinsola A. An appraisal of kidney dysfunction and its risk factors in patients with sickle cell disease. *Nephron Clin Pract* 2011;**118**(3):c225–31.
88. Ephraim RK, Osakunor DN, Cudjoe O, Oduro EA, Asante-Asamani L, Mitchell J, et al. Chronic kidney disease is common in sickle cell disease: a cross-sectional study in the Tema Metropolis, Ghana. *BMC Nephrol* 2015;**16**:75.
89. Maigne G, Ferlicot S, Galacteros F, Belenfant X, Ulinski T, Niaudet P, et al. Glomerular lesions in patients with sickle cell disease. *Medicine (Baltim)* 2010;**89**(1):18–27.
90. Okoro BA, Okafor HU. Nephrotic syndrome in Nigerian children with homozygous sickle cell disease. *East Afr Med J* 1997;**74**(12): 819–21.
91. Falk RJ, Scheinman J, Phillips G, Orringer E, Johnson A, Jennette JC. Prevalence and pathologic features of sickle cell nephropathy and response to inhibition of angiotensin-converting enzyme. *N Engl J Med* 1992;**326**(14):910–5.
92. Quinn CT, Saraf SL, Gordeuk VR, Fitzhugh CD, Creary SE, Bodas P, et al. Losartan for the nephropathy of sickle cell anemia: a phase-2, multicenter trial. *Am J Hematol* 2017;**92**(9):E520–8.
93. Geard A, Pule GD, Chetcha Chemegni B, Ngo Bitoungui VJ, Kengne AP, Chimusa ER, et al. Clinical and genetic predictors of renal dysfunctions in sickle cell anaemia in Cameroon. *Br J Haematol* 2017;**178**(4):629–39.
94. Saraf SL, Zhang X, Shah B, Kanias T, Gudehithlu KP, Kittles R, et al. Genetic variants and cell-free hemoglobin processing in sickle cell nephropathy. *Haematologica* 2015;**100**(10):1275–84.
95. Kormann R, Jannot AS, Narjoz C, Ribeil JA, Manceau S, Delville M, et al. Roles of APOL1 G1 and G2 variants in sickle cell disease patients: kidney is the main target. *Br J Haematol* 2017;**179**(2):323–35.
96. Tsaras G, Owusu-Ansah A, Boateng FO, Amoateng-Adjepong Y. Complications associated with sickle cell trait: a brief narrative review. *Am J Med* 2009;**122**(6):507–12.
97. Derebail VK, Nachman PH, Key NS, Ansede H, Falk RJ, Kshirsagar AV. High prevalence of sickle cell trait in African Americans with ESRD. *J Am Soc Nephrol* 2010;**21**(3):413–7.
98. Naik RP, Irvin MR, Judd S, Gutierrez OM, Zakai NA, Derebail VK, et al. Sickle cell trait and the risk of ESRD in blacks. *J Am Soc Nephrol* 2017;**28**(7):2180–7.
99. Naik RP, Derebail VK, Grams ME, Franceschini N, Auer PL, Peloso GM, et al. Association of sickle cell trait with chronic kidney disease and albuminuria in African Americans. *J Am Med Assoc* 2014;**312**(20):2115–25.
100. Hicks PJ, Langefeld CD, Lu L, Bleyer AJ, Divers J, Nachman PH, et al. Sickle cell trait is not independently associated with susceptibility to end-stage renal disease in African Americans. *Kidney Int* 2011;**80**(12):1339–43.
101. Mukendi K, Lepira FB, Makulo JR, Sumaili KE, Kayembe PK, Nseka MN. Sickle cell trait is not associated with chronic kidney disease in adult Congolese patients: a clinic-based, cross-sectional study. *Cardiovasc J Afr* 2015;**26**(3):125–9.
102. Storey B, Osafo C, Ekem I, Bates I, Haynes R, Adu D. *Prevalence of sickle cell trait in Ghanaian patients with chronic kidney disease stages 3-5*. 2018 [Unpublished].
103. Luyckx VA, Steenkamp V, Stewart MJ. Acute renal failure associated with the use of traditional folk remedies in South Africa. *Ren Fail* 2005;**27**(1):35–43.
104. Luyckx VA. Nephrotoxicity of alternative medicine practice. *Adv Chron Kidney Dis* 2012;**19**(3):129–41.
105. James PB, Wardle J, Steel A, Adams J. Traditional, complementary and alternative medicine use in Sub-Saharan Africa: a systematic review. *BMJ Glob Health* 2018;**3**(5):e000895.
106. Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. *Kidney Int* 2008;**74**(2):158–69.
107. Lunyera J, Mohottige D, Von Isenburg M, Jeuland M, Patel UD, Stanifer JW. CKD of uncertain etiology: a systematic review. *Clin J Am Soc Nephrol* 2016;**11**(3):379–85.
108. Gifford FJ, Gifford RM, Eddleston M, Dhaun N. Endemic nephropathy around the World. *Kidney Int Rep* 2017;**2**(2):282–92.
109. El Minshawy O. End-stage renal disease in the El-Minia Governorate, upper Egypt: an epidemiological study. *Saudi J Kidney Dis Transpl* 2011;**22**(5):1048–54.
110. Kamel E, El-Minshawi O. Environmental factors incriminated in the development of end stage renal disease in El-Minia Governorate, Upper Egypt. *Int J Nephrol Urol* 2010;**2**(3):431–7.
111. Abid S, Hassen W, Achour A, Skhiri H, Maaroufi K, Ellouz F, et al. Ochratoxin A and human chronic nephropathy in Tunisia: is the situation endemic? *Hum Exp Toxicol* 2003;**22**(2):77–84.
112. Ekiti ME, Zambo JB, Assah FK, Agbor VN, Kekay K, Ashuntantang G. Chronic kidney disease in sugarcane workers in Cameroon: a cross-sectional study. *BMC Nephrol* 2018;**19**(1):10.
113. Ameh OI, Kengne AP, Jayne D, Bello AK, Hodkinson B, Gcelu A, et al. Standard of treatment and outcomes of adults with lupus nephritis in Africa: a systematic review. *Lupus* 2016;**25**(11):1269–77.
114. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015;**386**(10003):1546–55.
115. Gilbert RD, Wiggelinkhuizen J. The clinical course of hepatitis B virus-associated nephropathy. *Pediatr Nephrol* 1994;**8**(1):11–4.
116. Hong YS, Ryu S, Chang Y, Cainzos-Achirica M, Kwon MJ, Zhao D, et al. Hepatitis B virus infection and development of chronic kidney disease: a cohort study. *BMC Nephrol* 2018;**19**(1):353.
117. Cai QC, Zhao SQ, Shi TD, Ren H. Relationship between hepatitis B virus infection and chronic kidney disease in Asian populations: a meta-analysis. *Ren Fail* 2016;**38**(10):1581–8.
118. Fabrizi F, Donato FM, Messa P. Association between hepatitis B virus and chronic kidney disease: a systematic review and meta-analysis. *Ann Hepatol* 2017;**16**(1):21–47.
119. Fabrizi F, Donato FM, Messa P. Association between hepatitis C virus and chronic kidney disease: a systematic review and meta-analysis. *Ann Hepatol* 2018;**17**(3):364–91.
120. Eastwood JB, Corbishley CM, Grange JM. Tuberculosis and the kidney. *J Am Soc Nephrol* 2001;**12**(6):1307–14.
121. Hodel NC, Hamad A, Praehauser C, Mwangoka G, Kasella IM, Reither K, et al. The epidemiology of chronic kidney disease and the association with non-communicable and communicable disorders in a population of sub-Saharan Africa. *PLoS One* 2018; **13**(10):e0205326.
122. Davids MR, Caskey FJ, Young T, Balbir Singh GK. Strengthening renal registries and ESRD research in Africa. *Semin Nephrol* 2017; **37**(3):211–23.
123. Plange-Rhule J, Phillips R, Acheampong JW, Saggar-Malik AK, Cappuccio FP, Eastwood JB. Hypertension and renal failure in Kumasi, Ghana. *J Hum Hypertens* 1999;**13**(1):37–40.

124. Adjei DN, Adu D, Quayson SE, Kardaun JW, Erskine IJ, Lartey IS, et al. 20 year trends in renal disease mortality in Ghana: A review of autopsies. *Nephrology* 2019;**24**(4):387–94.
125. Ulasi II, Ijoma CK. The enormity of chronic kidney disease in Nigeria: the situation in a teaching hospital in South-East Nigeria. *J Trop Med* 2010;**2010**:501957.
126. Arogundade FA, Sanusi AA, Hassan MO, Akinsola A. The pattern, clinical characteristics and outcome of ESRD in Ile-Ife, Nigeria: is there a change in trend? *Afr Health Sci* 2011;**11**(4): 594–601.
127. Barsoum RS. Burden of chronic kidney disease: North Africa. *Kidney Int Suppl* 2013;**3**(2):164–6.
128. Banaga AS, Mohammed EB, Siddig RM, Salama DE, Elbashir SB, Khojali MO, et al. Causes of end stage renal failure among haemodialysis patients in Khartoum State/Sudan. *BMC Res Notes* 2015;**8**: 502.
129. Davids MR, Jardine T, Marais N, Jacobs C. South African renal registry 2016. *Afr J Nephrol* 2018;**21**(1):61–72.
130. Boima V, Tannor EK, Awuku Y, Okyere P, Osafo CO, Matekole M, et al. *The Ghana renal registry*. 2017.
131. Anand S, Bitton A, Gaziano T. The gap between estimated incidence of end-stage renal disease and use of therapy. *PLoS One* 2013;**8**(8):e72860.
132. Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet* 2015;**385**(9981):1975–82.
133. Ashuntantang G, Osafo C, Olowu WA, Arogundade F, Niang A, Porter J, et al. Outcomes in adults and children with end-stage kidney disease requiring dialysis in sub-Saharan Africa: a systematic review. *Lancet Global Health* 2017;**5**(4):e408–17.
134. Sumaili EK, Krzesinski JM, Zinga CV, Cohen EP, Delanaye P, Munyanga SM, et al. Prevalence of chronic kidney disease in Kinshasa: results of a pilot study from the Democratic Republic of Congo. *Nephrol Dial Transplant* 2009;**24**(1):117–22.
135. Seck SM, Doupa D, Gueye L, Dia CA. Epidemiology of chronic kidney disease in northern region of Senegal: a community-based study in 2012. *Pan Afr Med J* 2014;**18**:307.
136. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease – a systematic review and meta-analysis. *PLoS One* 2016;**11**(7): e0158765.

QUESTIONS AND ANSWERS

Question 1

Increased susceptibility to CKD due *APOL1* renal risk variants has been demonstrated in patients with the following disease conditions except?

A. Sickle cell disease
B. HIV-associated nephropathy
C. Diabetic nephropathy
D. Systemic lupus erythematosus
E. Hypertension-associated kidney disease

Answer: C

APOL1 variants are associated with an increased risk of HIVAN, hypertensive CKD, focal segmental glomerulosclerosis, sickle cell nephropathy, and lupus with ESRD but not with diabetic nephropathy.

Question 2

Schistosoma mansoni infection can cause all the following glomerular histological lesions except

A. Mesangioproliferative glomerulonephritis
B. Diffuse proliferative glomerulonephritis
C. Focal segmental glomerulosclerosis
D. Amyloidosis
E. Thin basement membrane disease

Answer: E

The histological glomerular lesions associated with *Schistosoma mansoni* infection are mesangioproliferative glomerulonephritis, diffuse proliferative glomerulonephritis, mesangiocapillary glomerulonephritis, focal segmental glomerulosclerosis and amyloidosis.

Question 3

Which of the following statements is true about hypertension and CKD in Africa?

A. Across the WHO regions, the highest prevalence of hypertension is found in Africa with an age-adjusted prevalence in individuals over 18 years of 27.4% (95% CI: 24.5−30.4)
B. The prevalence rates of hypertension are similar all over Africa
C. Hypertension is not a recognized risk factor of CKD in Africa
D. The prevalence of CKD in Africans with hypertension has been reported to be 5%
E. The prevalence of hypertension in Africa decreases with increasing age

Answer: A

Question 4

A 60-year-old man with HIV infection who is not treated with antiretroviral medications presented with impaired kidney function and proteinuria. The most likely cause of his renal insufficiency is:

A. Collapsing focal segmental glomerulosclerosis
B. Mesangiocapillary glomerulonephritis
C. Contrast-induced nephropathy
D. Minimal change disease
E. Urolithiasis

Answer: A

The causes of kidney disease in individuals with HIV infection include HIV-associated nephropathy, collapsing focal segmental glomerulosclerosis, HIV-associated immune complex renal disease, and kidney injury from nephrotoxicity from antiretroviral drugs. The risk of HIV-associated renal diseases is reduced in patients treated with antiretroviral drugs.

Question 5

Which of the following is false regarding Tenofovir nephrotoxicity?

A. Tenofovir alafenamide is more nephrotoxic than tenofovir disoproxyl fumarate
B. Tenofovir nephrotoxicity may present as Fanconi's syndrome
C. Tenofovir disoproxil fumarate enters proximal tubular cells through basolateral organic anion transporters and is excreted into the lumen through multidrug resistance associated protein (MRP4) but not MRP2
D. Tenofovir may cause acute kidney injury
E. Tenofovir is associated with increased risk of developing CKD although the size of this effect is unclear

Answer: A

Tenofovir disoproxyl fumarate is more nephrotoxic than tenofovir alafenamide.

Question 6

Which of the following is a risk factor for albuminuria in patients with sickle cell disease in Sub-Saharan Africa?

A. Female sex
B. High hemoglobin level
C. Sequestration crises
D. West African origin
E. Frequent blood transfusions

Answer: A

In a study of 2582 patients with sickle cell disease from four SSA countries, risk factors for albuminuria were increasing age, female sex, high lactic dehydrogenase, and low hemoglobin concentration.

CHAPTER

12

Ethnicity and Chronic Kidney Disease in China

Bixia Gao[a], *Jinwei Wang*[a], *Luxia Zhang*[a], *Shougang Zhuang*[b]

[a]Renal Division, Department of Medicine, Peking University First Hospital; Peking University Institute of Nephrology, Beijing, China; [b]Department of Nephrology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China

Abstract

Chronic kidney disease (CKD) has been recognized as a major public health issue worldwide. China is the most populous country in the world, thus, the impact of CKD on public health and socioeconomics are profound both in China and worldwide. In the past decade, booming trends in diabetes, hypertension, and obesity, coupled with an aging population, will exacerbate the burden of CKD unless effective control and prevention strategies are implemented. Changes in environmental and behavioral factors, as well as reforms in health care systems, all have profound effects on the spectrum, prognosis, and treatment of patients with CKD in China. The prevalence, incidence, and spectrum of CKD, as well as the comorbidities, treatment, and prognosis of patients with CKD in China, have changed enormously.

SCOPE OF THE PROBLEM/PUBLIC HEALTH IMPLICATIONS

China is the most populous country in the world. After rapid economic growth for nearly four decades, China is now the second largest economy in the world. Abundant food supply and a sedentary lifestyle exert great influence on disease patterns among the Chinese population. The prevalence of obesity, hypertension, diabetes, metabolic syndrome, and the related cardiovascular and kidney diseases has increased greatly since China initiated its economic reforms in the late 1970s.[1] A survey conducted in 2009–2010 with a nationally representative population showed the prevalence of chronic kidney disease (CKD), in China to be 10.8%.[2] The figure is equivalent to the level of 10%–16% among other major developed and developing countries.[3] The prevalence of CKD stages in China were 5.7%, 3.4%, 1.6%, and 0.1% for stage 1 through 4, respectively.[2] The corresponding rates in Japan were 0.6%, 1.7%, 10.4%, and 0.2%, respectively,[4] and in the US were 1.8%, 3.2%, 7.7%, and 0.35%, respectively.[5] A larger proportion of patients with CKD in China were in early stages. The prevalence of hypertension and diabetes has continuously increased in recent decades in China.[6,7] It may take several years for patients with hypertension and/or diabetes to exhibit kidney disease, and they may progress to renal functional decline after decades. Hence, although the majority of patients with CKD in China are in early stages, more patients are expected to progress to late stages in the future, similar to the situation seen in developed countries.

In addition, there is a different spectrum of epidemiology of CKD between rural and urban areas and across levels of per capita GDP in China. According to the study by Zhang et al.[2] the prevalence of albuminuria was higher in rural than that in urban areas (10.1% vs. 7.0%). Conversely, the prevalence of eGFR less than 60 mL/min/1.73 m^2 was higher in urban than in rural areas (2.3% vs. 1.6%). Further stratification by per capita GDP showed different patterns in rural and urban areas. In rural areas, the prevalence of albuminuria increased through higher levels of per capita GDP, while that of eGFR less than 60 mL/min/1.73 m^2 remained stable. However, in urban areas, both the prevalence of albuminuria and eGFR less than 60 mL/min/1.73 m^2 decreased through per capita GDP levels.[2] The pattern of epidemiology of CKD in China indicates there is a unique opportunity to prevent advanced disease, given low stages accounted for the majority of patients. Lifestyle changes associated with economic growth could exert an adverse effect on the burden of CKD, as seen in rural areas of China. However, we propose that improvement in health literacy and health care access may effectively curb the epidemic of CKD, as seen in urban areas of China, where economic and social

https://doi.org/10.1016/B978-0-12-815876-0.00012-7

development is substantially superior to that in rural areas.

Routinely collected medical record data may provide a unique opportunity for estimating the disease burden of CKD according to etiology, treatment, comorbidity, mortality, and costs.[8] Based on a hospital discharge record database (Hospital Quality Monitoring System, HQMS), which covers nearly half of tertiary hospitals in China, Zhang and colleagues made a comprehensive annual report regarding CKD in China.[9] The proportion of patients with CKD varied from 3% in Shanghai to 7.2% in Guangxi (Figure 12.1). Taken together, there were nearly 1.8 million hospitalizations due to a main claim of CKD in fiscal year 2013, which accounted for only 1.6% of the total estimated number of CKD patients (10.8% of the total adult population, equivalent to 113.8 million patients with CKD). However, the average cost of 9.5 thousand yuan per each hospitalization due to CKD (a total estimate of 17.5 billion yuan) has generated a huge burden for the health care system. If the comorbidities of cardiovascular disease (CVD) were considered, the economic burden of CKD would be even higher.

In addition, the current incidence and prevalence of end-stage renal disease (ESRD) is still low in China, with an estimated incidence of 15.4 cases per million population (pmp), and an estimated prevalence of 237.3 cases pmp in 2012.[10] However, in some developed regions/countries such as Taiwan and Japan, where genetic characteristics of the population are similar to those in China, the corresponding rates were more than 10 times higher than those in China.[11,12] Patients with ESRD need costly renal replacement therapy to maintain life. Thus, the economic burden in China may be even greater if there are not effective measures to control CKD.

PATHOPHYSIOLOGY

There is currently not a nation-wide registry for kidney disease in China. To know the spectrum of CKD, we reviewed the best available evidence based on large-scale renal biopsy series and a national database for hospitalized patients, where CKD was identified through ICD codes. In an analysis of 13,519 renal

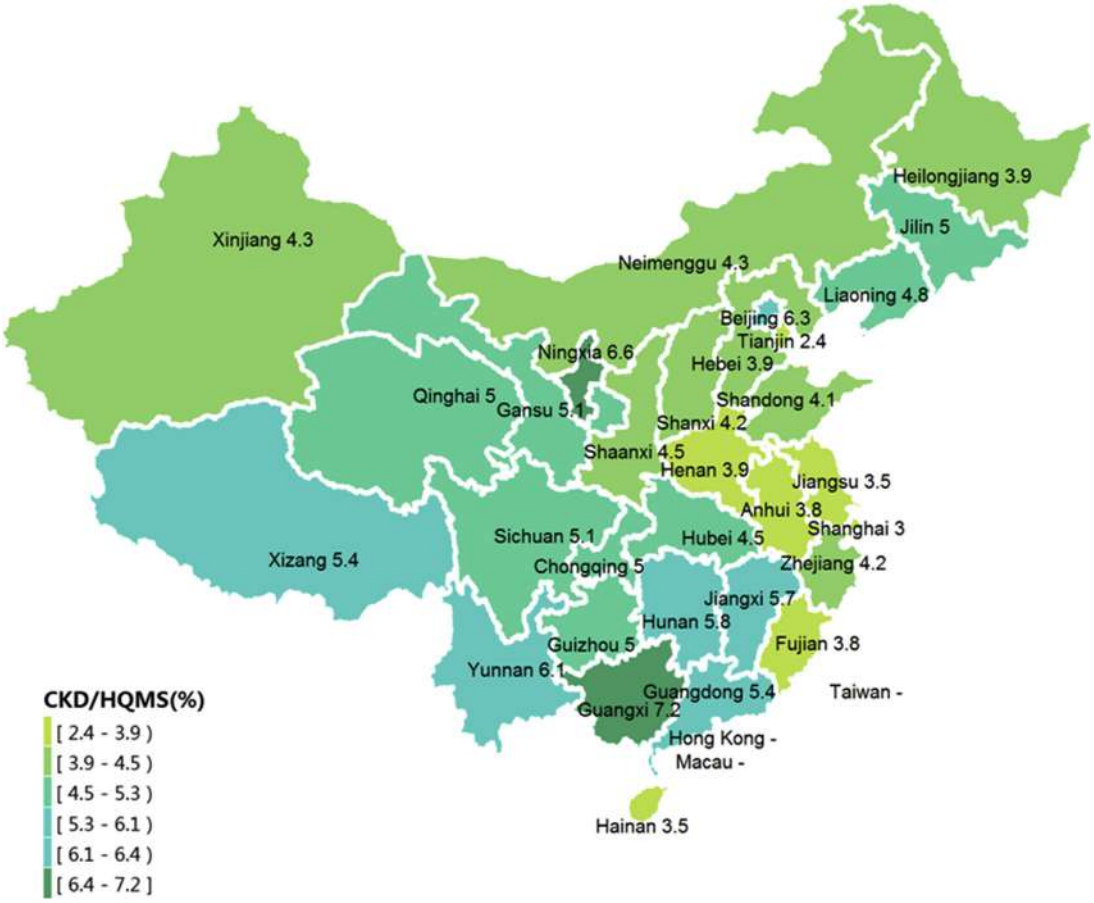


FIGURE 12.1 Geographic distribution of residence of patients with chronic kidney disease. *Adapted from Zhang L, Wang H, Long J, et al. China Kidney Disease Network (CK-NET) 2014 annual data report.* Am J Kidney Dis *2017;**69**(6S2):S1—147. Copyright (2016), with permission from Elsevier.*

biopsies accumulated from 1979 to 2002 in a central clinical center located in southeast China, Li et al. systematically evaluated pathologic types of kidney disease. Primary glomerulopathy was the most prevalent type of kidney disease, accounting for 68.6% of total cases.[13] IgA nephropathy (IgAN) was the most common type of primary glomerulopathy, accounting for 45.3% of cases. Non-IgA diffuse mesangial proliferative lesion comprised 25.6% and idiopathic membranous nephropathy (MN) 9.9% of cases.[13] The pattern was different from that reported in Western countries, where MN and minimal change disease (MCD) are typically more prevalent. Another renal biopsy series (2004–2014) of 71,151 patients conducted in 938 hospitals in 282 cities across China replicated the findings. IgAN was the most prevalent type of glomerulopathy (37.4%), while MN and MCD were also common (28.0% and 22.2% of primary glomerulopathies, respectively), similar[14] to reports in Western countries. MCD was the most prevalent type among children (20.4% in all primary and secondary glomerulopathies in the 0–14 age group). IgAN was most prevalent among young to middle-aged patients (36.0% of all primary and secondary glomerulopathies in the 15–39 age group). MN was the most prevalent type among middle-aged and elderly patients (31.9% in the 40–64 age group and 45.0% in the 65 and above age group).

Although biopsy series provide valid diagnoses for different types of kidney disease, results may be biased in reflecting the spectrum of CKD because patients undergoing renal biopsy may be more likely to have obvious clinical syndromes. In the cited nation-wide renal biopsy series, 45.4% of patients undergoing renal biopsy had nephrotic syndrome and 40.4% of patients had urinary abnormalities as indications for biopsy.[14] Thus, the burden of metabolic diseases related to kidney disease may be underestimated. For example, diabetic nephropathy only accounted for 1.7% of the total glomerulopathies, listed after lupus glomerulopathy (7.4%), purpuric glomerulopathy (3.4%), and thin basement membrane nephropathy (2.0%).[14] However, according to the annual data report of kidney disease based on HQMS in fiscal year 2013, although primary glomerulonephritis is the most common pathologic type of CKD, accounting for 17.6% of CKD, diabetic nephropathy, and CKD with hypertension occupied a prominent position compared with reports based on renal biopsies. There was nearly an equivalent proportion of primary glomerular disease attributed to diabetic nephropathy (17.4% of all CKD) and CKD related to hypertension (14.4%) (Figure 12.2).

Patients with glomerulonephritis were younger than those with diabetic nephropathy, with a median age of 48 (interquartile range [IQR]: 35–61) years vs. 63 (IQR: 53–72) years. Among the 18–44 year old group, glomerulonephritis was the most common type of CKD (23.3% in men and 19.2% in women). In the 45–64 year old group and the ≥65 year old group, diabetic nephropathy was predominant (28.0% in men and 18.4% in women in the 45–64 year group; 23.3% in men and 20.7% in women in the ≥65 year group).

There was geographical variation in the pathologic types of CKD in China. The proportion of glomerulonephritis was higher in provinces located in north China, while the proportion of obstructive nephropathy was higher in those located in south China.[9]

According to the annual data report of kidney disease, IgAN, MN, and MCD were the most common

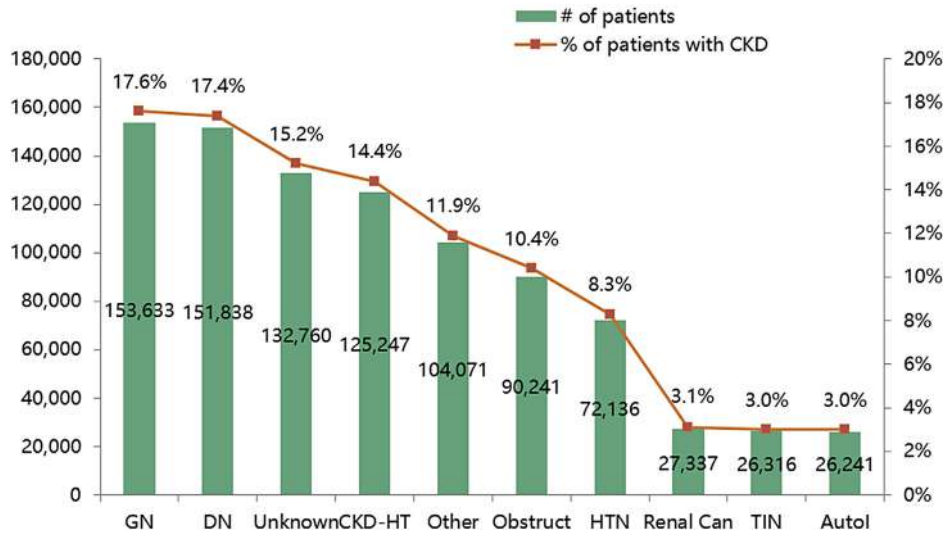


FIGURE 12.2 Patients with chronic kidney disease (CKD), stratified by cause. *Adapted from Zhang L, Wang H, Long J, et al. China Kidney Disease Network (CK-NET) 2014 annual data report.* Am J Kidney Dis *2017;**69**(6S2):S1–147. Copyright (2016), with permission from Elsevier.*

types of primary glomerulonephritis among hospitalized patients, accounting for 10.3%, 8.5%, and 1.9% of all patients, respectively, and 43.8%, 35.9%, and 8.1% of patients with pathological diagnoses, respectively.[9] The most common types were consistent with those reported in renal biopsy series.

Over time, the spectrum of primary glomerulonephritis has changed significantly in China. Li et al. conducted a study using the same HQMS data; however, they included all 0.3 million patients with primary glomerulonephritis from 2010 through 2015. They found the percentage of MN as primary glomerulonephritis doubled from 4.6% in 2010 to 8.8% in 2015, while that of IgAN decreased from 19.0% in 2010 to 10.6% in 2015. In places in north and northeast China, the proportion of MN already exceeded that of IgAN since 2014 and became the predominant type of primary glomerulonephritis (Figure 12.3). The authors also reported a disproportionate increase of the proportion of MN in urban and rural areas. In urban areas, the proportion of MN increased from 5.0% in 2010 to 11.4% in 2015, while there was only a slight increase from 6.1% to 7.4% in the same period observed in rural areas. By linking the air pollution database, they detected an association between the concentration of atmospheric particulate matter with a diameter of less than 2.5 micrometers (PM2.5) and the frequency of MN, as well as a disproportionately high frequency of MN in some minorities, especially the Zhuang, who live in south China.[15]

During the past decades, the prevalence of diabetes mellitus has increased dramatically from less than 1.0% in 1980 to 11.6% in 2010 in China.[7,16] This trend of increased prevalence of diabetes will surely exert an influence on the etiology of CKD in the future. Before Zhang and colleagues used the national database of hospitalized patients to address the problem, some findings from local disease registries demonstrated the impact of diabetes. For example, Gan and colleagues reported that the leading cause of incident ESRD has changed from chronic glomerulonephritis to diabetes since 2010 in the Beijing-based hemodialysis registry, although chronic glomerulonephritis remained the most important cause of prevalent ESRD.[17] Besides using one year data to present the epidemiologic characteristics of kidney disease, Zhang et al. used serial data from hospitalized patients from 2010 to 2015 to compare the prevalence of CKD with diabetes and glomerulonephritis in China.[18] The percentage of CKD with diabetes and that with glomerulonephritis were 0.82% and 1.01%, respectively, in 2010. However, the percentage of CKD with diabetes surpassed that of CKD with glomerulonephritis from 2011. The percentage gap between the two types continued to increase afterward. The corresponding percentages were 1.10% and 0.75%, respectively, in 2015.[18] However, the pattern in urban and rural areas was different. In urban areas, percentage of CKD with diabetes was higher than in rural areas from 2010 through 2015. In rural areas, the percentage of CKD

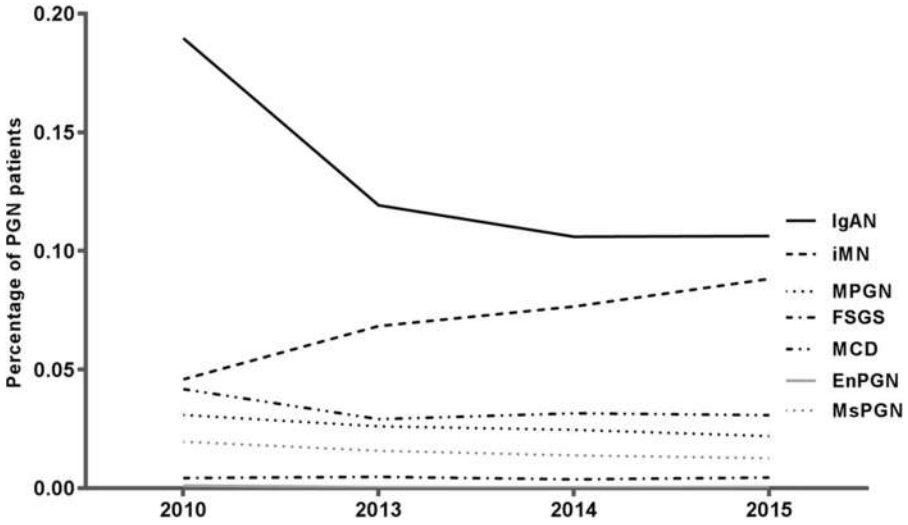


FIGURE 12.3 The changing pathology of primary glomerular disease in China. The figure shows the changing percentage of different primary pathological types among patients over time. The percentage of iMN increased almost twofold, while the percentage of IgAN decreased. *EnPGN*, endocapillary proliferative glomerulonephritis; *FSGS*, focal segmental glomerulosclerosis; *IgAN*, IgA nephropathy; *iMN*, idiopathic membranous nephropathy; *MCD*, minimal change disease; *MPGN*, membranoproliferative glomerulonephritis; *MsPGN*, non-IgA mesangioproliferative glomerulonephritis; *PGN*, Primary glomerular nephropathy. *Adapted from Li J, Cui Z, Long J, et al. Primary glomerular nephropathy among hospitalized patients in a national database in China.* Nephrol Dial Transplant, *2018. https://doi.org/10.1093/ndt/gfy022. Copyright (2018), with permission from Oxford University Press on behalf of ERA-EDTA.*

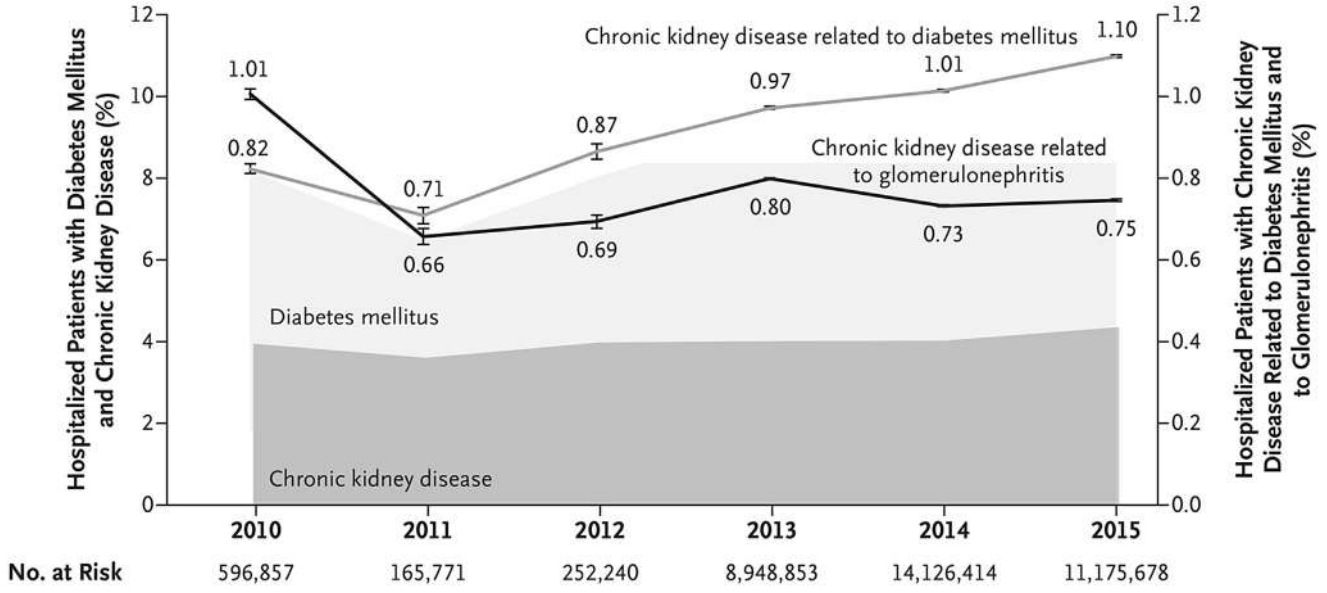


FIGURE 12.4 Trends in CKD related to glomerulonephritis among hospitalized patients in China. The percentages shown were calculated among hospitalized patients each year. The number of hospitalized patients for each year (numbers at risk) was obtained from the Hospital Quality Monitoring System, a mandatory patient-level national database for hospital accreditation, under the authority of the National Health and Family Planning Commission of the People's Republic of China. *Adapted from Zhang L, Long J, Jiang W, et al. Trends in chronic kidney disease in China.* N Engl J Med *2016;**375**(9):905–6. Copyright (2016), with permission from Massachusetts Medical Society.*

with diabetes increased gradually but was still less than the percentage of glomerulonephritis during the same period[18] (Figure 12.4). The crossover of the etiologies of CKD among patients treated with dialysis has been observed in other countries/regions of Asia as well.[19,20]

DIAGNOSIS

Prevalence of CKD

Previous regional cross-sectional studies from economically developed cities in China, including Beijing, Shanghai, and Guangdong, reported the prevalence of CKD was 11.8%–13.0%.[21–23] However, those studies used different sampling methods, screening procedures, and diagnostic criteria. In 2012, a national survey used a multistage, stratified sampling approach to obtain a representative sample of the adult population in China.[2] In this survey, CKD was defined by the presence of eGFR lower than 60 mL/min/1.73 m^2 and/or urinary albumin:creatinine ratio higher than 30 mg/g creatinine. A total of 47,204 participants were included. The prevalence of CKD was 10.8% [95% confidence interval (CI) 10.2%–11.3%],[2] comparable to that reported in developed countries.[5] Based on the huge population of China, the number of CKD patients was estimated as up to 119.5 million. Thus, the impact of CKD on public health and socioeconomics are profound.

Despite the high prevalence, the awareness of CKD in the Chinese population is extremely low. For example, one prospective cohort study containing 462,293 adult participants in Taiwan in 1994 reported that prevalence of CKD was 11.93%, but only 3.54% of participants were aware of their disorder.[24] In 2011, another study in Taiwan enrolled 6001 subjects and reported the awareness rates were 8.0% for individuals with stage 3 CKD, 25.0% for those with stage 4 CKD, and 71.4% for those with stage 5 CKD.[25] In 2010, the national CKD survey in China revealed that the adjusted awareness rate of the predialysis CKD population was 12.5%[2] and only 38.2% in those with stages 4–5 CKD. The awareness of CKD is closely related to the management and prognosis of the CKD population, thus, educating patients with CKD to be aware of their kidney disease is a first step in CKD care in China.

Epidemiologic Characteristics of CKD

The distribution of CKD stages is different between China and the US. Individuals in China are at relatively early stage of CKD. For example, the prevalence of CKD stages 3–5 is lower in China (1.7%, 95% CI 1.5%–1.9%),[2] compared with 8.2% in the US[5] Further, the majority of participants had CKD due to albuminuria (prevalence of 9.4%)[2] compared with 5.0% in the US.[5] Previous studies reported that diabetic kidney disease (DKD) in Asian populations is more likely to present as albuminuria.

In the Microalbuminuria in Patients with Diabetes study, the prevalence of microalbuminuria and macroalbuminuria in type 2 diabetic Asian patients with 6.9 years duration of diabetes was 38% and 18%, respectively.[26] In contrast, in the United Kingdom Prospective Diabetes Study, the prevalence of microalbuminuria and macroalbuminuria 10 years after diagnosis of diabetes was 24.9% and 5.3%, respectively.[27] Ethnic differences in CKD patterns need to be further investigated.

Other issues regarding the characteristics of CKD in China are regional differences and socioeconomic disparities. The prevalence of albuminuria among rural residents is higher than those among urban residents (10.1% vs. 7.0%), especially for those from economically improving rural areas (14.8%).[2] In addition, the north and southwest have relatively higher prevalence rates of CKD, 16.9% (95% CI 15.1%–18.7%) and 18.3% (95% CI 16.4%–20.1%), respectively.[2] A cohort study in Taiwan enrolled 56,977 CKD participants and found that in those with low socioeconomic status, the prevalence of CKD was nearly three times higher than that in the high socioeconomic group (19.87% vs. 7.33%).[24] This difference was most substantial for participants with stage 3–5 disease, for whom low socioeconomic status was between four and eight times higher.[24] Reasons for this difference are not fully understood and might be due to multiple factors, including the differences in environment and behavioral factors across different regions, economic, social, or educational disadvantage, access to and uptake of care, lower achievement of treatment goals, lower screening rates, and suboptimal early treatment of complications.

Major Risk Factors of CKD

In the last decades, the lifestyle changes that accompanied the economic boom in China, as well as the surging prevalence of obesity, diabetes, and hypertension have led to a change in the spectrum of CKD in China. Despite glomerulonephritis as the leading cause of CKD and ESRD in China, DKD and hypertensive nephropathy constitute the major proportion of CKD in the elderly CKD population.[28] A recent analysis based on the HQMS dataset reported that DKD has become the leading cause of CKD in the hospitalized population.[18] Over the past two decades, the prevalence of hypertension has doubled. A nation-wide survey of hypertension in 1991 examined 950,356 residents aged ≥15 years and suggested the overall prevalence of hypertension among those residents was 11.26%.[29] Ten years later, the results of the International Collaborative Study of Cardiovascular Disease in Asia[30] suggested 27.2% of the Chinese adult population aged 35–74 years had hypertension. A more recent national survey from Wang et al.[31] reported that the prevalence of hypertension among the adult population in China was 29.6%. Using data from the China Health and Nutrition Survey, Mi et al. analyzed the trend of overweight and obesity from 1993 to 2009 in China. The prevalence of overweight (BMI 25–27.49 kg/m) increased from 8.0% to 17.1% among men and from 10.7% to 14.4% among women. The prevalence of obesity (BMI>27.5 kg/m^2) increased from 2.9% to 11.4% among men and from 5.0% to 10.1% among women. Without effective control, the increasing trend of these metabolic disorders will result in an even greater burden of CKD in the future. Thus, the primary prevention focuses on these high-risk populations and integration of surveillance of CKD in the management of the population with hypertension and diabetes at a national level should be recommended.

In addition to these metabolic risk factors, Chinese herbs containing nephrotoxic agents were identified as an important risk factor for CKD in China. A longitudinal study from Taiwan indicated that regular users of Chinese herbal medicines had a 20% increased risk of developing CKD.[24] A recent study using a national-representative sample in China indicated that long-term intake of herbs containing aristolochic acid (AA) was independently associated with eGFR <60 mL/min/1.7 m^s and albuminuria, with odds ratio of 1.83 (95% CI 1.22–2.74) and 1.39 (95% CI, 1.03–1.87), respectively.[32] Longitudinal studies from Taiwan revealed use of AA containing herbs, especially >60 g of Mu Tong or Fangchi from herbal supplements, is associated with increased risk of developing kidney failure.[33] In addition to the increased risk of developing CKD, the AA-containing herbs were found to be associated with urothelial malignancy, even several years after their discontinuation.[34] Despite the Food and Drug Administration's warnings concerning the safety of botanical remedies containing AA, these herbs are still sold *via* the Internet.

Environmental pollution–associated CKD has become an issue of global concern.[35] Hou et al. analyzed data from an 11-year (2004–2014) national renal biopsy series including 71,151 patients from 938 hospitals in 282 cities across China. During the study period, the level of PM2.5 exposure varied from 6 $\mu g/m^3$ to 114 $\mu g/m^3$ (mean 52.6 $\mu g/m^3$) among the 282 cities. The prevalence of MN increased from 12% to 24% during the decade, while the prevalence of other major glomerular diseases remained relatively stable.[14] Each 10 $\mu g/m^3$ increase in PM2.5 concentration was associated with 14% higher odds for MN (odds ratio, 1.14; 95% CI 1.10–1.18) in regions with PM2.5 concentration >70 $\mu g/m^3$.[14] Similarly, a longitudinal study of over 2 million US veterans with no previous history of kidney disease found that long-term exposure to PM2.5,

PM10, nitrogen dioxide, and carbon monoxide was associated with an increased risk of incident CKD, CKD progression, and development of ESRD.[36] The pathogenic mechanisms underlying the association between air pollution and kidney injury remain to be completely elucidated. In addition to air pollution, heavy metals polluting the drinking water and food have been considered another major threat to human health. Studies have revealed the nephrotoxicity of some heavy metals, such as mercury,[37] cadmium,[38] and lead.[38,39] China produces the largest number of major pollutants in the world, which cause serious air pollution. In addition, approximately 10% of farmland soil and 14% of grain production in China is estimated to be contaminated with heavy metals through irrigation and the use of fertilizers.[40] Thus, the management of environmental pollution in China is urgent. Further studies are needed to elucidate the causal relationships between exposure to environment pollutants and the development of kidney disease, as well as pathogenic mechanisms of environmental nephrotoxins.

PREVALENCE AND INCIDENCE OF ESRD IN CHINA

In 2010, the prevalence of CKD was 10.8%, and ESRD accounted for 0.03% of the general population in China.[2] Glomerulonephritis remained the leading cause of ESRD, followed by diabetes and hypertension. The estimated prevalence of ESRD in China is about 200–250 cases pmp.[41] The cost of treatment for a patient with ESRD in China is approximately US $13,850–$15,380 per year,[42] which puts a large economic burden on individuals and health care resources.

The Dialysis and Transplantation Registration Group of the Chinese Society of Nephrology release of an annual data report on dialysis and transplantation in China began in 2001.[43] However, the response rate of regions other than Beijing and Shanghai was lower than 50%, and the status of kidney transplantation was not mentioned in the report. Thus, the burden of ESRD in China was largely underestimated. In 2008, the Chinese Society of Blood Purification distributed a survey to each provincial Society for Blood Purification in mainland China, to collect information on dialysis facilities.[44] Among 31 provinces/regions in mainland China, 27 participated in the survey and further distributed the survey to each local dialysis facility. Based on this survey, the point prevalence of dialysis and annual incidence of treated ESRD in 2008 were estimated to be 71.9 pmp and 36.1 pmp, respectively.[44] In April 2010, with an endorsement from the Ministry of Health of China, the Chinese Society of Nephrology launched the first nation-wide, web-based, prospective renal data registration platform, the Chinese National Renal Data System (CNRDS), to collect structured demographic, clinical, and laboratory data on dialysis patients, as well as to establish a kidney disease database for researchers and policymakers.[10] According to a presentation regarding data analyses of that system at the annual conference of Chinese Society of Nephrology, the prevalence of maintenance HD in China increased substantially to 237.3 pmp in 2012, while the incidence remained stable (estimated at 15.4 pmp).

Besides these national registries, some regional registries in economically developed cities also release their local dialysis reports. For example, in 2011, the Beijing Hemodialysis Quality Control and Improvement Center (BJHDQCIC) and Shanghai Hemodialysis Quality Control Center reported that the prevalence and incidence of maintenance hemodialysis were 524.6 and 107.3 pmp in Beijing, and 544.7 and 82.9 pmp in Shanghai.[45,46] In Taiwan, the prevalence of patients with ESRD treated with dialysis reached 2584 PMP in 2010, while a rate of 1106 pmp was reported in Hong Kong.[47] The prevalence reported among these economically developed cities are substantially higher than national levels, reflecting disparities of medical resources across China.

TREATMENT AND PROGNOSIS

Use of Renin–Angiotensin–Aldosterone System Blockade

Inhibition of the renin–angiotensin–aldosterone system (RAAS) with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) is a well-evidenced strategy for delaying the progression of CKD, particularly in those with mild to moderate renal insufficiency (serum creatinine concentration (S[Cr]) <3 mg/dL).[48,49] In China, national data on use of RAAS blockers in the CKD population are lacking. One prospective cohort in Hong Kong included 4421 type 2 diabetic outpatients between 1995 and 2000 and revealed that the percentage of use of RAAS blockers was 68.7% in stage 3 CKD participants, and 53.5% in stage 4 CKD participants.[50] In comparison, the Chronic Renal Insufficiency Cohort (CRIC) study, a national prospective CKD cohort in the US, reported that the percent use of RAAS blockers among stage 1–4 CKD patients was 74%.[51]

The renoprotective effect of RAAS blockade in advanced CKD has always be a topic of concern. A few high-quality studies have shown potential benefits of these drugs among the advanced CKD population.

One randomized, double-blind study enrolled 244 nondiabetic CKD patients with S[Cr] of 3.1−5.0 mg/dL. These patients were randomly assigned to receive 20 mg of benazepril per day (112 patients) or placebo (112 patients) and then followed up for a mean of 3.4 years.[52] Compared with placebo, benazepril was associated with a 43% reduction in the risk of the primary endpoint (defined as composite of a doubling of the S[Cr] level, ESRD, or death), independent of the control of BP.[52] The overall incidence of major adverse events (such as hyperkalemia) in the benazepril and placebo subgroups was similar.[52] Recently, a large prospective cohort in Taiwan showed that stage 5 predialysis CKD patients (S[Cr] >6 mg/dL) who received therapy with ACEIs/ARBs exhibited moderately reduced incidence of dialysis without increasing the risk of death.[53] The analysis of this study came from the NHI Research Database, which contains health care utilization data for more than 95% of the hospitals in Taiwan and 99% of the entire 23 million persons enrolled in the NHI program.[53] Overall, a total of 28,497 hypertensive adult patients with predialysis stage 5 CKD were included. 49.5% participants had at least one prescription for an ACEI/ARB. In a median follow-up of 7 months, 20,152 patients (70.7%) required long-term dialysis and 5696 (20.0%) died before progression to ESRD requiring dialysis. Use of ACEIs/ARBs was associated with a lower risk for long-term dialysis (HR, 0.94 [95% CI, 0.91−0.97]) and the composite outcome of long-term dialysis or death (0.94 [0.92−0.97]).[53]

Hypertension, Anemia, CKD-MBD, CVD, and Mortality in CKD

CKD has become an increasing public health issue. Complications of CKD include increased all-cause and cardiovascular mortality, kidney-disease progression, acute kidney injury, cognitive decline, anemia, mineral and bone disorders (MBDs), and fractures.[3] Despite it being a public health problem, studies on CKD complications are relatively limited in China. Most of the epidemiologic features of CKD complications come from regional, small sample studies. The Chinese Cohort Study of Chronic Kidney Disease (C-STRIDE) is the first national prospective CKD cohort in China, which started in 2011 with 39 clinical centers in different geographic regions of China.[54] It aims to provide a comprehensive understanding of the CKD population in China, including CKD complications and treatment, comorbidities, health resource utilization, cognitive function, and quality of life, as well as exploring associations between these factors and CKD progression and other adverse consequences. It has enrolled about 3000 Chinese predialysis CKD patients and provides data representing the Chinese CKD population.

Hypertension is a common comorbidity in patients with CKD, and it is also an important determinant of CKD development and progression. The C-STRIDE enrolled 2873 predialysis CKD participants. The prevalence of hypertension in predialysis CKD patients is 78.4%,[55] lower than that reported in the CRIC study in the US (85.7%).[51] Based on the subgroup analysis of C-STRIDE, the awareness, treatment, and control rates (defined as BP <140/90 mm Hg) of hypertension among 2251 hypertensive CKD subjects were 80.7%, 95.6%, and 57.1%, respectively,[55] worse than that reported in the CRIC study. The CRIC study reported the awareness and treatment rates of hypertension were 98.9% and 98.3% (67.1% and 46.1% had hypertension controlled to <140/90 and <130/80 mm Hg, respectively). Over 50% of study subjects were prescribed two or more antihypertensive medications. Only 7% were prescribed diuretics.[55] Compared with another national survey between 2004 and 2005, despite minimal change in the awareness of hypertension in the CKD population, the treatment and control rates significantly improved (95.6% vs. 85.9% and 57.1% vs. 30.0%, respectively) over the past decades.[6]

Anemia is another frequent complication in patients with advanced CKD, and it is associated with poor quality of life, impaired cognition, and increased all-cause mortality.[56] A multicenter survey of 2420 predialysis patients with CKD from 25 hospitals in Shanghai reported that the prevalence of anemia was 51.5%. Prevalence increased with advancing CKD stage (from 22.4% in CKD stage 1%−90.2% in CKD stage 5).[57] The overall awareness and treatment rates were 67.5% and 44.9%, respectively. Further, 22.7% patients initiated treatment of anemia when hemoglobin (Hb) was less than 7 g/dL. The target-achieving rate (Hb at 11−12 g/dL) was only 8.2%. Among patients receiving dialysis, the target-achieving rate was also significantly worse in China than in developed countries. Results of the Dialysis Outcomes and Practice Patterns Study[58] reported the status of anemia in 11,041 HD patients from 12 countries. The target-achieving rate was 73% in the US, but only 21.3% in China.[59]

MBD in patients with CKD is associated with increased morbidity and mortality. However, MBD is suboptimal among Chinese CKD patients. In the C-STRIDE, the proportions of predialysis CKD patients with hyperphosphatemia were 2.6%, 2.9%, 6.8%, and 27.1% in CKD Stages 3a, 3b, 4, and 5, respectively. Moreover, 71.6% of patients with hyperphosphatemia did not receive any phosphate binder.[60] Another cross-sectional study of 2074 dialysis patients from 28 hospitals in China (1711 HD and 363 peritoneal dialysis [PD]) revealed that only 38.5%, 39.6%, and 26.6% of

participants were within the optimal level of S[P], corrected S[Ca], and iPTH recommended by the Kidney Disease Outcomes Quality Initiative (K/DOQI) guideline. In comparison, results from the DOPPS reported that percentages of optimal S[P], S[Ca], and iPTH were 49.8%, 50.4%, and 31.4%, respectively.[61]

CKD entails excess risk of CVD and mortality, even at early stages. One large prospective cohort in Taiwan enrolled 56,977 CKD individuals and followed them for a median duration of 7.5 years. 5987 CKD died. Participants with CKD had 83% higher risk of all-cause mortality (HR 1·83 [1·73–1·93]) than those without.[24] Another prospective study of 4421 type 2 diabetic patients revealed that all-cause mortality rate increased from 1.2% (95% CI 0.8–1.7) to 18.3% (9.1–27.5) as renal function deteriorated from stage 1 (eGFR 90 mL/min/1.73 m^2) to stage 4 (15–29 mL/min/1.73 m^2). Despite limited data being available about CVD burden in individuals with CKD in China, a few studies provide some useful information. Among 3168 CKD stage 1–4 participants in C-STRIDE, the prevalence of CVD was 9.8%, much higher than the overall percentage of 1.4% in the general Chinese population.[62] Cerebrovascular disease was most common subtype, accounting for 69.1% of CVD population, followed by myocardial infarction (20.6%) and congestive heart failure (9.0%).[62] Using HQMS data, the pattern of CVDS is quite different from outpatients with CKD in the C-STRIDE. In hospitalized CKD patients the prevalence of CVD (defined by ICD-10 coding) was 27.8% in 2014. Coronary heart disease was most common, followed by congestive heart failure and stroke.

Treatment and Prognosis of Dialysis Patients

For the past decades, the Chinese government has paid increasing attention to the treatment available for patients with ESRD, as uremia is one of eight major serious diseases covered by National Social Medical Insurance. Recently, with the advancement of health care system reforms in China, basic medical insurance now covers 95% of urban and rural residents, and a high-reimbursement policy for catastrophic diseases including ESRD has been established. Despite this, there are still disparities between ESRD care in China and Western countries.

Due to limited medical and economic resources, particularly in the countryside and remote areas, the proportion of individuals with ESRD who are treated with dialysis in China is only about 20%.[63] Both national registries reported the majority of Chinese ESRD patients received HD, accounting for 89.5% in 1999 and 89.1% in 2012, respectively.[43] In Shanghai in 2012,[45] 77.5% of patients receiving dialysis therapy were on HD, slightly lower than national levels. HD in China still faces many challenges. Almost all HD centers are located at hospitals in urban areas. The development of HD services in various regions remains uneven. Dialysis equipment, as well as the professional skills of medical staff, needs to be improved in remote and rural locations. Currently, more than 90% of dialysis equipment and 80% of HD consumables in China are imported. Accelerating the research and development of blood purification products in China is crucial to reducing the cost of dialysis and providing treatment to more Chinese ERSRD patients. According to the annual data report from BJHDQCIC, the annual mortality rate was approximately 7.0%–9.2% from 2007 to 2013. This was lower than that reported by USRDS, which was approximately 15%. In 2009, the mortality rate for prevalent White, African American, and Asian American maintenance HD patients in the US and for Chinese HD patients in mainland China was 236.3, 156.7, 147.9, and 77.3 per 1000 patient-years, respectively.[64] The annual mortality rate was decreasing in the US but was increasing in mainland China. The low mortality rate in mainland China might be partly attributed to the fact that all dialysis facilities were hospital-based and doctors were always present during hemodialysis sessions, or to factors related to patient selection.

Compared with HD, PD has minimal requirements for equipment support and electricity, which is important for patients in rural and remote areas. The annual cost of PD is comparatively lower than hemodialysis ($15,034 US dollars vs. $16,625 US dollars for hemodialysis).[47] PD has grown at a rate of 30% annually recently,[63] but most of the centers are located in big cities. Currently, approximately 1024 hospitals offer PD to more than 40,000 ESRD patients throughout the nation, accounting for 20% of the total patients with ESRD receiving dialysis in China. However, 90% of PD solutions used in China are imported. Therefore, to increase the affordability and accessibility to renal replacement therapy (especially for patients in rural areas), the Chinese government is planning to support the local manufacture of PD solutions. However, lack of training, education, and quality control systems for PD in rural or remote areas are still major constraints to the diffusion of treatment. Renji Hospital in Shanghai reported patient survival rates at 1, 2, 3, and 5 years of 90%, 79%, 71%, and 64% (similar to the results of Canadian PD centers) death censored technique survival rates of 97%, 93%, 90%, and 88%, respectively; and incidence of peritonitis of 0.198 per patient-year.[65]

Kidney transplantation is one alternative choice for patients with ESRD. Kidney transplantation began in

China in the 1960s. Since September 1, 2013, it became mandatory to allocate organs through the China Organ Transplant Response System (COTRS), a national open and transparent organ allocation computer system. Recently, the Work Group of CK-NET provided information about the kidney transplantation waiting list using a dataset from the China COTRS.[9] From September 1, 2013, through August 31, 2014, there were 19,354 candidates on the waiting list, with male preponderance (67.8%). Nearly two-thirds of candidates were of age 18–45 years. Altogether, 4285 candidates were removed from the waiting list during the time period. Of these, 90.1% received a kidney transplant. The median waiting time was 10.3 (interquartile range, 4.7–17.2) months.[9]

CONCLUSIONS

CKD is an important public health issue with escalating affects on the health care system in China. The management of CKD and its complications in China is currently suboptimal. Despite the majority of the CKD population in China being at relatively early stages, the industrialization and urbanization, and the increase in metabolic disorders could result in a greater burden of CKD in the near future. More research on Chinese CKD is needed to promote the best quality health outcomes. Prevention, treatment, and control strategies should be developed and implemented according to local levels of economic development and resources.

References

1. Wang L, Kong L, Wu F, Bai Y, Burton R. Preventing chronic diseases in China. *Lancet (London, England)* 2005;**366**(9499):1821–4.
2. Zhang L, Wang F, Wang L, Wang W, Liu B, Liu J, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet (London, England)* 2012;**379**(9818):815–22.
3. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. *Lancet (London, England)* 2013;**382**(9888):260–72.
4. Imai E, Horio M, Iseki K, Yamagata K, Watanabe T, Hara S, et al. Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. *Clin Exp Nephrol* 2007;**11**(2):156–63.
5. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. *J Am Med Assoc* 2007;**298**(17):2038–47.
6. Wang Y, Zhang L, Li X, Xu Y, Yang M, Qian J, et al. Improvement of awareness, treatment and control of hypertension among chronic kidney disease patients in China from 1999 to 2005. *Hypertens Res* 2009;**32**(6):444–9.
7. Xu Y, Wang L, He J, Bi Y, Li M, Wang T, et al. Prevalence and control of diabetes in Chinese adults. *J Am Med Assoc* 2013;**310**(9):948–59.
8. Saran R, Steffick D, Bragg-Gresham J. The China Kidney Disease Network (CK-NET): "Big Data-Big Dreams". *Am J Kidney Dis* 2017;**69**(6):713–6.
9. Zhang L, Wang H, Long J, Shi Y, Bai K, Jiang W, et al. China Kidney Disease Network (CK-NET) 2014 annual data report. *Am J Kidney Dis* 2017;**69**(6S2):A4.
10. Xie F, Zhang D, Wu J, Zhang Y, Yang Q, Sun X, et al. Design and implementation of the first nationwide, web-based Chinese Renal Data System (CNRDS). *BMC Med Inf Decis Mak* 2012;**12**:11.
11. Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, et al. Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet (London, England)* 2015;**385**(9981): 1975–82.
12. Saran R, Robinson B, Abbott KC, Agodoa LY, Albertus P, Ayanian J, et al. US renal data system 2016 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2017;**69**(3 Suppl. 1):A7–a8.
13. Li LS, Liu ZH. Epidemiologic data of renal diseases from a single unit in China: analysis based on 13,519 renal biopsies. *Kidney Int* 2004;**66**(3):920–3.
14. Xu X, Wang G, Chen N, Lu T, Nie S, Xu G, et al. Long-term exposure to air pollution and increased risk of membranous nephropathy in China. *J Am Soc Nephrol* 2016;**27**(12):3739–46.
15. Li J, Cui Z, Long J, Huang W, Wang J, Zhang H, et al. Primary glomerular nephropathy among hospitalized patients in a national database in China. *Nephrol Dial Transplant* 2018;**33**(12):2173–81.
16. A mass survey of diabetes mellitus in a population of 300,000 in 14 provinces and municipalities in China. *Zhonghua Nei Ke Za Zhi* 1981;**20**:678–83.
17. Gan L, Zuo L. Current ESRD burden and its future trend in Beijing, China. *Clin Nephrol* 2015;**83**(7 Suppl. 1):17–20.
18. Zhang L, Long J, Jiang W, Shi Y, He X, Zhou Z, et al. Trends in chronic kidney disease in China. *N Engl J Med* 2016; **375**(9):905–6.
19. Jin DC, Yun SR, Lee SW, Han SW, Kim W, Park J, et al. Lessons from 30 years' data of Korean end-stage renal disease registry, 1985-2015. *Kidney Res Clin Pract* 2015;**34**(3):132–9.
20. Yang WC, Hwang SJ. Incidence, prevalence and mortality trends of dialysis end-stage renal disease in Taiwan from 1990 to 2001: the impact of national health insurance. *Nephrol Dial Transplant* 2008; **23**(12):3977–82.
21. Chen N, Wang W, Huang Y, Shen P, Pei D, Yu H, et al. Community-based study on CKD subjects and the associated risk factors. *Nephrol Dial Transplant* 2009;**24**(7):2117–23.
22. Chen W, Chen W, Wang H, Dong X, Liu Q, Mao H, et al. Prevalence and risk factors associated with chronic kidney disease in an adult population from southern China. *Nephrol Dial Transplant* 2009; **24**(4):1205–12.
23. Zhang L, Zhang P, Wang F, Zuo L, Zhou Y, Shi Y, et al. Prevalence and factors associated with CKD: a population study from Beijing. *Am J Kidney Dis* 2008;**51**(3):373–84.
24. Wen CP, Cheng TY, Tsai MK, Chang YC, Chan HT, Tsai SP, et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. *Lancet (London, England)* 2008;**371**(9631):2173–82.
25. Hsu CC, Hwang SJ, Wen CP, Chang HY, Chen T, Shiu RS, et al. High prevalence and low awareness of CKD in Taiwan: a study on the relationship between serum creatinine and awareness from a nationally representative survey. *Am J Kidney Dis* 2006; **48**(5):727–38.
26. Leske MC, Wu SY, Hennis A, Hyman L, Nemesure B, Yang L, et al. Hyperglycemia, blood pressure, and the 9-year incidence of diabetic retinopathy: the Barbados Eye Studies. *Ophthalmology* 2005; **112**(5):799–805.
27. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int* 2003;**63**(1):225–32.

28. Cao Y, Li W, Yang G, Liu Y, Li X. Diabetes and hypertension have become leading causes of CKD in Chinese elderly patients: a comparison between 1990-1991 and 2009-2010. *Int Urol Nephrol* 2012; **44**(4):1269–76.
29. Wu X, Duan X, Gu D, Hao J, Tao S, Fan D. Prevalence of hypertension and its trends in Chinese populations. *Int J Cardiol* 1995;**52**(1): 39–44.
30. Gu D, Reynolds K, Wu X, Chen J, Duan X, Muntner P, et al. Prevalence, awareness, treatment, and control of hypertension in China. *Hypertension* 2002;**40**(6):920–7.
31. Wang J, Zhang L, Wang F, Liu L, Wang H, China National Survey of Chronic Kidney Disease Working G. Prevalence, awareness, treatment, and control of hypertension in China: results from a national survey. *Am J Hypertens* 2014;**27**(11):1355–61.
32. Zhang J, Zhang L, Wang W, Wang H, China National Survey of Chronic Kidney Disease Working G. Association between aristolochic acid and CKD: a cross-sectional survey in China. *Am J Kidney Dis* 2013;**61**(6):918–22.
33. Lai MN, Lai JN, Chen PC, Hsieh SC, Hu FC, Wang JD. Risks of kidney failure associated with consumption of herbal products containing Mu Tong or Fangchi: a population-based case-control study. *Am J Kidney Dis* 2010;**55**(3):507–18.
34. Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. *Kidney Int* 2008;**74**(2):158–69.
35. Xu X, Nie S, Ding H, Hou FF. Environmental pollution and kidney diseases. *Nat Rev Nephrol* 2018;**14**(5):313–24.
36. Bowe B, Xie Y, Li T, Yan Y, Xian H, Al-Aly Z. Particulate matter air pollution and the risk of incident CKD and progression to ESRD. *J Am Soc Nephrol* 2017;**29**(1):218–30.
37. Li SJ, Zhang SH, Chen HP, Zeng CH, Zheng CX, Li LS, et al. Mercury-induced membranous nephropathy: clinical and pathological features. *Clin J Am Soc Nephrol* 2010;**5**(3):439–44.
38. Navas-Acien A, Tellez-Plaza M, Guallar E, Muntner P, Silbergeld E, Jaar B, et al. Blood cadmium and lead and chronic kidney disease in US adults: a joint analysis. *Am J Epidemiol* 2009;**170**(9):1156–64.
39. Lai LH, Chou SY, Wu FY, Chen JJ, Kuo HW. Renal dysfunction and hyperuricemia with low blood lead levels and ethnicity in community-based study. *Sci Total Environ* 2008;**401**(1–3):39–43.
40. Zhang X, Zhong T, Liu L, Ouyang X. Impact of soil heavy metal pollution on food safety in China. *PLoS One* 2015;**10**(8):e0135182.
41. Chen Z. Good news for end stage renal disease patients. *Chin Med J* 2013;**126**(22):4203.
42. Xiao Y, Sui BY, Zhao K. Epidemiological features of the end-stage renal disease and the application, cost and payment of dialysis care in China. *Natl Health Dev Res Center* 2011;(5):29–33.
43. Dialysis and Transplantation Registration Group. The report about the registration of dialysis and transplantation in China 1999. *Chin J Nephrol* 2001;(2):77–8.
44. Zuo L, Wang M, Chinese Association of Blood Purification Management of Chinese Hospital A. Current burden and probable increasing incidence of ESRD in China. *Clin Nephrol* 2010;**74**(Suppl. 1):S20–2.
45. Beijing Hemodialysis Quality Control and Improvement Center. Annual data report of Beijing hemodialysis registry—2012. *Chin J Blood Purif* 2012;**z1**(11).
46. Zhang W, Qian J. Current status of dialysis therapy in Shanghai (results from Shanghai renal registry, 2011). *Chin J Blood Purif* 2012;(5):233–6.
47. Liu ZH. Nephrology in China. *Nat Rev Nephrol* 2013;**9**(9):523–8.
48. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet (London, England)* 1997;**349**(9069):1857–63.
49. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**(12):861–9.
50. So WY, Kong AP, Ma RC, Ozaki R, Szeto CC, Chan NN, et al. Glomerular filtration rate, cardiorenal end points, and all-cause mortality in type 2 diabetic patients. *Diabetes Care* 2006;**29**(9): 2046–52.
51. Muntner P, Anderson A, Charleston J, Chen Z, Ford V, Makos G, et al. Hypertension awareness, treatment, and control in adults with CKD: results from the chronic renal insufficiency cohort (CRIC) study. *Am J Kidney Dis* 2010;**55**(3):441–51.
52. Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006;**354**(2):131–40.
53. Hsu TW, Liu JS, Hung SC, Kuo KL, Chang YK, Chen YC, et al. Renoprotective effect of renin-angiotensin-aldosterone system blockade in patients with predialysis advanced chronic kidney disease, hypertension, and anemia. *JAMA Intern Med* 2014;**174**(3): 347–54.
54. Gao B, Zhang L, Wang H, Zhao M. Chinese cohort study of chronic kidney disease: design and methods. *Chin Med J* 2014;**127**(11): 2180–5.
55. Yan Z, Wang Y, Li S, Wang J, Zhang L, Tan H, et al. Hypertension control in adults with CKD in China: baseline results from the Chinese cohort study of chronic kidney disease (C-STRIDE). *Am J Hypertens* 2018;**31**(4):486–94.
56. Toto RD. Anemia of chronic disease: past, present, and future. *Kidney Int Suppl* 2003;(87):S20–3.
57. Li Y, Shi H, Wang WM, Peng A, Jiang GR, Zhang JY, et al. Prevalence, awareness, and treatment of anemia in Chinese patients with nondialysis chronic kidney disease: first multicenter, cross-sectional study. *Medicine (Baltim)* 2016;**95**(24):e3872.
58. Pisoni RL, Bragg-Gresham JL, Young EW, Akizawa T, Asano Y, Locatelli F, et al. Anemia management and outcomes from 12 countries in the dialysis outcomes and practice patterns study (DOPPS). *Am J Kidney Dis* 2004;**44**(1):94–111.
59. Zhang D. *Establishment of national hemodialysis case information registration system and analysis of anemia treatment of hemodialysis patients: PLA academy of military medical studies*. 2012.
60. Zhou C, Wang F, Wang JW, Zhang LX, Zhao MH. Mineral and bone disorder and its association with cardiovascular parameters in Chinese patients with chronic kidney disease. *Chin Med J* 2016; **129**(19):2275–80.
61. Tentori F. Mineral and bone disorder and outcomes in hemodialysis patients: results from the DOPPS. *Semin Dial* 2010;**23**(1):10–4.
62. Yuan J, Zou XR, Han SP, Cheng H, Wang L, Wang JW, et al. Prevalence and risk factors for cardiovascular disease among chronic kidney disease patients: results from the Chinese cohort study of chronic kidney disease (C-STRIDE). *BMC Nephrol* 2017; **18**(1):23.
63. Yu X, Yang X. Peritoneal dialysis in China: meeting the challenge of chronic kidney failure. *Am J Kidney Dis* 2015;**65**(1):147–51.
64. Cheng X, Nayyar S, Wang M, Li X, Sun Y, Huang W, et al. Mortality rates among prevalent hemodialysis patients in Beijing: a comparison with USRDS data. *Nephrol Dial Transplant* 2013;**28**(3):724–32.
65. Fang W, Qian J, Lin A, Rowaie F, Ni Z, Yao Q, et al. Comparison of peritoneal dialysis practice patterns and outcomes between a Canadian and a Chinese centre. *Nephrol Dial Transplant* 2008; **23**(12):4021–8.

QUESTIONS AND ANSWERS

Question 1

Which of the following describes the current prevalence of CKD among the general population in China?

A. <5%
B. 5%–9.9%
C. 10%–14.9%
D. 15%–19.9%
E. ≥20%

Answer: C

According to the latest national survey of CKD conducted in China, the prevalence of CKD among adults in China is 10.8%.[2]

Question 2

Which of the following choices correctly describe the epidemiology of CKD in China?

A. Reduced eGFR (<60 mL/min/1.73 m^2) accounted for the majority of prevalence of CKD
B. Albuminuria accounted for the majority of prevalence of CKD
C. Both prevalence of eGFR <60 mL/min/1.73 m^2 and albuminuria were higher in rural than in urban areas
D. Both prevalence of eGFR <60 mL/min/1.73 m^2 and albuminuria were higher in urban than in rural areas
E. Prevalence of eGFR <60 mL/min/1.73 m^2 was higher in urban than in rural, while prevalence of albuminuria was higher in rural than in urban

Answers: B and E

According to the latest conducted national survey of CKD in China, prevalence of CKD stratified by stage was 5.7% for stage 1, 3.4% for stage 2, 1.6% for stage 3, and 0.1% for stage 4. Albuminuria without an eGFR <60 mL/min/1.73 m^2 accounted for the majority of patients. In addition, the prevalence of albuminuria was higher in rural than in urban areas (10.1% vs. 7.0%). Conversely, the prevalence of eGFR <60 mL/min/1.73 m^2 was higher in urban than in rural areas (2.3% vs. 1.6%).[2]

Question 3

What are the top three major subtypes of primary glomerular nephropathy in China according to the latest evidence from both renal biopsy registry and hospital databases?

A. IgAN
B. Idiopathic membranous nephropathy
C. Membranoproliferative glomerulonephritis
D. Focal segmental glomerulosclerosis
E. MCD

Answers: A, B, and E

According to both the nation-wide renal biopsy registry and the database for hospitalized patients, IgAN, idiopathic membranous nephropathy, and MCD are the top three major primary glomerulopathies in China.[14,15] The proportion of IgAN has decreased through the years but is still the leading cause of primary glomerulopathy. The proportion of idiopathic membranous nephropathy has increased through the years (Figure 12.3).

Question 4

Which of the following statements best describe the change in causes of CKD and ESRD in China recently?

A. Glomerulonephritis is increasing, and diabetes is decreasing
B. Glomerulonephritis is decreasing, whereas diabetes is increasing
C. Both glomerulonephritis and diabetes are increasing
D. The current pattern for causes of CKD is different in rural and urban areas of China

Answer: B and D

Explanations: The percentage of CKD due to diabetes and that due to glomerulonephritis was 0.82% and 1.01%, respectively, in 2010. However, the percentage of CKD due to diabetes surpassed that of CKD due to glomerulonephritis since 2011. The current pattern for causes of CKD is different in rural and urban areas of China.

Question 5

Which of the following is not true regarding CKD in China?

A. Compared with the US, individuals in China are at relatively early stages of CKD
B. Individuals of low socioeconomic status present with higher risk of developing CKD
C. Long-term intake of herbs containing aristolochic acid is independently associated with CKD and urothelial malignancy
D. Environmental pollution–associated CKD has become an issue of global concern, especially in China
E. CKD complications are well controlled in China

Answer: E

Answers A through D are true. Complications of CKD include increased all-cause and cardiovascular mortality, kidney-disease progression, acute kidney

injury, cognitive decline, anemia, mineral and bone disorders, and fractures. Both national and regional studies indicate the management of CKD and its complications are suboptimal.

Question 6

Which of the following is not true regarding the ESRD population in China?

A. The proportion of individuals with ESRD who are treated with dialysis in China is about 20%
B. Hemodialysis is the major treatment modality of ESRD in China
C. Currently, greater than 90% of dialysis equipment and 80% of HD consumables in China are imported
D. Kidney transplantation is the major renal replacement therapy for patients with ESRD in China
E. In China, the annual cost of peritoneal dialysis is comparatively lower than that of hemodialysis

Answer: D

The proportion of individuals with ESRD who are treated with dialysis in China is about 20%. Both national registries indicate the majority of patients receive HD. Currently, greater than 90% of dialysis equipment and 80% of HD consumables in China are imported. Compared with HD, PD has the advantage of minimal requirements for equipment support and electricity. Furthermore, the annual cost of peritoneal dialysis is comparatively lower than hemodialysis ($15,034 US dollars vs. $16,625 US dollars).

CHAPTER

13

Poverty and Chronic Kidney Disease

Jenna M. Norton, Paul Eggers

National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, United States

Abstract

Once considered diseases of affluence, many chronic conditions—including chronic kidney disease (CKD)—are now recognized as diseases of social disadvantage. Risk for CKD and end-stage renal disease (ESRD) is increased among individuals of low socioeconomic status. This increased risk is mediated by negative social determinants of health—such as poor access to healthy foods, unsafe communities, poor health literacy and numeracy, limited access to transportation, lack of paid sick leave, lack of health insurance, poor housing quality and stability and limited social support, among others. These negative social determinants create barriers to health-promoting lifestyles and behaviors, reduce access to healthcare, increase risk for environmental exposures, elevate stress and allostatic load, and contribute to harmful developmental programming and epigenetic changes. These mechanisms contribute to poor kidney outcomes directly and indirectly, through increased risk of causal (e.g. diabetes, hypertension, HIV) and complicating (e.g. depression) diseases.

SCOPE OF THE PROBLEM AND PUBLIC HEALTH IMPLICATIONS

Chronic diseases were once widely considered "diseases of affluence," an unfortunate side effect of lifestyles enabled by the wealth of Western societies. Evidence generated in recent decades suggests the opposite: many chronic diseases are in fact diseases of poverty and social disadvantage. In the early 1980s, the seminal Whitehall study demonstrated that mortality from coronary heart disease was elevated in those with low compared to high employment grade among 17,530 male civil servants in London tracked over 10 years.[1] Since then, disparities along socioeconomic lines have been identified in several chronic diseases.[2]

Chronic kidney disease (CKD) is no exception. Recent systematic reviews demonstrate significant associations between low socioeconomic status (SES), defined in different ways, and increased incidence and prevalence of CKD and end-stage renal disease (ESRD). A 2015 review and meta-analysis of 35 studies, including more than 3.6 million participants and 800,000 cases of CKD, found low SES is associated with prevalence of CKD—defined by presence of either reduced estimated glomerular filtration rate (eGFR), elevated urine albumin levels, or both—and incidence of ESRD.[3] A 2018 review and meta-analysis of 43 studies across multiple countries found incidence and progression of CKD were each associated with lower income, occupation level, and overall SES but not with lower education, while elevated prevalence of CKD was associated with lower income, education, and overall SES but not with occupation.[4] The effect of income on CKD prevalence was greater in the US compared to Europe, Asia, and Latin America,[4] which may reflect differences across these regions in social programs, insurance systems, health care practice, cultures, lifestyles, or other potentially moderating factors.

Associations between area poverty and negative kidney outcomes have been mixed, perhaps due to differences in the size of the areas studied and the resulting differences in variability of wealth and resources within those areas, as well as the so-called "ecological fallacy," the attribution to individuals of characteristics found at group levels. In an analysis of 23,314 Reasons for Geographic and Racial Differences in Stroke (REGARDS) participants, incidence of ESRD was not associated with county level poverty after adjusting for age, sex, race, education, and income.[5] County level assessment may, however, have masked within county variation in wealth. In 4735 Cardiovascular Health Study participants aged 65 and older, living in a census tract within the lowest, compared to highest, SES quartile was associated with 50% greater risk of progressive CKD over four years, after adjusting for age, gender, study site, baseline serum creatinine concentration

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00013-9

(S[Cr]), lifestyle risk factors, diabetes, hypertension, and individual SES,[6] suggesting community poverty may increase risk independently from individual poverty.

Additionally, in an analysis of linked US Renal Data System (USRDS) and Census data for nearly 1.4 million incident ESRD patients, those living in a high poverty zip code had a 23% higher incidence of ESRD compared to patients in low poverty zip codes, after adjustment for age, sex, race/ethnicity, and time period.[7] In 14,086 individuals from the ARIC study with baseline eGFR >60 mL/min/1.73 m^2, higher zip code level deprivation was associated with increased incidence of both CKD and ESRD in a dose–response manner, after adjusting for age, sex, race, and baseline eGFR. The association was attenuated but remained significant for incident ESRD (but not CKD) after adjusting for smoking status, alcohol intake, physical activity, BMI, hypertension, diabetes, total cholesterol, HDL cholesterol, and lipid-lowering medication use, suggesting that these factors may be on the causal pathway for both CKD and ESRD, but that—at least for ESRD—these factors do not fully explain the association.[8] Higher area level deprivation was also associated with faster rates of eGFR decline in crude, covariate-, and fully adjusted models.[8]

Mortality is also elevated in individuals with CKD of low compared to high SES. In a prospective analysis of 2761 participants with CKD from the REGARDS study, participants with baseline income of less than $20,000 a year had a higher hazard of all-cause mortality than those with higher incomes.[9] Living in a higher, vs. lower, income area was associated with increased survival among 589,036 ESRD patients in an analysis of merged USRDS and Census data.[10] Among 1794 incident dialysis recipients in an Irish tertiary center, those from the lowest SES quartile based on a spatial index of deprivation had lower survival compared to those in the highest quartile after adjusting for age, gender, and dialysis modality.[11] In 10,392 White ESRD patients from the UK Renal Registry, living in an area of high social deprivation (measured by area unemployment, home and car ownership, and overcrowding) was associated with poorer survival after adjustment for age, gender, and cause of renal failure.[12]

Inequities in wealth along racial and ethnic lines likely interact with biologic and clinical factors, contributing to racial disparities in CKD.[13] Compared to White Americans, ESRD incidence in 2015 was 8.4 times higher among Native Hawaiians/Pacific Islanders, 3.0 times greater in Black Americans, and 1.2 times greater in American Indians/Alaska Natives.[14] Compared to non-Hispanic Americans, incidence of ESRD in 2015 was 1.3 times greater for Hispanic Americans.[14] In analyses of data of 11,027 ESRD patients from the USRDS and Census, Black ESRD patients residing in low-SES neighborhoods had greater mortality than their White counterparts, after adjusting for baseline demographics, clinical characteristics, rural residence, and access to care factors, but the disparity was significantly attenuated in higher SES neighborhoods—suggesting poverty accounts for some, but not all, of the disparity between Black and White patients.[15] Similar conclusions were reached in an analysis of a 5% Medicare random sample including nearly 1.2 million patients with and without CKD, which found the higher sex-and-age–adjusted mortality in Black compared to White beneficiaries was fully attenuated when controlling for "buy-in" status—a proxy for poverty—suggesting the greater mortality in Black compared to White beneficiaries is accounted for by the greater poverty in Black compared to White beneficiaries.[16]

POTENTIAL MECHANISMS OF POOR KIDNEY OUTCOMES DUE TO POVERTY—SOCIAL DETERMINANTS OF HEALTH

Two models of the interplay between contextual factors and health outcomes may help to conceptualize the mechanisms of poor kidney outcomes due to poverty.[17,18] First, McLeroy's adaptation of the social ecological model to health promotion[19] (Figure 13.1) facilitates a comprehensive perspective of the potential mechanisms along the pathway from poverty to poor kidney outcomes, providing a framework to consider factors across public policy, community, organizational, interpersonal and individual domains. More importantly, this model reminds us that individual health factors are not independent of the other domains but rather are subject to the interpersonal, organizational, community, and public policy context in which a given individual exists. For example, behaviors relating to physical activity may depend on an individual's interest in physical activity, the patterns of physical activity among that individual's social circles, the presence or absence of wellness policies at the person's workplace, and the availability of sidewalks in her or his community, which in turn depend on local infrastructure policies.

Second, the World Health Organization defines these contextual factors—the "conditions in which people are born, grow, live, work, and age"[20]—as the social determinants of health. Poverty contributes to a complex set of negative social determinants that combine and interact with clinical and biological factors, producing poor health outcomes, including CKD.[13] Social determinants of health may include availability of safe places for physical activity, housing quality and safety, access to grocery stores or other sources of healthful food, level of support from social networks, availability of paid leave for seeking medical care, health insurance coverage status, access to transportation, proximity to health care centers, and health literacy level, among

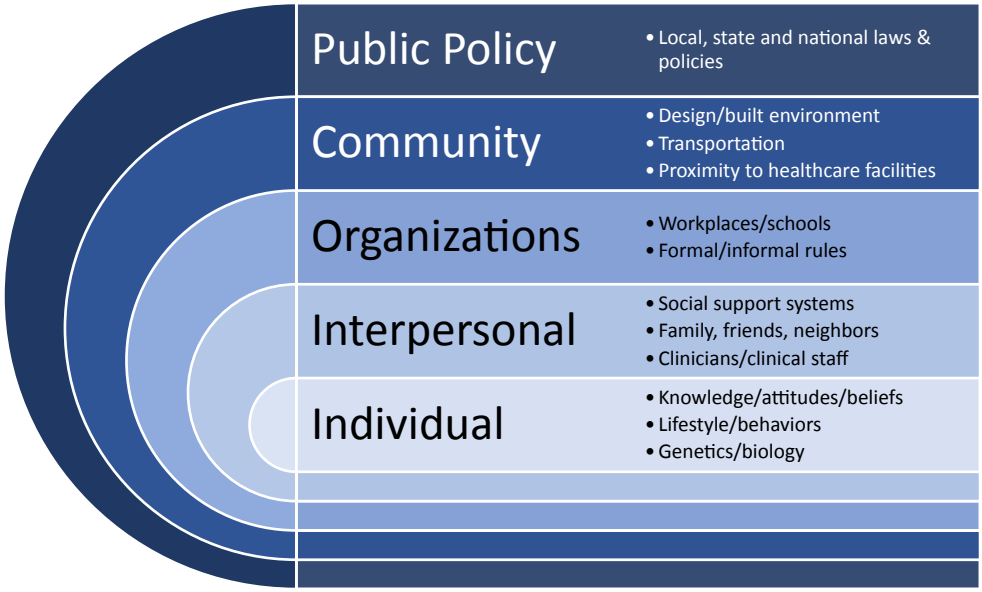


FIGURE 13.1 **Social ecological model of health promotion.** McLeroy's Social Ecological Model of Health Promotion provides a framework to consider the influence of interacting factors across public policy, community, organizational, interpersonal, and individual domains on health outcomes and behaviors. *Source: McLeroy et al. (1988).*

other factors. These social determinants act as facilitators or barriers that affect each individual's ability to engage in health-promoting behaviors and activities, likelihood of exposure to disease-causing pollutants, and level of stress and capacity for coping with stressors (Figure 13.2). In addition, social determinants may have lifelong or even multigenerational effects, through processes of developmental programming or by engendering epigenetic changes. In turn, poor health contributes to job loss and loss of insurance in a vicious cycle of poverty and disease (Figure 13.3).

Poverty, Clinical Risk Factors, and Complications

The increased prevalence of the two leading causes of ESRD—diabetes and hypertension—in low SES groups is well known.[21,22] Research suggests that socioeconomic disparities in these conditions contribute to similar disparities in CKD. Indeed, controlling for diabetes and hypertension attenuated the association between SES and CKD in an analysis of 5,799 participants who had valid S[Cr] values in the Health Survey for England, a random, nationally representative study.[23] Similarly, an analysis by Vart et al. of potentially modifiable factors mediating the relationship between SES and CKD in 9,823 NHANES participants found comorbid factors, including diabetes, hypertension, obesity, and hypercholesterolemia, accounted for 32% of the SES–CKD association.[24] The association between area deprivation and poorer survival in ESRD patients from the UK Renal Registry was attenuated after adjusting for baseline comorbidity, including vascular disease, smoking,

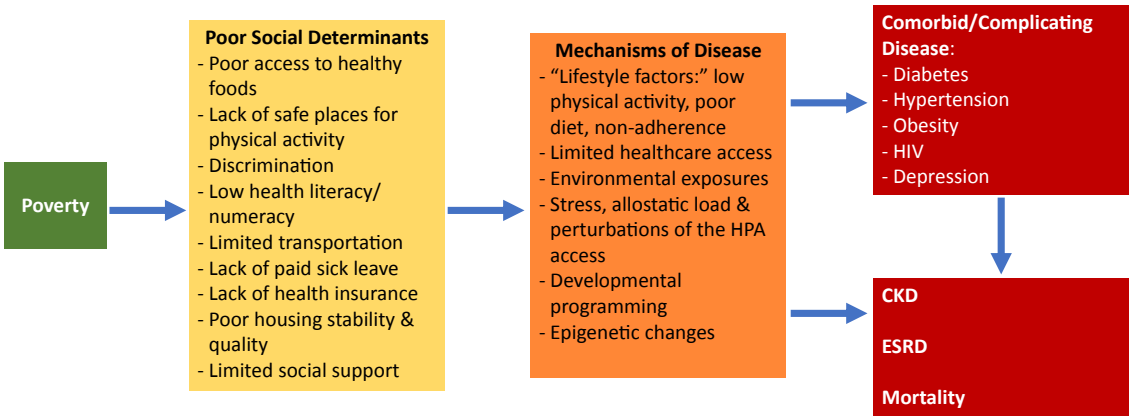


FIGURE 13.2 **Pathway from poverty to poor kidney outcomes: a conceptual model.** Poverty contributes to a cadre of negative social determinants of health, which act as barriers to healthy lifestyles and behaviors, reduce health care access, increase environmental exposures, elevate stress and allostatic load, and contribute to harmful developmental programming and epigenetic changes. Such mechanisms of disease contribute to poor kidney outcomes directly and indirectly, through increased risk of causal comorbid and complicating diseases.

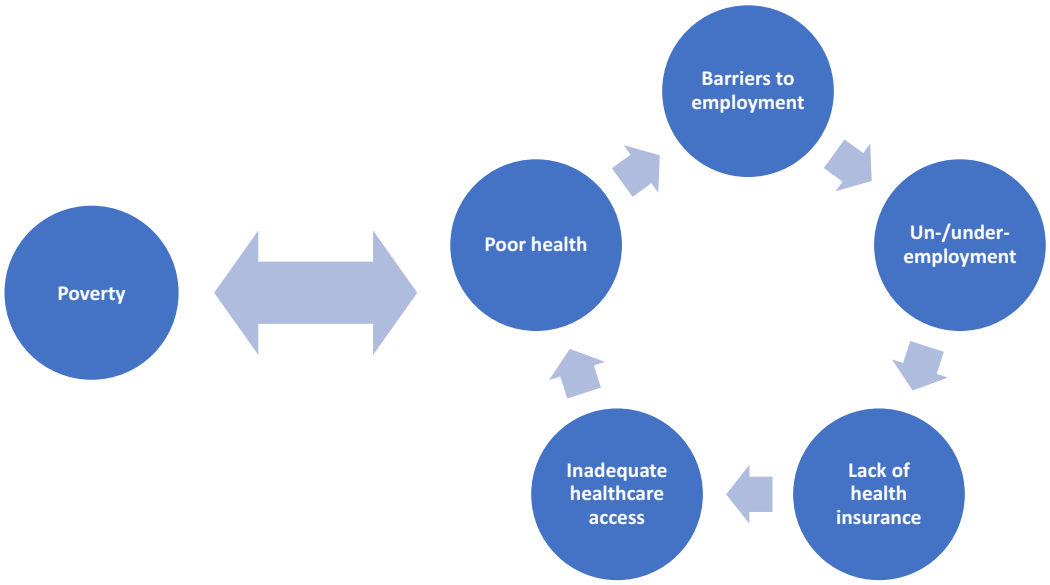


FIGURE 13.3 **The cycle of poverty, disease, and job loss.** Poverty increases risk for poor health, which creates barriers to acquiring and maintaining employment and leads to under- or unemployment. Without full time employment, many individuals lose health insurance, resulting in inadequate access to healthcare, which exacerbates poor health and poverty.

malignancy, COPD, diabetes, and liver disease, suggesting these conditions may be on the causal pathway between disadvantage and mortality in ESRD.[12]

Poverty appears to also raise the likelihood of complications in both CKD and ESRD patients. In a 2016 systematic review of 58 studies assessing cardiovascular outcomes in 8.9 million people with prevalent CKD or ESRD from 10 countries, low education and income were associated with increased cardiovascular events and all-cause mortality.[17] Similarly, an analysis of 9270 adults with moderate to severe CKD from the Study of Heart and Renal Protection randomized controlled trial found increased risk of poor vascular outcomes with decreasing education level, and two-fold higher all-cause mortality in participants with no formal education compared to those with a tertiary education.[18]

Comorbidities associated with poverty in CKD extend beyond cardiovascular diseases. In NHANES participants with CKD, prevalence of disability was higher for those with low (compared to high) income and education.[25] In a cohort study of 2171 peritoneal dialysis (PD) patients from 7 US dialysis centers, high-income patients had a significantly lower risk of peritonitis than low-income patients, after matching for age, hemoglobin, albumin, PD center, and regional SES, though no association was found for education.[26] A large study of 2032 PD patients recruited from 114 dialysis centers in Brazil, however, did demonstrate an association between low education and peritonitis in PD patients.[27] Low education levels have also been associated with increased likelihood of graft failure in kidney transplant recipients.[28]

Depression is a less well studied, but potentially contributing factor to disparities in kidney outcomes along lines of wealth and poverty. Rates of depression are elevated among those with lower SES, both in the general and in CKD populations. A 2003 meta-analysis of 56 studies on SES and depression concluded that prevalence of depression is increased in low-SES groups.[29] A 2018 systematic review and meta-analysis of 12 studies showed greater risk of depression in populations with higher- vs. lower-income inequality, with several studies reporting greater impacts in low-income populations.[30] In a sample of 2500 NHANES participants with CKD, depression was more likely in those with less than high school education compared to those who graduated high school, and in those with an annual income less than $20,000/year compared to those with incomes at or above $20,00/year.[31]

Depression might exacerbate kidney outcomes by modifying immunologic and stress responses, decreasing nutritional status, and creating a barrier for adherence to medical regimens and self-management practices.[32] In a nationally representative prospective cohort of 933,211 US Veterans with diabetes, depression—ascertained by ICD-9 code or prescription of antidepressant medication—was associated with a 20% increased risk of incident CKD and a 25% increased risk of all-cause mortality.[33] However, several cross-sectional studies have shown no association between depression and the prevalence of CKD.[34–37] A systematic review of 22 prospective studies comprising 12,063

cases of depression in CKD (including nondialysis dependent, dialysis, and transplant patients) found that depression consistently was associated with increased risk of all-cause death in people with CKD to a greater degree than in the general population.[38] Since this review, the association has been replicated in additional populations.[39–43] Depression among people with CKD has also been associated with incidence of ESRD,[44] increased morbidity,[45] and more frequent hospitalizations.[46]

Lifestyle and CKD in the Context of Poverty

Negative health behaviors—such as poor diet, low physical activity, smoking, and drug and alcohol abuse—are generally more common among low-income groups. These factors likely contribute to the pathway from poverty to CKD. In the Vart et al. analysis of factors mediating the relationship between SES and CKD among NHANES participants, health behaviors—including physical activity, smoking, and alcohol intake—accounted for 20% of the SES–CKD association. Neither fruit and vegetable intake, nor sedentary time was found to mediate the relationship.[24] Yet, in a cross-sectional study of 2058 community-dwelling adults in Baltimore, poor adherence to Dietary Approaches to Stop Hypertension nutrient intake targets was associated with prevalence of CKD among individuals with low, but not high, SES,[47] suggesting dietary patterns may have greater impact on CKD for individuals living in poverty.

However, targeting such behaviors as a root, rather than intermediary, cause of disease in low-income groups is likely an ineffective strategy. As McLeroy cautions with regard to health promotion activities that emphasize individuals' behaviors, "…use of terms like 'lifestyle' and 'health behavior' may focus attention on changing individuals, rather than changing the social and physical environment which serves to maintain and reinforce unhealthy behaviors".[19] The community in which an individual lives determines to a great degree the health behavior promoting resources she or he can access. Compared to high-income areas, low-income communities have fewer walkable areas, safe places for physical activity, and sources of healthy food,[48–52] but a higher density of fast food restaurants and convenience stores.[53]

Resources that enable healthy food choices are particularly relevant in CKD, given the complexity of dietary recommendations for the disease.[54] Low availability of fresh fruits and vegetables in high-poverty areas may contribute to increased acid load, which has been associated with reduced eGFR,[55] increased albuminuria,[55] and progression of CKD to ESRD.[56] Among adults in the NHANES sample, those living in a food desert—compared to those not living in a food desert—had lower levels of serum carotenoids—a biomarker of fruit and vegetable intake—and higher systolic blood pressure, though not higher odds of CKD.[57] In a cross-sectional analysis of 9126 NHANES participants, lack of reliable access to sufficient amounts of affordable, nutritious foods—or "food insecurity"—was associated with greater odds of CKD for individuals with hypertension or diabetes.[58] In a separate study of 1486 NHANES participants with low income and CKD, food insecurity was associated with an increased incidence of ESRD, identified through the USRDS, over a median of 14.2 years.[59]

Phosphate content of food is another potential factor on the pathway from poverty to CKD. High serum phosphate (S[P]) levels are associated with mortality in individuals with CKD,[60] yet manufacturers are not currently required to list phosphate content on food labels, and therefore, consumables may contain undisclosed amounts of phosphorus.[61] This may pose a particular challenge for individuals in high-poverty areas, where processed foods—which are often high in phosphate content—are widely available. The Chronic Renal Insufficiency Cohort Study participants with the lowest incomes had higher S[P] than participants with the highest incomes.[62]

Poverty and Capacity to Access and Engage in Health Care

Poverty generates numerous barriers to accessing health care. In a systematic review of 24 studies in the nondialysis CKD population and 34 studies in the ESRD population, including 8.9 million participants from 10 countries, dialysis recipients with low education, no health insurance, low occupational level, or no home ownership were significantly less likely to access cardiovascular health care. People with non–dialysis-dependent CKD with low health insurance and no home ownership were significantly less likely to access cardiovascular and nephrology health services than their more advantaged counterparts.[17] It is perhaps not surprising then that adult kidney transplantation recipients, identified through the Scientific Registry of Transplant Recipients, who received insurance through Medicaid were listed with more severe organ failure and shorter transplant wait times and had lower post-transplantation survival compared to privately insured individuals.[63] An analysis of USRDS data for 669,206 hemodialysis patients who initiated treatment between 2007 and 2012, those with dual eligibility for Medicare and Medicaid—a proxy measure for poverty—were significantly less likely to initiate dialysis with an arteriovenous fistula, the preferred method of vascular access in dialysis, suggesting delayed access to

nephrology care.[64] Similarly, in a retrospective cohort of more than 700,000 dialysis patients, dual Medicare/Medicaid eligibility, higher area poverty by zip code, Black race, and Hispanic ethnicity were each associated with lower likelihood of pre-ESRD nephrology care in adjusted models.[65]

Reduced health insurance coverage is a widely recognized barrier to health care access, with well documented consequences. In 903 NHANES participants aged 18–64 with albuminuria, lack of insurance and coverage through public insurance were each associated with increased all-cause mortality compared to having private insurance.[66] Among 86,588 participants of the Kidney Early Evaluation Program, lack of health insurance was associated with increased risk of ESRD incidence and death, after adjusting for age, race, ethnicity, education level, and smoking status.[67]

Although health insurance coverage is often used as a proxy for health care access, an individual's ability to access health care must be considered from a broader perspective. Andersen's Behavioral Model of Health Services Use posits that health care access is a function of individual and contextual factors that predispose (e.g. demographics, education, community composition, cultural norms), enable (e.g. income, insurance status, transportation access, proximity to care), and generate real or perceived need for (e.g. functional status, or injuries related to occupation or crime) an individual to use health care.[68,69] Andersen's model ensures a comprehensive view of health care access, encouraging looking beyond health insurance for potential barriers that may limit access to care, including costs of care after coverage, limited transportation to and from medical appointments, lack of paid leave from work or child care, poor health literacy or numeracy, and limited availability of social support systems.

A diverse sample of publicly insured adults enrolled in Minnesota Health Care Programs reported barriers to care despite insurance coverage, which included inability to cover cost, transportation problems, incompatible clinic hours, and lack of child care.[70] Similar barriers—including transportation difficulties, economic challenges, and lack of time off from work—were cited by predominantly low income, African American "safety net" CKD patients receiving primary care at two facilities in Buffalo, NY.[71] In addition, studies in the United Kingdom, Denmark, and Australia found that low SES is associated with CKD prevalence, incidence of ESRD, and reduced dialysis survival despite availability of universal health care coverage—suggesting presence of health insurance alone is not sufficient to mitigate the effects of poverty on CKD.[12,23,72–75] Further, in the Medicare population, low income is associated with lower use of services—despite equal insurance coverage.[76]

Health literacy and health numeracy are defined, respectively, as the degree to which individuals have the capacity to "obtain, process, and understand basic information and services"[77] and "access, process, interpret, communicate, and act on numerical, quantitative, biostatistical, and probabilistic health information".[78] Both are necessary to make effective health decisions and are major contributors to an individual's ability to access and use health care resources. Poor health literacy is more common among individuals who have limited education, lack insurance, or are insured through Medicaid or Medicare, compared to their high education or privately insured counterparts.[79] Poor health literacy and numeracy, along with the related lack of plain language information on CKD, have been cited as major barriers to successful patient education and self-management.[80]

Poor health literacy is associated with lower levels of CKD knowledge,[81] reduced kidney function,[82,83] poor self-management capacity,[84] and lower rates of kidney transplantation.[85] In individuals with ESRD, low health literacy increases risk for poor blood pressure control,[86] reduced self-management ability,[87,88] more frequent hospitalizations,[88] and greater mortality risk.[89] In incident dialysis, incident transplant, and transplant wait-listed patients in the United Kingdom, poor health literacy was associated with low SES, and patients with low health literacy were less likely to be placed on the transplantation waiting list or to receive preemptive or live donor transplantation.[90] Limited health numeracy has been associated with similar barriers to kidney transplantation. In a prospective cohort of 187 late-stage CKD or ESRD patients, higher health numeracy was significantly associated with receipt of a transplant or active waiting list status.[91]

Poverty may also represent a barrier to accessing health information *via* digital channels. In a study of more than 2,000 individuals seen in four nephrology clinics affiliated with an academic medical center, electronic health record (EHR) portal users were more likely to be non-Black, to be married, to have private insurance, and to have higher neighborhood median household income.[92] Such disparities in access to health data may contribute to disparities in outcomes by posing a barrier to self-management.

The association of poverty with smaller, less-robust social support systems may also interfere with ability to access and engage in health care. In a cross-sectional analysis of 410 African American and Hispanic/Latina women in Texas, neighborhood disadvantage—measured by six indices including low-wage jobs, joblessness, percent of professionals and managers, percent high school graduates, female headed households, and poverty—was associated with reduced peer social support.[93] In a cross-sectional analysis of a cohort

of 4814 middle-aged, urban-dwelling adults in Germany, low (vs. higher) income and education were each associated with poor social support.[94]

Social support—which includes emotional (e.g. empathy), informational (e.g. advice), and instrumental (e.g. transportation to health appointments) support from family, friends, neighbors, community members, and health care providers, among others—may facilitate access to health care and engagement in self-management through monetary support, transportation, advice on how and where to access care, reinforcement of positive health behaviors, and company at medical appointments. A lack of social support was associated with delaying needed medical care, after adjusting for demographics, SES, comorbidities and access to care, among 18,980 Minnesota and Tennessee residents in a cross-sectional analysis of data from the Behavioral Risk Factor Surveillance System.[95] A higher level of social support was associated with improved self-management in a cross-sectional sample of 410 patients with various stages of CKD drawn from nephrology clinics in Taiwan.[84] In dialysis recipients, higher levels of social support are associated with improved dietary, fluid[96] and medication[97] adherence and self-management.[98] A systematic review of 37 studies on factors associated with nonadherence in kidney transplant recipients concluded low social support was associated with poorer adherence.[99]

Social support may be particularly instrumental in management of depression in kidney disease, as it appears to buffer against the disease. Depression is more likely with lower levels of social support in patients with ESRD[100,101] and is more likely in transplant recipients with perceptions of negative social support.[102] Social support also mediated the relationship between depression and quality of life in ESRD patients.[103]

Level of social support appears to be a major determinant of negative health outcomes—though the mechanisms of this association likely extend beyond health care access and engagement to include elevated perception of quality of life,[104,105] improved immune function,[106] and increased ability to cope with stress.[32,107] In a prospective cohort study of 6916 middle-aged adults with nonalbuminuric diabetes followed for 5.5 years, small social network size was associated with incident CKD and mortality,[108] with a population-attributable fraction of 6.28% for mortality.[109] In a cross-sectional study of 382 adults with CKD in Sri Lanka, low social support—defined as support from less than 13 people—and poor satisfaction with social support were each associated with psychological distress.[110] In dialysis recipients, lower levels of social support have been associated with increased hospitalizations,[104,111] elevated mortality,[112,113] reduced patient satisfaction,[104] and poorer psychological[114] and general well-being.[115]

Stress and Allostatic Load

Increased stress has been widely theorized as a mechanism through which poverty increases risk of developing poor health outcomes. Poverty and associated negative social determinants may impede allostasis—the ability to maintain physiologic homeostasis in response to physical and psychological demands of stress through appropriately matched physiologic responses in the endocrine, cardiovascular, metabolic, immune, and autonomic systems.[116] In addition these factors may increase allostatic load—repeated stress responses or heightened and/or sustained activity of systems to maintain allostasis resulting from (1) frequent stress, (2) inability to adapt to repeated stress, (3) inability to shut off stress response, and (4) an unbalance allostatic response requiring compensatory responses from other systems.[117,118] Elevated stress and allostatic load may lead to increased sympathetic nervous system activity, perturbations of the hypothalamic–pituitary–adrenal axis, and altered inflammatory cytokine and endothelin-A levels, which might affect outcomes, related to kidney disease.[32]

In addition, stress may contribute to poor health outcomes by increasing risk for negative health behaviors. In a cross-sectional study of 1010 socioeconomically disadvantaged patients attending a publicly funded sexually transmitted disease clinic, an association between low SES and poor health was mediated by perceived stress, and perceived stress fully accounted for a relationship between SES and health-compromising behaviors, suggesting a causal pathway from low SES to stress to health-compromising behavior to poor perceived health.[119]

A 2009 systematic review of 26 studies assessing the relationship between SES and markers of stress or allostatic load in various populations identified inconsistent findings regarding the relationship between SES and stress, concluding that existing evidence of an association was weak.[120] Inconsistent findings may be due to variation in methods and timing for measurement of stress (e.g. biomarkers vs. self-report, weekday vs. weekend assessments, diurnal vs. life-course variation) and SES (e.g. income vs. education vs. occupation) or differences in study populations.[120]

However, since that 2009 review, the body of evidence has greatly expanded. In 1693 individuals from a cross-sectional substudy of the Midlife in the US Study (MIDUS), individuals with only high school education or who were non-White were more likely to have less healthy, or "flatter" cortisol rhythms measured at four

time points over four days, compared to college graduates and White individuals, respectively.[121] A cross-sectional substudy of more than 900 participants from the Multi-Ethnic Study of Atherosclerosis (MESA), which included a racially and ethnically diverse cohort of adults without cardiovascular disease at baseline, found higher income–wealth index score, but not education, was consistently associated with lower cortisol, epinephrine, norepinephrine, and dopamine after adjustment for age, gender, race/ethnicity, medications, education, psychosocial factors, BMI, smoking, and alcohol use.[122] The association was modified by race, with a greater level of effect for non-Hispanic Black compared to non-Hispanic White and Hispanic Americans.[122]

A longitudinal analysis of 6135 participants from the MESA examining the relationship between childhood and adult SES—measured by parental and adult education level, respectively—and a composite measure of allostatic load based on metabolic and cardiovascular variables found high adult education was associated with slower progression of allostatic load, but the relationship was only significant for those with lower baseline allostatic load, suggesting the association may vary with accumulation of risk.[123] In a prospective study of 3080 young adults followed since birth through the Cebu Longitudinal Health and Nutrition Survey, lower SES—measured by income, education and assets—was associated with less healthy cortisol profiles. The association was greater with chronically low SES and as compared to low SES during individual time periods.[124] A prospective, community-based study of 999 adults in Scotland found lower social class over the 20-year study period was associated with elevated levels of a composite measure of allostatic load, based on cardiovascular, metabolic, and inflammatory markers at final follow up. The association was attenuated only partly—by 24%—when adjusting for health-damaging behaviors, including smoking, alcohol consumption, diet, and physical activity.[125]

Stress may pose a particular problem in individuals with CKD, where downregulation of the stress response may be impeded due to reduced ability to clear and metabolize stress hormones by the kidneys, leading to a heightened or prolonged stress response consistent with elevated allostatic load.[32] In adults with CKD, stress has been associated with reduced quality of life,[126] which is in turn associated with poor outcomes in kidney disease.[127] Increasing serum cortisol levels have been associated with decreasing eGFR and increasing creatinine and cystatin C in people with CKD[128,129]; however, due to the cross-sectional nature of these studies, one cannot determine whether stress contributes to decrements in GFR, worsening CKD leads to increased stress, or both. A randomized, nonblinded trial of mindfulness-based stress reduction in people with diabetes and albuminuria showed decreased UACR and blood pressure in the intervention vs. control group at one year. Differences, however, were not detected at 2- and 3-year follow up.[130]

Environmental Exposures and CKD

Greater risk of exposure to environmental contaminants may be one mechanism of increased risk for kidney damage in individuals living in high-poverty areas. Relative to their high-income counterparts, low-income communities have more toxic waste sites,[131] poorer air quality,[132,133] elevated crime rates,[134] and poorer quality of housing, including contamination with lead, molds, and other toxins.[135] Growing evidence demonstrates an association between development of CKD and low-level environmental exposure to lead, cadmium, and mercury, and such exposures are hypothesized to contribute to the epidemic of CKD of unknown origin affecting low-income agricultural communities in India, Egypt, and Latin America.[136,137]

Developmental Programming

Developmental programming, defined in the *Prenatal Antecedents of Chronic Kidney Disease* chapter of this text as "the ability of the normal developing organism to undergo durable changes in response to environmental conditions without changes in DNA sequence," may contribute to the increased risk of poor renal outcomes seen among those living in poverty. Maternal–fetal undernutrition (MFUN), maternal–fetal energy excess (MFEE), and maternal–fetal psychosocial stress (MFPS) may result in a mismatch between kidney capacity and excretory demand by altering epigenetic regulation of gene expression, resulting in low nephron number and changing postnatal energy homeostasis contributing to increased growth and excretory load. MFUN, MFEE, and MFPS may also increase risk for diabetes and hypertension in offspring, which may interact with stress placed on the kidney by nephron number: body mass mismatch, thereby further increasing risk for kidney disease.

These key drivers of developmental programming—MFUN, MFEE, and MFPS—and resulting perturbations in birth weight appear to occur at disproportionate rates among women living in poverty, in part as a result of higher rates of food insecurity, diabetes, obesity, and stress among low-SES women. Developmental programming was first recognized as a result of severe socioeconomic disparities driven by the Industrial Revolution in England and Wales and the resulting elevated rates of coronary death in later life.[138] An analysis of data on 37,620 singleton births from nationally representative

data sets across the US, the United Kingdom, Canada, and Australia showed a graded association between income quintile and low birth weights of less than 2500 grams, with stronger associations in the US where social support systems are relatively sparse.[139] In a study of 1498 women with gestational diabetes, maternal psychosocial vulnerability—measured by material goods, money, friend/family networks, health care, and leisure—was associated with delivery of infants who were large for gestational age (LGA).[140] In a longitudinal pregnancy cohort study of 2068 maternal–infant pairs from Alberta, Canada, serial mediation analysis suggested that lower neighborhood SES is associated with higher prepregnancy BMI, and in turn, increased risk of macrosomia and LGA.[141]

Clinical Considerations

Individuals of low SES may receive lower quality care than their higher-income counterparts, particularly with regard to access to transplantation. Data from numerous studies show that kidney failure patients with low income, less education, unemployment or underemployment are less likely to be placed on the transplantation waiting list, less likely to receive a kidney transplant, and more likely to receive an expanded criteria donor kidney compared to their higher SES peers.[142–147] In all but one[146] of these studies, the association remained despite controlling for potential confounders, including demographic and clinical factors that may influence clinical decisions for advancing the kidney transplantation process, insurance status, which may influence overall access to care, and transplantation center.

One possible explanation for these disparities is implicit or unconscious biases that may influence clinician decisions regarding course of care. In contrast to conscious biases, these implicit biases often influence behavior without knowledge or awareness of the existence of these biases. Studies using implicit association tests in clinicians including medical students, registered nurses, and surgeons suggest some clinicians experience unconscious preference for people of higher SES and White race; however, studies assessing potential effects of such associations on provision of care have shown variable findings.[148–150] These mixed findings may result from differences in the context under which decisions are made, as research suggests implicit biases are more likely to affect decision-making in situations of high stress and time pressure.[151] Those interested in assessing implicit biases regarding race, ethnicity, gender, and other factors may consult publicly available implicit association tests, such as the ones available through Harvard's Project Implicit: https://implicit.harvard.edu/implicit/iatdetails.html.

System-wide clinical interventions implemented within the Indian Health Service may provide a model for provision of high-quality CKD care in disadvantaged communities. These interventions, which were based on Wagner's Chronic Care Model[152] and included interdisciplinary approaches to care, routine eGFR reporting, yearly urine albumin monitoring, use of renin–angiotensin aldosterone system blockers, blood pressure control, and patient and provider education, have been associated with a 54% decrease in age-adjusted incidence of ESRD from diabetes in Native Americans, despite the high rates of poverty and low availability of resources in this population.[153] "Treating the adjacent neighborhood as a patient" through community partnerships that target negative social determinants of health may provide additional pathways for improving poverty-related health outcomes.[154]

Individual clinicians may improve their clinical care by considering their patients from a broad perspective that includes both clinical and contextual factors, such as poverty and the social determinants of health. Clinicians and their patients may benefit from remaining alert to the health risks of poverty. A study of community-dwelling adults in the Netherlands suggested screening for CKD in individuals with low SES may be more beneficial than screening among the elderly.[155] In addition, poverty and associated negative social determinants may act as barriers to engaging in health care and self-management. Therefore, patient counseling and education must be conducted in context of such potential barriers. For example, dietary counseling of patients must be conducted with recognition of the environmental barriers to accessing healthy foods and maintaining dietary recommendations for CKD.[54] The American College of Physicians recently acknowledged the role of social determinants in health and called for efforts to properly educate and equip clinicians with the requisite knowledge and skills to appropriately screen for, identify, and manage social determinants of health.[156] Such care, informed by broad contextual factors, may be facilitated by numerous ongoing efforts to better incorporate data on social determinants of health into the EHR.

CONCLUSION

Major disparities exist in both CKD and ESRD along socioeconomic lines. Poverty lies at the base of an interconnected web of negative social determinants of health that appear to interact with biological and clinical factors to increase risk for poor kidney health outcomes. While system level changes are needed to fully address the role of poverty in poor health, individual clinicians may improve the care they provide by considering patients from a broad perspective that incorporates contextual, as well as clinical, factors.

References

1. Marmot MG, Shipley MJ, Rose G. Inequalities in death–specific explanations of a general pattern? *Lancet* 1984;**1**(8384):1003–6.
2. Shaw KM, Theis KA, Self-Brown S, Roblin DW, Barker L. *Chronic disease disparities by county economic status and metropolitan classification, behavioral risk factor surveillance system, 2013*. Atlanta, GA: Centers for Disease Control and Prevention; 2016. Available from: https://www.cdc.gov/pcd/issues/2016/16_0088.htm.
3. Vart P, Gansevoort RT, Joosten MM, Bultmann U, Reijneveld SA. Socioeconomic disparities in chronic kidney disease: a systematic review and meta-analysis. *Am J Prev Med* 2015;**48**(5):580–92.
4. Zeng X, Liu J, Tao S, Hong HG, Li Y, Fu P. Associations between socioeconomic status and chronic kidney disease: a meta-analysis. *J Epidemiol Community Health* 2018;**72**(4):270–9.
5. Crews DC, Gutiérrez OM, Fedewa SA, Luthi JC, Shoham D, Judd SE, et al. Low income, community poverty and risk of end stage renal disease. *BMC Nephrol* 2014;**15**.
6. Merkin SS, Diez Roux AV, Coresh J, Fried LF, Jackson SA, Powe NR. Individual and neighborhood socioeconomic status and progressive chronic kidney disease in an elderly population: the Cardiovascular Health Study. *Soc Sci Med* 2007;**65**(4):809–21.
7. Garrity BH, Kramer H, Vellanki K, Leehey D, Brown J, Shoham DA. Time trends in the association of ESRD incidence with area-level poverty in the US population. *Hemodial Int* 2016;**20**(1):78–83.
8. Vart P, Grams ME, Ballew SH, Woodward M, Coresh J, Matsushita K. Socioeconomic status and risk of kidney dysfunction: the Atherosclerosis Risk in Communities study. *Nephrol Dial Transplant* 2018; gfy142.
9. Fedewa SA, McClellan WM, Judd S, Gutierrez OM, Crews DC. The association between race and income on risk of mortality in patients with moderate chronic kidney disease. *BMC Nephrol* 2014;**15**:136.
10. Kimmel PL, Fwu CW, Eggers PW. Segregation, income disparities, and survival in hemodialysis patients. *J Am Soc Nephrol* 2013;**24**(2):293–301.
11. Ward FL, O'Kelly P, Donohue F, O'Haiseadha C, Haase T, Pratschke J, et al. The influence of socioeconomic status on patient survival on chronic dialysis. *Hemodial Int* 2015;**19**(4):601–8.
12. Caskey FJ, Roderick P, Steenkamp R, Nitsch D, Thomas K, Ansell D, et al. Social deprivation and survival on renal replacement therapy in England and Wales. *Kidney Int* 2006;**70**(12):2134–40.
13. Norton JM, Moxey-Mims MM, Eggers PW, Narva AS, Star RA, Kimmel PL, et al. Social determinants of racial disparities in CKD. *J Am Soc Nephrol* 2016;**27**(9):2576–95.
14. Saran R, Robinson B, Abbott KC, Ayanian J, Balkrishnan R, Bragg-Gresham J, et al. US renal data system 2017 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2018;**71**(3 Suppl. 1). Svii, S1–S672.
15. Johns TS, Estrella MM, Crews DC, Appel LJ, Anderson CA, Ephraim PL, et al. Neighborhood socioeconomic status, race, and mortality in young adult dialysis patients. *J Am Soc Nephrol* 2014;**25**(11):2649–57.
16. Kimmel PL, Fwu C-W, Abbott KC, Ratner J, Eggers PW. Racial disparities in poverty account for mortality differences in US Medicare beneficiaries. *SSM Popul Health* 2016;**2**:123–9.
17. Morton RL, Schlackow I, Mihaylova B, Staplin ND, Gray A, Cass A. The impact of social disadvantage in moderate-to-severe chronic kidney disease: an equity-focused systematic review. *Nephrol Dial Transplant* 2016;**31**(1):46–56.
18. Morton RL, Schlackow I, Staplin N, Gray A, Cass A, Haynes R, et al. Impact of educational attainment on health outcomes in moderate to severe CKD. *Am J Kidney Dis* 2016;**67**(1):31–9.
19. McLeroy KR, Bibeau D, Steckler A, Glanz K. An ecological perspective on health promotion programs. *Health Educ Q* 1988;**15**(4):351–77.
20. World Health Organization. *What are social determinants of health?*. 2015. Available from: http://www.who.int/social_determinants/sdh_definition/en/.
21. Division of Diabetes Translation NCfCDPaHP. *National diabetes statistics report, 2017: estimates of diabetes and its burden in the United States*. Atlanta, GA: U.S. Centers for Disease Control and Prevention; 2017.
22. Fang J, Gillespie C, Ayala C, Loustalot F. Prevalence of self-reported hypertension and antihypertensive medication use among adults aged ≥18 years — United States, 2011–2015. *MMWR Morb Mortal Wkly Rep* 2018;**67**:219–24.
23. Fraser SD, Roderick PJ, Aitken G, Roth M, Mindell JS, Moon G, et al. Chronic kidney disease, albuminuria and socioeconomic status in the Health Surveys for England 2009 and 2010. *J Public Health* 2014;**36**(4):577–86.
24. Vart P, Gansevoort RT, Crews DC, Reijneveld SA, Bultmann U. Mediators of the association between low socioeconomic status and chronic kidney disease in the United States. *Am J Epidemiol* 2015;**181**(6):385–96.
25. Plantinga LC, Johansen KL, Schillinger D, Powe NR. Lower socioeconomic status and disability among US adults with chronic kidney disease, 1999-2008. *Prev Chronic Dis* 2012;**9**:E12.
26. Wang Q, Hu KJ, Ren YP, Dong J, Han QF, Zhu TY, et al. The association of individual and regional socioeconomic status on initial peritonitis and outcomes in peritoneal dialysis patients: a propensity score-matched cohort study. *Perit Dial Int* 2016;**36**(4):395–401.
27. Martin LC, Caramori JC, Fernandes N, Divino-Filho JC, Pecoits-Filho R, Barretti P. Geographic and educational factors and risk of the first peritonitis episode in Brazilian Peritoneal Dialysis study (BRAZPD) patients. *Clin J Am Soc Nephrol* 2011;**6**(8):1944–51.
28. Goldfarb-Rumyantzev AS, Sandhu GS, Barenbaum A, Baird BC, Patibandla BK, Narra A, et al. Education is associated with reduction in racial disparities in kidney transplant outcome. *Clin Transplant* 2012;**26**(6):891–9.
29. Lorant V, Deliège D, Eaton W, Robert A, Philippot P, Ansseau M. Socioeconomic inequalities in depression: a meta-analysis. *Am J Epidemiol* 2003;**157**(2):98–112.
30. Patel V, Burns JK, Dhingra M, Tarver L, Kohrt BA, Lund C. Income inequality and depression: a systematic review and meta-analysis of the association and a scoping review of mechanisms. *World Psychiatry* 2018;**17**(1):76–89.
31. Shirazian S, Diep R, Jacobson AM, Grant CD, Mattana J, Calixte R. Awareness of chronic kidney disease and depressive symptoms: National Health and Nutrition Examination Surveys 2005-2010. *Am J Nephrol* 2016;**44**(1):1–10.
32. Cukor D, Cohen SD, Peterson RA, Kimmel PL. Psychosocial aspects of chronic disease: ESRD as a paradigmatic illness. *J Am Soc Nephrol* 2007;**18**(12):3042–55.
33. Novak M, Mucsi I, Rhee CM, Streja E, Lu JL, Kalantar-Zadeh K, et al. Increased risk of incident chronic kidney disease, cardiovascular disease, and mortality in patients with diabetes with comorbid depression. *Diabetes Care* 2016;**39**(11):1940–7.
34. Fischer MJ, Kimmel PL, Greene T, Gassman JJ, Wang X, Brooks DH, et al. Sociodemographic factors contribute to the depressive affect among African Americans with chronic kidney disease. *Kidney Int* 2010;**77**(11):1010–9.

35. Gholson GK, Mwendwa DT, Wright RS, Callender CO, Campbell AL. The combined influence of psychological factors on biomarkers of renal functioning in African Americans. *Ethn Dis* 2015;**25**(2):117–22.
36. McClellan WM, Abramson J, Newsome B, Temple E, Wadley VG, Audhya P, et al. Physical and psychological burden of chronic kidney disease among older adults. *Am J Nephrol* 2010;**31**(4): 309–17.
37. Nguyen HA, Anderson CAM, Miracle CM, Rifkin DE. The association between depression, perceived health status, and quality of life among individuals with chronic kidney disease: an analysis of the National Health and Nutrition Examination Survey 2011-2012. *Nephron* 2017;**136**(2):127–35.
38. Palmer SC, Vecchio M, Craig JC, Tonelli M, Johnson DW, Nicolucci A, et al. Association between depression and death in people with CKD: a meta-analysis of cohort studies. *Am J Kidney Dis* 2013;**62**(3):493–505.
39. Fan L, Sarnak MJ, Tighiouart H, Drew DA, Kantor AL, Lou KV, et al. Depression and all-cause mortality in hemodialysis patients. *Am J Nephrol* 2014;**40**(1):12–8.
40. Barros A, Costa BE, Mottin CC, d'Avila DO. Depression, quality of life, and body composition in patients with end-stage renal disease: a cohort study. *Rev Bras Psiquiatr* 2016;**38**(4):301–6.
41. Chiang HH, Guo HR, Livneh H, Lu MC, Yen ML, Tsai TY. Increased risk of progression to dialysis or death in CKD patients with depressive symptoms: a prospective 3-year follow-up cohort study. *J Psychosom Res* 2015;**79**(3):228–32.
42. Chilcot J, Guirguis A, Friedli K, Almond M, Day C, Da Silva-Gane M, et al. Depression symptoms in haemodialysis patients predict all-cause mortality but Not kidney transplantation: a cause-specific outcome analysis. *Ann Behav Med* 2018;**52**(1): 1–8.
43. Molnar MZ, Streja E, Sumida K, Soohoo M, Ravel VA, Gaipov A, et al. Pre-ESRD depression and post-ESRD mortality in patients with advanced CKD transitioning to dialysis. *Clin J Am Soc Nephrol* 2017;**12**(9):1428–37.
44. Yu MK, Weiss NS, Ding X, Katon WJ, Zhou XH, Young BA. Associations between depressive symptoms and incident ESRD in a diabetic cohort. *Clin J Am Soc Nephrol* 2014;**9**(5):920–8.
45. Dobbels F, Skeans MA, Snyder JJ, Tuomari AV, Maclean JR, Kasiske BL. Depressive disorder in renal transplantation: an analysis of Medicare claims. *Am J Kidney Dis* 2008;**51**(5):819–28.
46. Hedayati SS, Bosworth HB, Briley LP, Sloane RJ, Pieper CF, Kimmel PL, et al. Death or hospitalization of patients on chronic hemodialysis is associated with a physician-based diagnosis of depression. *Kidney Int* 2008;**74**(7):930–6.
47. Crews DC, Kuczmarski MF, Miller 3rd ER, Zonderman AB, Evans MK, Powe NR. Dietary habits, poverty, and chronic kidney disease in an urban population. *J Ren Nutr* 2015;**25**(2): 103–10.
48. Powell LM, Slater S, Chaloupka FJ, Harper D. Availability of physical activity-related facilities and neighborhood demographic and socioeconomic characteristics: a national study. *Am J Public Health* 2006;**96**(9):1676–80.
49. Moore LV, Diez Roux AV, Evenson KR, McGinn AP, Brines SJ. Availability of recreational resources in minority and low socioeconomic status areas. *Am J Prev Med* 2008;**34**(1):16–22.
50. Moore LV, Diez Roux AV. Associations of neighborhood characteristics with the location and type of food stores. *Am J Public Health* 2006;**96**(2):325–31.
51. Walker RE, Keane CR, Burke JG. Disparities and access to healthy food in the United States: a review of food deserts literature. *Health Place* 2010;**16**(5):876–84.
52. Bower KM, Thorpe Jr RJ, Rohde C, Gaskin DJ. The intersection of neighborhood racial segregation, poverty, and urbanicity and its impact on food store availability in the United States. *Prev Med* 2014;**58**:33–9.
53. Hilmers A, Hilmers DC, Dave J. Neighborhood disparities in access to healthy foods and their effects on environmental justice. *Am J Public Health* 2012;**102**(9):1644–54.
54. Gutierrez OM. Contextual poverty, nutrition, and chronic kidney disease. *Adv Chron Kidney Dis* 2015;**22**(1):31–8.
55. Banerjee T, Crews DC, Wesson DE, Tilea A, Saran R, Rios Burrows N, et al. Dietary acid load and chronic kidney disease among adults in the United States. *BMC Nephrol* 2014; **15**:137.
56. Banerjee T, Crews DC, Wesson DE, Tilea AM, Saran R, Rios-Burrows N, et al. High dietary acid load predicts ESRD among adults with CKD. *J Am Soc Nephrol* 2015;**26**(7):1693–700.
57. Suarez JJ, Isakova T, Anderson CA, Boulware LE, Wolf M, Scialla JJ. Food access, chronic kidney disease, and hypertension in the U.S. *Am J Prev Med* 2015;**49**(6):912–20.
58. Crews DC, Kuczmarski MF, Grubbs V, Hedgeman E, Shahinian VB, Evans MK, et al. Effect of food insecurity on chronic kidney disease in lower-income Americans. *Am J Nephrol* 2014;**39**(1):27–35.
59. Banerjee T, Crews DC, Wesson DE, Dharmarajan S, Saran R, Rios Burrows N, et al. Food insecurity, CKD, and subsequent ESRD in US adults. *Am J Kidney Dis* 2017;**70**(1):38–47.
60. Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. *JAMA* 2011;**305**(11):1119–27.
61. Moser M, White K, Henry B, Oh S, Miller ER, Anderson CA, et al. Phosphorus content of popular beverages. *Am J Kidney Dis* 2015; **65**(6):969–71.
62. Gutierrez OM, Anderson C, Isakova T, Scialla J, Negrea L, Anderson AH, et al. Low socioeconomic status associates with higher serum phosphate irrespective of race. *J Am Soc Nephrol* 2010;**21**(11):1953–60.
63. DuBay DA, MacLennan PA, Reed RD, Shelton BA, Redden DT, Fouad M, et al. Insurance type and solid organ transplantation outcomes: a historical perspective on how Medicaid expansion might impact transplantation outcomes. *J Am Coll Surg* 2016; **223**(4):611–620 e4.
64. Nee R, Moon DS, Jindal RM, Hurst FP, Yuan CM, Agodoa LY, et al. Impact of poverty and health care insurance on arteriovenous fistula use among incident hemodialysis patients. *Am J Nephrol* 2015; **42**(4):328–36.
65. Nee R, Yuan CM, Hurst FP, Jindal RM, Agodoa LY, Abbott KC. Impact of poverty and race on pre-end-stage renal disease care among dialysis patients in the United States. *Clin Kidney J* 2017; **10**(1):55–61.
66. Saunders MR, Ricardo AC, Chen J, Chin MH, Lash JP. Association between insurance status and mortality in individuals with albuminuria: an observational cohort study. *BMC Nephrol* 2016;**17**:27.
67. Jurkovitz CT, Li S, Norris KC, Saab G, Bomback AS, Whaley-Connell AT, et al. Association between lack of health insurance and risk of death and ESRD: results from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2013;**61**(4 Suppl. 2): S24–32.
68. Andersen RM. *Families' use of health services: a behavioral model of predisposing, enabling and need components* [dissertation]. West Lafayette: Purdue University; 1968.

69. Andersen RM, Davidson PL. Improving access to care in America: individual and contextual indicators. In: Andersen RM, Rice TH, Kominski EF, editors. *Changing the US health care system: key issues in health services, policy, and management*. San Francisco, CA: Jossey-Bass; 2001. p. 3–30.
70. Call KT, McAlpine DD, Garcia CM, Shippee N, Beebe T, Adeniyi TC, et al. Barriers to care in an ethnically diverse publicly insured population: is health care reform enough? *Med Care* 2014; **52**(8):720–7.
71. Kahn LS, Vest BM, Madurai N, Singh R, York TR, Cipparone CW, et al. Chronic kidney disease (CKD) treatment burden among low-income primary care patients. *Chronic Illness* 2015;**11**(3): 171–83.
72. So BH, Methven S, Hair MD, Jardine AG, MacGregor MS. Socio-economic status influences chronic kidney disease prevalence in primary care: a community-based cross-sectional analysis. *Nephrol Dial Transplant* 2015;**30**(6):1010–7.
73. Krishnasamy R, Gray NA. Low socioeconomic status adversely effects dialysis survival in Australia. *Nephrology* 2018;**23**(5): 453–60.
74. Grace BS, Clayton P, Cass A, McDonald SP. Socio-economic status and incidence of renal replacement therapy: a registry study of Australian patients. *Nephrol Dial Transplant* 2012;**27**(11):4173–80.
75. Hommel K, Rasmussen S, Kamper AL, Madsen M. Regional and social inequalities in chronic renal replacement therapy in Denmark. *Nephrol Dial Transplant* 2010;**25**(8):2624–32.
76. Gornick ME, Eggers PW, Reilly TW, Mentnech RM, Fitterman LK, Kucken LE, et al. Effects of race and income on mortality and use of services among Medicare beneficiaries. *N Engl J Med* 1996; **335**(11):791–9.
77. Institute of Medicine Committee on Health Literacy. *Health literacy: a prescription to end confusion*. Washington, DC: Institute of Medicine of the National Academies; 2004.
78. Golbeck AL, Ahlers-Schmidt CR, Paschal AM, Dismuke SE. A definition and operational framework for health numeracy. *Am J Prev Med* 2005;**29**(4):375–6.
79. Office of Disease Prevention and Health Promotion. *America's health literacy: why we need accessible health information*. US Department of Health and Human Services; 2008.
80. Narva AS, Norton JM, Boulware LE. Educating patients about CKD: the path to self-management and patient-centered care. *Clin J Am Soc Nephrol* 2016;**11**(4):694–703.
81. Wright JA, Wallston KA, Elasy TA, Ikizler TA, Cavanaugh KL. Development and results of a kidney disease knowledge survey given to patients with CKD. *Am J Kidney Dis* 2011;**57**(3):387–95.
82. Devraj R, Borrego M, Vilay AM, Gordon EJ, Pailden J, Horowitz B. Relationship between health literacy and kidney function. *Nephrology* 2015;**20**(5):360–7.
83. Ricardo AC, Yang W, Lora CM, Gordon EJ, Diamantidis CJ, Ford V, et al. Limited health literacy is associated with low glomerular filtration in the Chronic Renal Insufficiency Cohort (CRIC) study. *Clin Nephrol* 2014;**81**(1):30–7.
84. Chen YC, Chang LC, Liu CY, Ho YF, Weng SC, Tsai TI. The roles of social support and health literacy in self-management among patients with chronic kidney disease. *J Nurs Scholarsh* 2018;**50**(3): 265–75.
85. Kazley AS, Hund JJ, Simpson KN, Chavin K, Baliga P. Health literacy and kidney transplant outcomes. *Prog Transplant* 2015;**25**(1): 85–90.
86. Adeseun GA, Bonney CC, Rosas SE. Health literacy associated with blood pressure but not other cardiovascular disease risk factors among dialysis patients. *Am J Hypertens* 2012;**25**(3):348–53.
87. Lai AY, Ishikawa H, Kiuchi T, Mooppil N, Griva K. Communicative and critical health literacy, and self-management behaviors in end-stage renal disease patients with diabetes on hemodialysis. *Patient Educ Couns* 2013;**91**(2):221–7.
88. Green JA, Mor MK, Shields AM, Sevick MA, Arnold RM, Palevsky PM, et al. Associations of health literacy with dialysis adherence and health resource utilization in patients receiving maintenance hemodialysis. *Am J Kidney Dis* 2013;**62**(1):73–80.
89. Cavanaugh KL, Wingard RL, Hakim RM, Eden S, Shintani A, Wallston KA, et al. Low health literacy associates with increased mortality in ESRD. *J Am Soc Nephrol* 2010;**21**(11):1979–85.
90. Taylor DM, Bradley JA, Bradley C, Draper H, Johnson R, Metcalfe W, et al. Limited health literacy in advanced kidney disease. *Kidney Int* 2016;**90**(3):685–95.
91. Abdel-Kader K, Dew MA, Bhatnagar M, Argyropoulos C, Karpov I, Switzer G, et al. Numeracy skills in CKD: correlates and outcomes. *Clin J Am Soc Nephrol* 2010;**5**(9):1566–73.
92. Jhamb M, Cavanaugh KL, Bian A, Chen G, Ikizler TA, Unruh ML, et al. Disparities in electronic health record patient portal use in nephrology clinics. *Clin J Am Soc Nephrol* 2015; **10**(11):2013–22.
93. Soltero EG, Hernandez DC, O'Connor DP, Lee RE. Does social support mediate the relationship among neighborhood disadvantage, incivilities, crime and physical activity? *Prev Med* 2015;**72**: 44–9.
94. Weyers S, Dragano N, Mobus S, Beck EM, Stang A, Mohlenkamp S, et al. Low socio-economic position is associated with poor social networks and social support: results from the Heinz Nixdorf Recall Study. *Int J Equity Health* 2008;**7**:13.
95. Reisinger MW, Moss M, Clark BJ. Is lack of social support associated with a delay in seeking medical care? A cross-sectional study of Minnesota and Tennessee residents using data from the Behavioral Risk Factor Surveillance System. *BMJ Open* 2018;**8**(7): e018139.
96. Lambert K, Mullan J, Mansfield K. An integrative review of the methodology and findings regarding dietary adherence in end stage kidney disease. *BMC Nephrol* 2017;**18**(1):318.
97. Van Camp YP, Vrijens B, Abraham I, Van Rompaey B, Elseviers MM. Adherence to phosphate binders in hemodialysis patients: prevalence and determinants. *J Nephrol* 2014;**27**(6): 673–9.
98. Li H, Jiang YF, Lin CC. Factors associated with self-management by people undergoing hemodialysis: a descriptive study. *Int J Nurs Stud* 2014;**51**(2):208–16.
99. Belaiche S, Decaudin B, Dharancy S, Noel C, Odou P, Hazzan M. Factors relevant to medication non-adherence in kidney transplant: a systematic review. *Int J Clin Pharm* 2017;**39**(3): 582–93.
100. Ng HJ, Tan WJ, Mooppil N, Newman S, Griva K. Prevalence and patterns of depression and anxiety in hemodialysis patients: a 12-month prospective study on incident and prevalent populations. *Br J Health Psychol* 2015;**20**(2):374–95.
101. Liu X, Yang X, Yao L, Zhang Q, Sun D, Zhu X, et al. Prevalence and related factors of depressive symptoms in hemodialysis patients in northern China. *BMC Psychiatry* 2017;**17**(1):128.
102. Vasquez V, Novarro N, Valdes RA, Britton GB. Factors associated to depression in renal transplant recipients in Panama. *Indian J Psychiatry* 2013;**55**(3):273–8.
103. Khalil AA, Abed MA. Perceived social support is a partial mediator of the relationship between depressive symptoms and quality of life in patients receiving hemodialysis. *Arch Psychiatr Nurs* 2014;**28**(2):114–8.
104. Plantinga LC, Fink NE, Harrington-Levey R, Finkelstein FO, Hebah N, Powe NR, et al. Association of social support with outcomes in incident dialysis patients. *Clin J Am Soc Nephrol* 2010; **5**(8):1480–8.
105. Kim K, Kang GW, Woo J. The quality of life of hemodialysis patients is affected Not only by medical but also psychosocial factors: a canonical correlation study. *J Korean Med Sci* 2018;**33**(14): e111.

106. Cohen SD, Sharma T, Acquaviva K, Peterson RA, Patel SS, Kimmel PL. Social support and chronic kidney disease: an update. *Adv Chron Kidney Dis* 2007;**14**(4):335–44.
107. House JS, Landis KR, Umberson D. Social relationships and health. *Science* 1988;**241**(4865):540–5.
108. Dunkler D, Kohl M, Heinze G, Teo KK, Rosengren A, Pogue J, et al. Modifiable lifestyle and social factors affect chronic kidney disease in high-risk individuals with type 2 diabetes mellitus. *Kidney Int* 2015;**87**(4):784–91.
109. Dunkler D, Kohl M, Teo KK, Heinze G, Dehghan M, Clase CM, et al. Population-attributable fractions of modifiable lifestyle factors for CKD and mortality in individuals with type 2 diabetes: a cohort study. *Am J Kidney Dis* 2016;**68**(1):29–40.
110. Hettiarachchi R, Abeysena C. Association of poor social support and financial insecurity with psychological distress of chronic kidney disease patients attending National Nephrology Unit in Sri Lanka. *Internet J Nephrol* 2018;**2018**. 5678781.
111. Flythe JE, Hilbert J, Kshirsagar AV, Gilet CA. Psychosocial factors and 30-day hospital readmission among individuals receiving maintenance dialysis: a prospective study. *Am J Nephrol* 2017; **45**(5):400–8.
112. Kimmel PL, Peterson RA, Weihs KL, Simmens SJ, Alleyne S, Cruz I, et al. Psychosocial factors, behavioral compliance and survival in urban hemodialysis patients. *Kidney Int* 1998;**54**(1): 245–54.
113. Thong MS, Kaptein AA, Krediet RT, Boeschoten EW, Dekker FW. Social support predicts survival in dialysis patients. *Nephrol Dial Transplant* 2007;**22**(3):845–50.
114. Neumann D, Lamprecht J, Robinski M, Mau W, Girndt M. Social relationships and their impact on health-related outcomes in peritoneal versus haemodialysis patients: a prospective cohort study. *Nephrol Dial Transplant* 2018;**33**(7):1235–44.
115. Alshraifeen A, McCreaddie M, Evans JM. Quality of life and well-being of people receiving haemodialysis treatment in Scotland: a cross-sectional survey. *Int J Nurs Pract* 2014;**20**(5):518–23.
116. Sterling P, Eyer J. Allostasis: a new paradigm to explain arousal pathology. In: Fisher S, Reason J, editors. *Handbook of life stress, cognition and health*. New York, NY: John Wiley; 1988. p. 629–49.
117. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. *Arch Intern Med* 1993;**153**(18):2093–101.
118. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998;**338**(3):171–9.
119. Senn TE, Walsh JL, Carey MP. The mediating roles of perceived stress and health behaviors in the relation between objective, subjective, and neighborhood socioeconomic status and perceived health. *Ann Behav Med* 2014;**48**(2):215–24.
120. Dowd JB, Simanek AM, Aiello AE. Socio-economic status, cortisol and allostatic load: a review of the literature. *Int J Epidemiol* 2009; **38**(5):1297–309.
121. Karlamangla AS, Friedman EM, Seeman TE, Stawksi RS, Almeida DM. Daytime trajectories of cortisol: demographic and socioeconomic differences–findings from the National Study of Daily Experiences. *Psychoneuroendocrinology* 2013;**38**(11):2585–97.
122. Castro-Diehl C, Diez Roux AV, Seeman T, Shea S, Shrager S, Tadros S. Associations of socioeconomic and psychosocial factors with urinary measures of cortisol and catecholamines in the Multi-Ethnic Study of Atherosclerosis (MESA). *Psychoneuroendocrinology* 2014;**41**:132–41.
123. Merkin SS, Karlamangla A, Roux AV, Shrager S, Seeman TE. Life course socioeconomic status and longitudinal accumulation of allostatic load in adulthood: multi-ethnic study of atherosclerosis. *Am J Public Health* 2014;**104**(4):e48–55.
124. Desantis AS, Kuzawa CW, Adam EK. Developmental origins of flatter cortisol rhythms: socioeconomic status and adult cortisol activity. *Am J Hum Biol* 2015;**27**(4):458–67.
125. Robertson T, Benzeval M, Whitley E, Popham F. The role of material, psychosocial and behavioral factors in mediating the association between socioeconomic position and allostatic load (measured by cardiovascular, metabolic and inflammatory markers). *Brain Behav Immun* 2015;**45**:41–9.
126. Gemmell LA, Terhorst L, Jhamb M, Unruh M, Myaskovsky L, Kester L, et al. Gender and racial differences in stress, coping, and health-related quality of life in chronic kidney disease. *J Pain Symptom Manag* 2016;**52**(6):806–12.
127. Mapes DL, Bragg-Gresham JL, Bommer J, Fukuhara S, McKevitt P, Wikstrom B, et al. Health-related quality of life in the dialysis outcomes and practice patterns study (DOPPS). *Am J Kidney Dis* 2004;**44**(5 Suppl. 2):54–60.
128. Li X, Xiang X, Hu J, Goswami R, Yang S, Zhang A, et al. Association between serum cortisol and chronic kidney disease in patients with essential hypertension. *Kidney Blood Pres Res* 2016; **41**(4):384–91.
129. Afsar B. The relationship of serum cortisol levels with depression, cognitive function and sleep disorders in chronic kidney disease and hemodialysis patients. *Psychiatr Q* 2014;**85**(4):479–86.
130. Kopf S, Oikonomou D, Hartmann M, Feier F, Faude-Lang V, Morcos M, et al. Effects of stress reduction on cardiovascular risk factors in type 2 diabetes patients with early kidney disease - results of a randomized controlled trial (HEIDIS). *Exp Clin Endocrinol Diabetes* 2014;**122**(6):341–9.
131. General Accounting Office. *Siting of hazardous waste landfills and their correlation with racial and economic status of surrounding communities*. 1983. Washington, DC.
132. Clark LP, Millet DB, Marshall JD. National patterns in environmental injustice and inequality: outdoor NO_2 air pollution in the United States. *PLoS One* 2014;**9**(4):e94431.
133. Bell ML, Ebisu K. Environmental inequality in exposures to airborne particulate matter components in the United States. *Environ Health Perspect* 2012;**120**(12):1699–704.
134. Harrell E, Langton L, Berzofsky M, Couzens L, Smiley-McDonald H. *Household poverty and nonfatal violent victimization, 20082012*. Washington, DC: U.S. Department of Justice; 2014.
135. Jacobs DE. Environmental health disparities in housing. *Am J Public Health* 2011;**101**(Suppl. 1):S115–22.
136. Said S, Hernandez GT. Environmental exposures, socioeconomics, disparities, and the kidneys. *Adv Chron Kidney Dis* 2015; **22**(1):39–45.
137. Ekong EB, Jaar BG, Weaver VM. Lead-related nephrotoxicity: a review of the epidemiologic evidence. *Kidney Int* 2006;**70**(12): 2074–84.
138. Barker DJ, Osmond C, Law CM. The intrauterine and early postnatal origins of cardiovascular disease and chronic bronchitis. *J Epidemiol Community Health* 1989;**43**(3):237–40.
139. Martinson ML, Reichman NE. Socioeconomic inequalities in low birth weight in the United States, the United Kingdom, Canada, and Australia. *Am J Public Health* 2016;**106**(4):748–54.
140. Cosson E, Bihan H, Reach G, Vittaz L, Carbillon L, Valensi P. Psychosocial deprivation in women with gestational diabetes mellitus is associated with poor fetomaternal prognoses: an observational study. *BMJ Open* 2015;**5**(3):e007120.
141. Clayborne ZM, Giesbrecht GF, Bell RC, Tomfohr-Madsen LM. Relations between neighbourhood socioeconomic status and birth outcomes are mediated by maternal weight. *Soc Sci Med* 2017; **175**:143–51.
142. Sandhu GS, Khattak M, Pavlakis M, Woodward R, Hanto DW, Wasilewski MA, et al. Recipient's unemployment restricts access to renal transplantation. *Clin Transplant* 2013;**27**(4):598–606.
143. Patzer RE, Amaral S, Wasse H, Volkova N, Kleinbaum D, McClellan WM. Neighborhood poverty and racial disparities in kidney transplant waitlisting. *J Am Soc Nephrol* 2009;**20**(6): 1333–40.

144. Zhang Y, Jarl J, Gerdtham UG. Are there inequities in treatment of end-stage renal disease in Sweden? A longitudinal register-based study on socioeconomic status-related access to kidney transplantation. *Int J Environ Res Public Health* 2017;**14**(2).
145. Mohandas R, Casey MJ, Cook RL, Lamb KE, Wen X, Segal MS. Racial and socioeconomic disparities in the allocation of expanded criteria donor kidneys. *Clin J Am Soc Nephrol* 2013; **8**(12):2158–64.
146. Kihal-Talantikite W, Vigneau C, Deguen S, Siebert M, Couchoud C, Bayat S. Influence of socio-economic inequalities on access to renal transplantation and survival of patients with end-stage renal disease. *PLoS One* 2016;**11**(4):e0153431.
147. Choi Y, Shin J, Park JT, Cho KH, Park EC, Kim TH. Disparities in kidney transplantation access among Korean patients initiating dialysis: a population-based cohort study using National Health Insurance Data (2003-2013). *Am J Nephrol* 2017;**45**(1):32–9.
148. Haider AH, Sexton J, Sriram N, Cooper LA, Efron DT, Swoboda S, et al. Association of unconscious race and social class bias with vignette-based clinical assessments by medical students. *JAMA* 2011;**306**(9):942–51.
149. Haider AH, Schneider EB, Sriram N, Scott VK, Swoboda SM, Zogg CK, et al. Unconscious race and class biases among registered nurses: vignette-based study using implicit association testing. *J Am Coll Surg* 2015;**220**(6):1077–1086 e3.
150. Haider AH, Schneider EB, Sriram N, Dossick DS, Scott VK, Swoboda SM, et al. Unconscious race and social class bias among acute care surgical clinicians and clinical treatment decisions. *JAMA Surg* 2015;**150**(5):457–64.
151. van Ryn M, Fu SS. Paved with good intentions: do public health and human service providers contribute to racial/ethnic disparities in health? *Am J Public Health* 2003;**93**(2):248–55.
152. Wagner EH. Chronic disease management: what will it take to improve care for chronic illness? *Effect Clin Pract* 1998;**1**(1):2–4.
153. Bullock A, Burrows NR, Narva AS, Sheff K, Hora I, Lekiachvili A, et al. Vital signs: decrease in incidence of diabetes-related end-stage renal disease among American Indians/Alaska natives — United States, 1996–2013. *MMWR Morb Mortal Wkly Rep* 2017; **66**:26–32.
154. Kelleher K, Reece J, Sandel M. The healthy neighborhood, healthy families initiative. *Pediatrics* 2018;**142**(3): e20180261.
155. Vart P, Reijneveld SA, Bultmann U, Gansevoort RT. Added value of screening for CKD among the elderly or persons with low socioeconomic status. *Clin J Am Soc Nephrol* 2015;**10**(4):562–70.
156. Daniel H, Bornstein SS, Kane GC, for the H, Public Policy Committee of the American College of Physicians. Addressing social determinants to improve patient care and promote health equity: an American College of Physicians position paper. *Ann Intern Med* 2018;**168**(8):577–8.

QUESTIONS AND ANSWERS

Question 1

Which of the following is not a kidney-related outcome associated with poverty?

A. Increased incidence and prevalence of CKD
B. Increased incidence and prevalence of ESRD
C. Racial/ethnic disparities in CKD and ESRD
D. Increased risk of polycystic kidney disease
E. Increased mortality in CKD

Answer: D

Increased risk of polycystic kidney disease is genetically determined. Poverty has strong associations with risk of CKD (Answer choice A), risk of ESRD (Answer choice B), racial and ethnic disparities in CKD and ESRD (Answer choice C), and increased mortality in CKD (Answer choice E).

Question 2

Which of the following is not one of the five domains of McLeroy's Social Ecological Model of Health Promotion?

A. Public policy
B. Community
C. Organizational
D. Interpersonal
E. Biological

Answer: E

Answer choices A through D are all domains within McLeroy's Social Ecological Model of Health Promotion. Biological factors are a single element within the "individual" domain of the model.

Question 3

A patient with CKD presents to the clinic with uncontrolled hypertension, despite prescriptions for lisinopril (20 mg daily) and furosemide (20 mg daily). What is the best first course of action to address the uncontrolled blood pressure in this patient?

A. Increase the dose of lisinopril
B. Increase the dose of furosemide
C. Add an additional hypertensive medication
D. Determine if the patient is following the prescription regimen. If not discuss contextual barriers that may be interfering with the patient's ability to take their antihypertensive medications
E. Refer the patient for dietary counseling regarding sodium intake

Answer: D

Before making changes to the patient's treatment plan (Answer choices A through C and E), it is important to ensure that barriers to adherence do not prevent the patient from adhering to the existing medication regimen.

Question 4

Which of the following is not a potential mediator on the pathway from poverty to poor kidney outcomes?

A. Larger social support networks
B. Negative social determinants of health
C. Increased risk for harmful developmental programming
D. Reduced access to and engagement in health care
E. Barriers to engaging in health-promoting behaviors

Answer: A

Poverty is associated with smaller and less robust social support networks, which in turn increases risk for poor health outcomes through reduced emotional, informational, and instrumental support. Evidence suggests that negative social determinants of health, increased risk for harmful developmental programming, reduced access to and engagement in health care, and barriers to engaging in health-promoting behaviors (Answer choices D through E) all mediate the poverty-poor kidney outcomes relationship.

Question 5

What mechanisms may explain associations between stress and poor kidney outcomes?

A. Altered inflammatory cytokine and endothelin-A levels, increased risk for negative health behaviors, and maternal–fetal undernutrition
B. Increased allostatic load, elevated sympathetic nervous system activity, and perturbations of the hypothalamic–pituitary–adrenal axis
C. Increased allostatic load, elevated sympathetic nervous system activity, and a mismatch between nephron number and body mass
D. Increased risk for negative health behaviors, elevated sympathetic nervous system activity, and reduced access to health care
E. Altered inflammatory cytokine and endothelin-A levels, reduced ability to renally clear and metabolize stress hormones in people with CKD and maternal–fetal overnutrition

Answer: B

Maternal fetal undernutrition (Answer choice A), mismatch between nephron number and body mass (Answer choice C), and maternal–fetal overnutrition (Answer choice E) all relate to developmental

programming of kidney disease. Reduced access to health care (Answer choice D) is associated with poor kidney health outcomes, but stress does not appear to lead to reduced health care access.

Question 6

How might a broad perspective of health—including understanding the roles of clinical and contextual factors in health—improve the provision of health care?

A. By enabling clinicians to work with patients to identify and resolve barriers that may prevent patients from achieving optimal health.
B. By encouraging clinicians to recognize and address potential implicit biases that may influence how they provide care, particularly during high stress or high-pressure time periods.
C. By promoting collaborative, interdisciplinary care across clinical and community settings.
D. By encouraging health care institutions to address neighborhood-wide social determinants of health in addition to individual clinical issues.
E. All of the above.

Answer: E

Among individual clinicians, an understanding of how poverty and social determinants may influence the patient's health as well as their individual implicit biases regarding a patient may help clinicians address all factors affecting the patient's health in an unbiased manner. At the institutional level, recognition of the role of contextual factors in health outcomes may enable population health strategies that target the whole patient through interdisciplinary community collaboration.

CHAPTER

14

The Uremic Syndrome

Mirela A. Dobre[a], *Timothy W. Meyer*[b], *Thomas H. Hostetter*[c]

[a]Case Western Reserve University, School of Medicine, University Hospital Case Medical Center, Cleveland, OH, United States; [b]Stanford University, School of Medicine, Veterans Affairs Health Care System, Palo Alto, CA, United States; [c]Department of Medicine, University of North Carolina, Chapel Hill, NC, United States

Abstract

Uremia is the syndrome attributable to kidney failure. The causes of many of the most prominent signs and symptoms of uremia are poorly understood. Current dialysis therapy mitigates many but not all of these disabilities. The persistent illness with standard care probably derives at least in part from the failure of dialysis to replace normal kidney functions. Dialysis is particularly deficient in removing certain classes of molecules that are well cleared by the normal kidneys. These include small proteins, protein-bound solutes, intracellular sequestered compounds, and those which undergo high rates of active secretion by the normal tubule. The sources of these retained solutes are varied but include diet, enhanced production from human metabolism, and retention of metabolites originating from gut microbes. Recent approaches have begun to identify toxic compounds by epidemiologic studies and animal and cellular experiments, but clinical trials to more specifically remove or reduce production of candidate toxins are still wanting.

INTRODUCTION

Uremia is the syndrome caused by kidney failure. The term has been usually applied to the terminal phase of progressive chronic kidney disease (CKD), the condition now termed end-stage renal disease (ESRD). Modern ESRD treatment can maintain the inorganic solutes/electrolytes within normal ranges and thus interdict previously lethal aspects of uremia such as hyperkalemia and acidosis. The classic symptoms of uremia not attributable to electrolyte disorders are listed in Table 14.1. Those marked by an asterisk are substantially mitigated by current therapy including dialysis itself. Only a few, marked by two asterisks, are essentially completely abrogated by present approaches. Many, those without asterisks, are either only modestly improved or unaided. However, the pathophysiologic bases of even those features that can be remedied are poorly understood. For example, anemia is successfully treated with erythropoietin analogs, but the causes of the shortened red cell life span in uremia remain unknown, and dialysis does not correct this abnormality. Furthermore, the apparent toxicity associated with normalization of hemoglobin by erythropoietin is still obscure. Hypertension is usually improved by careful removal of excess extracellular fluid through ultrafiltration, but many patients still remain hypertensive despite best efforts at fluid management. Full blown uremia such as seen before the advent of dialysis or transplantation is now a rarity, at least in affluent countries. Thus, presently uremia may be defined as the illness which remains when the extracellular volume and inorganic ion concentrations are kept normal and the known renal synthetic products (e.g. erythropoietin) are replaced in patients without kidney function. Contemporary ESRD treatment still leaves patients with substantial morbidity.

SIGNS AND SYMPTOMS OF UREMIA

That a fundamental metabolic disturbance such as uremia should have such a wide variety of consequences is not remarkable. The complications of untreated diabetes or hyperthyroidism are similarly extensive. But uremia is different in that we cannot trace all its complications to dysregulation of a single key compound. In addition, except for renal transplantation, current therapy for uremia cannot return affected patients as close to normal as those who require thyroid hormone or insulin replacement.

The level of renal function at which uremia can be said to appear is unclear. There is no easily definable point in the fall of glomerular filtration rate (GFR) when uremia supervenes. Furthermore, the diminution

https://doi.org/10.1016/B978-0-12-815876-0.00014-0

TABLE 14.1 Symptoms and Signs of Uremia

Systemic	Gastrointestinal	Neurologic	Hematologic and Immunologic	Cardiovascular
Fatigue*	Decreased appetite*	Impaired cognition	Anemia*	Hypertension*
Hypothermia	Nausea*	Mental fatigue	Platelet dysfunction	Left ventricular hypertrophy
Insulin resistance	Vomiting*	Peripheral neuropathy*	Impaired antibody response	Accelerated vascular disease
Inflammation		Diminished taste and smell		Pericarditis**
		Restless legs		
		Pruritus		
		Coma**		
		Seizures**		

** Improved or mitigated by current end-stage renal disease (ESRD) treatments.*
*** Largely cured by current ESRD treatments.*

of renal functions other than solute clearance also likely contributes to the symptoms and signs of uremia. In general, these other functions such as ammoniagenesis, erythropoietin, and 1,25-dihydroxy vitamin D synthesis, urinary concentrating capacity, and tubular secretion tend to decline in parallel with GFR, but not always. Nevertheless, defining the level of kidney function solely by GFR may be misleading. For example, certain potentially toxic solutes depend more on tubular secretion than glomerular filtration for their excretion, and renal synthetic processes are probably linked to GFR only by virtue of the loss of functioning renal tissue. However, until particular renal dysfunctions are attached to specific aspects of the uremic syndrome, GFR (or its estimate) will remain the principal index of kidney function.

Most of the clinical and biochemical characteristics of uremia have been defined in ESRD or at a level of GFR very near to ESRD. Thus, uremic characteristics may be hard to dissect from complications of the dialysis procedure. Other morbidities that are considered separate from the uremia also commonly interact with it. For example, the cardiovascular disease suffered especially by patients with diabetes and hypertension appears to be accelerated by CKD.[1] But the myocardial infarctions, strokes, and peripheral vascular disease suffered by these patients have not traditionally been considered features of the uremic syndrome. These conditions nevertheless add to patients' disabilities in ways that are often not easily distinguishable from uremia or the "residual syndrome" of ESRD. Similarly, the peripheral neuropathy and gastroparesis of diabetes are difficult to disentangle from uremic neuropathy and uremic anorexia, nausea, and vomiting.

Well-Being and Physical Function

Given the spectrum of signs and symptoms in Table 14.1, it is not surprising that health-related quality of life (HRQOL) tends to decline in patients with CKD. Patients with CKD consistently score poorly on HRQOL and other measures of well-being.[2] The point in the course of CKD at which quality of life begins to decline has not been dissected in great detail but some data exist. The authors of the KDOQI guidelines concluded that notable reductions in well-being appeared when GFR was less than 60 mL/min.[3] For example, participants in the Modification of Diet in Renal Disease Study with GFRs between 25 and 55 mL/min/1.73 m^2 were queried with several survey instruments and reported fatigue and reduced stamina that correlated with GFR.[4] In another study using the Medical Outcomes Study Short Form 36, persons with GFR less than 50 mL/min/1.73 m^2 but not yet treated with dialysis (or transplantation) scored significantly lower than the general population in 8 of the 10 scales comprising the instrument.[5] Interestingly, this study did not detect a correlation between HRQOL scores and GFR over the range examined, but did detect a correlation between hemoglobin and HRQOL.[5] As with other aspects of uremia, it is difficult to distinguish the effects of treatment on HRQOL from those of uremia *per se*. Dialysis undoubtedly imposes a burden on patients. Comparisons of HRQOL in patients treated with dialysis and patients with advanced CKD who are not on dialysis have yielded discordant results.[5–8] Other, often neglected features of treatment, such as pill burden, may also contribute to reduction in the perception of quality of life.[9] Patients with ESRD are on average

more depressed than healthy controls. But it is difficult to distinguish the extent to which depression is caused by uremic solutes, compared with the effects of comorbid disease and the knowledge of ill health and limited life expectancy. Patients identify insomnia, fatigue, cramping, and dysphoria as chief among their burdens[10] Not surprisingly, transplantation has rather consistently been found to improve perception of quality of life.[2]

Physical functioning in patients treated with dialysis is decidedly below normal. The exercise capacity of patients treated with dialysis has been found to be about 50% of normal, with a range of 40–80%.[11] Treatment of anemia improves this situation but does not normalize it.[11,12] The most detailed studies have identified multiple defects that are associated with fatiguability.[13] These include both muscle energetic failure and neural defects. The degree to which they are attributable to the uremic environment itself, deconditioning, and/or comorbid conditions such as diabetes mellitus is difficult to establish. Even highly functional patients on dialysis display notable physical limitations. Blake and O'Meara[14] reported that middle-aged dialysis patients with good nutrition and no significant comorbidities exhibit a wide range of quantifiable deficiencies. For example, balance, walking speed, and sensory function in these patients were clearly below those of matched controls.

Neurologic Function

A particularly interesting group of uremic signs and systems reflect altered nerve function. Classic descriptions emphasized that uremic patients could appear alert despite defects in memory, planning, and attention.[15,16] As kidney function worsened, patients progressed to coma or catatonia which could be relieved by dialysis. Modern patients maintained on dialysis exhibit more subtle cognitive defects.[17] A difficulty in identifying the effects of uremia in these patients is that the hemodialysis procedure and/or associated factors (e.g. hypotension) may transiently impair cognitive function.[18] Studies in patients with CKD suggest that cognitive impairment can be detected when GFR falls below 60 mL/min/1.73 m^2 and worsens as GFR declines.[19–21] As with other signs and symptoms of uremia, the degree to which cognition is influenced by uremia as opposed to other comorbidities, especially cerebrovascular disease, is difficult to ascertain. The population studies cited above have identified cognitive impairment in CKD independent of clinically recognized vascular disease and other comorbidities. Imaging studies suggest that subclinical cerebrovascular disease is common in CKD patients and that its role in poor cognition needs further definition.[17,22,23] The finding that kidney transplantation improves cognitive function suggests, however, that at least some of the impairment observed in ESRD patients is due to solute accumulation.[24]

A further reflection of altered central nervous system function in uremia is impaired sleep.[25,26] Sleep disorders are common in ESRD patients and are associated with patients' perceptions of quality of life, as well as depressive affect.[27] Sleep is fragmented by brief arousals and apneic episodes which are often associated with bursts of repetitive leg movement. When awake, patients may feel a need to continuously move their legs, referred to as the restless legs syndrome.[28]

Sensorimotor neuropathy was a recognized component of the uremic syndrome decades ago.[15] Studies of conduction velocity and other nerve functions have since repeatedly found that the majority of patients with uremia have peripheral neuropathy, albeit often subclinical.[16,29,30] Morphologic studies have shown that these functional changes are associated with axonal loss.[30] The extent to which peripheral nerve function is impaired earlier in the course of CKD is not clear. Autonomic neuropathy also develops in ESRD patients but has been less extensively studied than peripheral neuropathy. As with other uremic disturbances the cause of neuropathy is unknown. Parathyroid hormone, multiple retention solutes, and more recently potassium have been associated with peripheral neuropathy but without definitive proof of causality.[16,29]

Appetite, Taste, and Smell

Loss of appetite is a common uremic symptom and presumably contributes to malnutrition in patients with advanced CKD. A large number of causes have been proposed. Acidosis and inflammatory cytokines including tumor necrosis factor (TNF) and various interleukins have been identified as contributing factors.[31] Attention has recently been focused on the accumulation of small proteins that are produced by the gut and adipose tissue and act on the brain to regulate appetite in normal people.[32,33] Levels of leptin, an anorexigen produced by adipose tissue, are elevated in ESRD. Levels of ghrelin, an orexigen produced by the gut, are also elevated, but data showing increased food intake with administration of exogenous ghrelin in ESRD patients suggest the uremia causes ghrelin resistance.[34]

Studies in partially nephrectomized mice have begun to dissect the cerebral mechanisms by which these hormonal changes reduce appetite and contribute to loss of body mass in uremia.[33,35] An interesting feature of uremic anorexia which remains to be explained is a disproportionate reduction in the intake of protein. Along with overall loss of appetite, erosion of taste and smell has long been recognized in the ESRD

population.[36,37] As with most defects associated with uremia, transplantation reverses the blunted sense of smell.[36] Some studies have reported that odor threshold declines gradually with creatinine clearance, whereas others have found that even in dialysis patients odor detection remains normal unless malnutrition is present.[36,38,39] Taste acuity has been reported as lower in dialysis patients than in those with renal insufficiency.[40] The factors responsible for these defects are again unknown. However, a pilot study suggested that intranasal theophylline increased odor identification in patients with ESRD.[39]

Cellular Functions

The most general cellular abnormality reported has been the inhibition of sodium-potassium ATPase (Na-K ATPase). Decreased Na-K ATPase activity in red cells of uremic patients was reported in 1964.[41] In general, subsequent reports have confirmed the observation, noted the same effect in other cell types, emphasizing that the inhibition was attributable to some factor in uremic serum.[42] The evidence for a circulating inhibitor includes the findings that dialysis reduces the inhibitory activity and uremic plasma can acutely suppress pump activity.[42] However, the factor or factors responsible have remained elusive. A number of candidates have been considered. Much attention has focused on digitalis-like substances. Recently, several such compounds have been found in excess in humans with ESRD. These include marinobufagenin and telocinobufagin, which have structures related to digitalis. In one report, the plasma concentrations of each of these substances was four- to fivefold higher in patients treated with dialysis compared with normal controls.[43] This study employed detailed mass spectrometry and nuclear magnetic resonance identification of the compounds with their concentrations determined by high-performance liquid chromatography. Many other investigations in the field have relied on antibody-based assays whose specificity may be less reliable.

The Na-K ATPase-suppressing compounds, including digitalis-like factors, have generally been sought among endogenous products of metabolism. The two compounds noted above, however, may be made by various animals and some others, but apparently not these two, are synthesized by plants (as, of course, is digitalis). Increased concentrations in renal failure could thus reflect impaired clearance of ingested materials rather than overproduction of endogenous products. Investigations in the field have not settled and indeed largely failed to address this question. A major deficiency in the case for endogenous digitalis-like factors has been the failure to define a biosynthetic pathway in mammals for these compounds, although they can be synthesized by plants and toads.[44] One study of subtotally nephrectomized rats did report an increase in both plasma levels and urinary excretion of marinobufagenin.[45] Because both the excretion rate and the plasma level were about double the control values, the results suggest that overproduction was responsible for the increased plasma level and that the diminished renal function played very little role. Similar measurements of the excretion or production of other digitalis-like compounds in humans or even in animals are not available.

Several considerations militate against digitalis-like substances as mediators of uremic toxicity. Some of the classical features of digitalis toxicity such as AV nodal conduction delays, ventricular extrasystole, and visual disturbances are not prominent even in older descriptions of untreated uremia. Other toxicities of digitalis such as anorexia are, of course, common in uremia. Cardiac fibrosis, a common complication of uremia, has been induced in rats with infusion of exogenous marinobufagenin.[46] As with many other putative uremic toxins, the association in humans of the cardiotonic steroids with clinical complications, in this case cardiac hypertrophy and hypertension, has not been extensively explored. There has also been little study of the degree to which Na-K ATPase is inhibited at different levels of impaired renal function. Most studies have used sera from patients or animals with complete renal failure although some, such as the study of marinobufagenin in rats, have used models of renal insufficiency.[45] A report examining the depression in muscle membrane potential in humans with ESRD showed not only that the electrophysiological abnormality was improved by dialysis but also that it was detectable only at a GFR below about 10 mL/min/1.73 m^2.[47] The depression in muscle membrane voltage would be consistent with Na-K ATPase inhibition, and, if so, it seems a late event in the course of renal disease.

CAUSES OF PERSISTENT UREMIA WITH CURRENT ESRD THERAPY

The set of signs and symptoms still present in people receiving dialysis currently defined as adequate has been described by Thomas Depner, who wrote "Patients who would have died from uremia but survive because of dialysis suffer from a previously non-existent life-threatening disease that is labeled here for lack of a better term the 'residual syndrome.'"[48] As he described, this syndrome likely has complex origins. We assume that at least some of these residual morbidities are due to retained organic solutes that are poorly removed by dialysis.

Dialysis as practiced does not faithfully reproduce normal renal function or the endocrine functions of the kidney. Conventional hemodialysis treatment aims at removing about two-thirds of the accumulated total body urea content during each of three weekly sessions. Urea itself seems to have little toxicity.[49] Conventional hemodialysis also removes other unidentified toxic solutes, but removes them as well as urea only if they too are small, unbound, and traffic readily across capillaries and cell membranes. Removal of other compounds may be limited due to large molecular size, protein binding, or sequestration within body compartments. Consequently, conventional dialysis has widely different effects on uremic solute levels owing to their different chemical characteristics. Surveys of small organics accumulating in ESRD patients find more than 270 compounds. When proteins and peptides are considered, an even larger list is generated.[50,51] The application of new analytic methods is lengthening this list.[52,53] Thus, identification of the chemicals responsible for the residual syndrome is a formidable task. A rational approach is to first consider those general classes of compounds that are poorly removed by dialysis compared with urea.

PROPERTIES OF POORLY DIALYZED SOLUTES

Large Molecule Solutes

The early dialysis membranes provided diminishing clearance of solutes larger than urea, which has a molecular weight of 60 D, and afforded very little clearance for solutes larger than 1000 D.[54] Development of more permeable, "high flux" membranes allowed the removal of the larger molecule β-2 microglobulin (molecular weight 12 kD), which had been associated with acquired amyloidosis. However, uremic solutes that are relatively large compared with urea, including β-2 microglobulin, are poorly cleared by even high flux dialyzers compared with the normal kidney. For example, the clearance of β-2 microglobulin by the normally functioning kidney is close to the GFR or about 100 mL/min, whereas the clearance of β-2 microglobulin by a high flux dialyzer is about 35 mL/min. Summed over a week, the normal kidneys thus provide about 1000 L of β-2 microglobulin clearance, whereas high flux dialysis provides about 20 L. Even with high flux membranes, levels of β-2 microglobulin in dialysis patients are therefore more than 20-fold higher than normal and would indeed rise even higher if there were not some nonrenal clearance of this solute.[55,56] By comparison, the typical time-averaged circulating urea levels are usually about threefold normal because usual dialysis presumably provides about one-third the weekly total urea clearance of normal kidneys (Figure 14.1). Examples of potentially toxic large molecule compounds in addition to β-2 microglobulin include complement factor D, various advanced glycosylation end products, and fragments of parathyroid hormone. The application of proteomic techniques adds steadily to this list.[57] Techniques designed to further increase convective clearance, especially hemodiafiltration, and thereby remove larger molecules

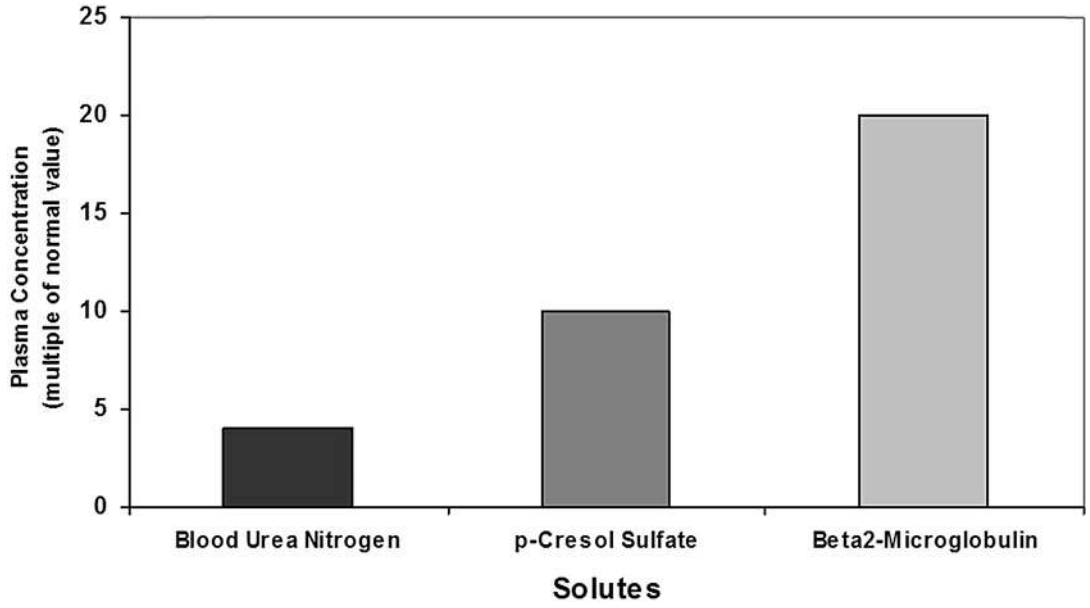


FIGURE 14.1 Time-average plasma solute levels in patients undergoing conventional thrice-weekly hemodialysis. Uremic solutes that are relatively large compared with urea are poorly cleared by even high flux dialyzers. The increase in the level of p-cresol sulfate would be of even greater magnitude if free rather than total plasma solute levels were compared.

have not shown consistent effects on outcomes such as cardiovascular events or mortality.[58–60] Furthermore, trials of this method have not as a group shown consistent lowering of β-2 microglobulin. Even in a trial that demonstrated lower levels with hemodiafiltration, the levels of β-2 microglobulin remained more than 10-fold normal.[58] This is not surprising because the clearances of such molecules by high flux membranes and novel dialytic approaches do not approach those of the normal kidneys.

Protein-Bound Solutes

The protein-bound uremic solutes have a low clearance because only the unbound fraction is available for diffusion across the dialysis membrane.[61–64] In the normally functioning kidney, the protein-bound solutes are removed through the active process of tubular secretion, which efficiently transports the free moiety across the tubule cells into the lumen. This process transpires with such efficiency that for many such solutes a large fraction of the incoming bound portion is removed in a single pass. Dialysis does not replicate secretion, however, and the weekly dialytic clearance of many of these compounds is less than one-tenth that provided by normal kidneys. As a result, their levels in people treated with maintenance dialysis are typically more than ten times their concentrations in normal serum.[64] The increase in plasma levels is of even greater magnitude if free rather than total solute concentrations are compared. Although experimental and clinical studies have suggested that the two most studied protein-bound solutes, indoxyl sulfate and p-cresol sulfate, have toxic effects both in experimental and clinical studies, some controversy still exists.[65–73] The time-averaged clearance of protein-bound solutes provided by peritoneal dialysis is even lower than that provided by hemodialysis. Yet plasma levels of p-cresol sulfate and indoxyl sulfate do not rise higher in peritoneal dialysis patients than in hemodialysis patients. The reasons for this are not completely understood, but appear to include reduced production of the solutes as residual renal function is lost in peritoneal dialysis patients.[62,63]

Sequestered Solutes

A third category of toxic solutes that are difficult to remove through conventional dialysis are those sequestered in compartments where their concentration does not equilibrate rapidly with that of the plasma. Dialysis rapidly reduces the plasma concentration of such solutes, but clears only a limited proportion of the total body solute content if they do not readily transfer out of intracellular water or other reservoirs. The best known example of a sequestered solute is phosphate, but some organic solutes including guanidinoacetic acid, guanidine, and methylguanidine appear to behave in this manner.[74] Similar to protein-bound solutes, sequestered molecules respond differently from urea to changes in the dialysis prescription.

Solute movement in and out of erythrocytes deserves additional consideration. Urea has selective membrane transporters that facilitate its diffusion in and out of red cells.[75] Therefore, with adequate dialysate flow and dialysis membrane size, urea is removed from both plasma and erythrocytes as blood transits the dialyzer. For this reason changes in hematocrit have little effect on urea clearance by hemodialysis.[76] Molecules without facilitated transport in and out of cells, like creatinine, cannot have a dialytic clearance exceeding plasma flow. Therefore, their dialytic clearances are lower than the dialytic urea clearance, and, unlike urea, their clearance may be dependent on hematocrit.

Methylamine and methylguanidine are molecules with higher intrared blood cell concentration compared with plasma.[77,78] They appear to be sequestered in other cellular compartments as they have volumes of distribution greater than the body water. For these reasons, their fractional removal by dialysis is less than that of urea and they display considerably more post dialysis rebound, as cellular compartments release them into the extracellular fluid after cessation of treatment.

Other Solutes with Very High Clearance by Native Kidneys

Urea and similar solutes are cleared at the highest rate by hemodialysis. All other solutes are cleared at lower rates. This is not true for the normal kidney. With normal renal function, urea clearance is only one-half of creatinine clearance. Other endogenous compounds, for example, hippurate, may be cleared at rates two or more fold the rate of GFR, or about five times the clearance of urea. Of course, these high clearances result from active tubular secretion, whereas dialytic clearance depends largely on diffusion. As a result of the much greater relative clearance by the native kidneys, patients treated with maintenance hemodialysis have hippurate levels twenty to forty times those in normal subjects.[79] Hippurate does not seem to be particularly toxic, but other undiscovered compounds that also have large secretory clearances by the normal kidney may be toxic and would also be expected to circulate in equally large multiples in dialysis patients. In 1939, the early renal physiologist James Shannon, who was also the first director of the National Institutes of Health, asked rhetorically whether loss of renal secretion might contribute to the symptoms of CKD. After raising this

possibility he wrote "The answer to this question must await the further identification of those substances which make up the unknown portion of the urinary constituents."[80] Studies of compounds secreted by people with normal kidney function have identified over 1000 protein-bound solutes that are secreted. The chemical identities of many of these are still unresolved, as they represent peaks in the chromatograms of high-resolution mass spectrometry. However, a subset that was chemically identified has extraordinarily high clearances of their free fraction, even exceeding renal plasma flow. For 11 of 13 such solutes, their levels in hemodialysis patients exceeded that in normal subjects by more than 20-fold.[81]

Sources of Retained Solutes

The sources of the compounds that accumulate to the largest molar concentrations in patients with CKD, urea and creatinine, are well known. They derive from protein metabolism and nonenzymatic breakdown of creatine, respectively. The retention of the inorganic components of the uremic extracellular fluid—potassium, phosphate, and hydrogen—is also well understood. The elevations in levels of small proteins such as β-2 microglobulin and complement Factor D seem largely to derive from their usual synthetic pathways in the face of impaired clearance. However, the origins of many retention products in patients with CKD are uncertain.

Uremia-induced increased production has been described for at least one solute long known to be elevated in the plasma of patients with CKD. Urinary guanidinosuccinic acid excretion rises in people with advanced CKD.[82] The biochemical causes for this increased production are not well worked out, but a complex interaction of urea, reduced protein intake, and homocysteine has been proposed.[83] Similarly, methylguanidine production seems to be increased in uremia. This finding is attributable to the reaction of creatinine with oxidants.[84]

The gut flora is an important source of many small solutes that accumulate in uremia.[85] One of the pioneers of dialysis therapy, Willem Kolff, suggested that this was likely to be so nearly 70 years ago. In a study comparing urine from control subjects and that from subjects with total colectomies, 91 solutes were four or more fold higher in the control urine, and 60 of these accumulated in ESRD patients. Many of these could be classed as secreted by the normal kidney and many were without previously known structure.[86] Evidence has begun to accumulate that some products of gut bacterial metabolism confer serious health risks. For example, trimethylamine oxide accumulates in uremia and is associated with cardiovascular disease in people with ESRD as well as those with normal renal function, suggesting that the accelerated vascular disease of uremia may be caused, at least in part, by this solute.[87–89]

Removal of Useful Vitamins and Minerals with Dialysis

Dialysis removes some important vitamins, minerals, and trace elements. Water-soluble vitamins are filtered through the dialysis membrane and require supplementation if intake is low. Vitamin C is one such compound. Hemodialysis removes 80–280 mg of vitamin C with each treatment.[90] Vitamin C deficiency is exacerbated by the restricted diets required for ESRD patients that prohibit potassium-rich foods which provide the major portion of dietary vitamin C. Another water-soluble vitamin, folic acid, was shown to be significantly cleared or lost during high-efficiency hemodialysis.[91] Furthermore, minerals like zinc are also removed by usual dialysis and may require supplementation. Loss of amino acids during dialysis has been documented and likely contributes to malnutrition in hemodialysis patients.[92] As there are presumably unknown toxic molecules that accumulate in dialysis patients, there may also be some unknown valuable molecules that are inappropriately removed by hemodialysis.

PROSPECTS FOR ADVANCES IN UREMIA THERAPY

Further dissection of the chemistry of uremia is possible with modern chemical techniques. However, additional complementary approaches are needed to determine which solutes are toxic and in what ways. Better endpoints than simply mortality or cardiovascular events are needed, and many of the disabilities presented in Table 14.1 should provide such targets. Epidemiologic associations of some solutes with standard endpoints have been determined, suggesting toxicities for indoxyl sulfate, p-cresol sulfate, and asymmetric dimethylarginine, for example.[69–71,93,94] Studies of specific solutes in intact animals have been few but seem a reasonable approach as do *in vitro* toxicity tests.[68,95] Selective reduction of a solute in ESRD patients, again with well-chosen endpoints, would be the most conclusive test of toxicity. Relatively straightforward adjustments to dialysis techniques enhance removal of protein-bound solutes, for example, but have not been tested for their effects on clinical endpoints.[96] Finally, understanding the origins of

established toxins might allow reduction in their production by dietary changes, sorbents, or manipulation of gut flora. Enhanced dialytic removal may not be the only route to better outcomes in uremia.

CONCLUSIONS

Hemodialysis has not only become widely available but has undoubtedly improved over the last 40 years. However, morbidities still persist, and attempts to understand their chemical etiologies have lagged behind other major advances in the field, such as more accurate ultrafiltration, bone and mineral therapy, and mitigation of anemia. Over the last decades, a few solutes have begun to receive serious attention as potential toxins, but progress has been slow. The reasons for this slow pace certainly include the chemical complexity of the uremic milieu and the multiplicity of clinical disturbances within the standardly dialyzed population. However, improving techniques for chemical analysis and the prospect of clinically meaningful quantifiable endpoints should propel more investigation. That one solute or even one class will account for all aspects of the residual syndrome seems unlikely. Undoubtedly, other components of chronic hemodialysis therapy beyond retained solutes, for example, episodic volume removal, also contribute to morbidities.

The effective therapy of most chronic conditions, however, requires targeting multiple mechanisms. Adequate treatment of diabetes encompasses not just glycemic control but also blood pressure and lipid therapies. Unraveling the complexity of the residual syndrome is daunting, but that does not mean that it is insoluble. Efforts to resolve the residual syndrome by employing yet more intensive dialysis based on urea removal may have some benefits. But such efforts will likely have only a modest impact on some important solutes, while significantly increasing the burden on patients and providers.

References

1. Vanholder R, Massy Z, Argiles A, Spasovski G, Verbeke F, Lameire N. Chronic kidney disease as cause of cardiovascular morbidity and mortality. *Nephrol Dial Transplant* 2005;**20**(6): 1048–56.
2. Kimmel PL, Patel SS. Quality of life in patients with chronic kidney disease: focus on end-stage renal disease treated with hemodialysis. *Semin Nephrol* 2006;**26**(1):68–79.
3. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**(2 Suppl. 1):S1–266.
4. Rocco MV, Gassman JJ, Wang SR, Kaplan RM. Cross-sectional study of quality of life and symptoms in chronic renal disease patients: the Modification of Diet in Renal Disease Study. *Am J Kidney Dis* 1997;**29**(6):888–96.
5. Perlman RL, Finkelstein FO, Liu L, et al. Quality of life in chronic kidney disease (CKD): a cross-sectional analysis in the Renal Research Institute-CKD study. *Am J Kidney Dis* 2005; **45**(4):658–66.
6. Walters BA, Hays RD, Spritzer KL, Fridman M, Carter WB. Health-related quality of life, depressive symptoms, anemia, and malnutrition at hemodialysis initiation. *Am J Kidney Dis* 2002; **40**(6):1185–94.
7. Wu AW, Fink NE, Marsh-Manzi JV, et al. Changes in quality of life during hemodialysis and peritoneal dialysis treatment: generic and disease specific measures. *J Am Soc Nephrol* 2004;**15**(3):743–53.
8. Abdel-Kader K, Unruh ML, Weisbord SD. Symptom burden, depression, and quality of life in chronic and end-stage kidney disease. *Clin J Am Soc Nephrol* 2009;**4**(6):1057–64.
9. Chiu YW, Teitelbaum I, Misra M, de Leon EM, Adzize T, Mehrotra R. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. *Clin J Am Soc Nephrol* 2009;**4**(6):1089–96.
10. Flythe JE, Hilliard T, Castillo G, et al. Symptom prioritization among adults receiving in-center hemodialysis: a mixed methods study. *Clin J Am Soc Nephrol* 2018;**13**(5):735–45.
11. Johansen KL. Physical functioning and exercise capacity in patients on dialysis. *Adv Ren Replace Ther* 1999;**6**(2):141–8.
12. Painter P. Physical functioning in end-stage renal disease patients: update 2005. *Hemodial Int* 2005;**9**(3):218–35.
13. Johansen KL, Doyle J, Sakkas GK, Kent-Braun JA. Neural and metabolic mechanisms of excessive muscle fatigue in maintenance hemodialysis patients. *Am J Physiol Regul Integr Comp Physiol* 2005; **289**(3):R805–13.
14. Blake C, O'Meara YM. Subjective and objective physical limitations in high-functioning renal dialysis patients. *Nephrol Dial Transplant* 2004;**19**(12):3124–9.
15. Schreiner G, Maher J. Biochemistry of uremia. In: *Uremia*. Springfield: Charles Thomas; 1960. p. 55–85.
16. Brouns R, De Deyn PP. Neurological complications in renal failure: a review. *Clin Neurol Neurosurg* 2004;**107**(1):1–16.
17. Madero M, Gul A, Sarnak MJ. Cognitive function in chronic kidney disease. *Semin Dial* 2008;**21**(1):29–37.
18. Murray AM, Pederson SL, Tupper DE, et al. Acute variation in cognitive function in hemodialysis patients: a cohort study with repeated measures. *Am J Kidney Dis* 2007;**50**(2):270–8.
19. Kurella M, Chertow GM, Fried LF, et al. Chronic kidney disease and cognitive impairment in the elderly: the Health, Aging, and Body Composition study. *J Am Soc Nephrol* 2005;**16**(7):2127–33.
20. Kurella M, Yaffe K, Shlipak MG, Wenger NK, Chertow GM. Chronic kidney disease and cognitive impairment in menopausal women. *Am J Kidney Dis* 2005;**45**(1):66–76.
21. Hailpern SM, Melamed ML, Cohen HW, Hostetter TH. Moderate chronic kidney disease and cognitive function in adults 20 to 59 years of age: third National Health and Nutrition Examination Survey (NHANES III). *J Am Soc Nephrol* 2007;**18**(7):2205–13.
22. Seliger SL, Longstreth Jr WT, Katz R, et al. Cystatin C and subclinical brain infarction. *J Am Soc Nephrol* 2005;**16**(12):3721–7.
23. Kim CD, Lee HJ, Kim DJ, et al. High prevalence of leukoaraiosis in cerebral magnetic resonance images of patients on peritoneal dialysis. *Am J Kidney Dis* 2007;**50**(1):98–107.
24. Griva K, Thompson D, Jayasena D, Davenport A, Harrison M, Newman SP. Cognitive functioning pre- to post-kidney transplantation–a prospective study. *Nephrol Dial Transplant* 2006;**21**(11): 3275–82.
25. Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. *N Engl J Med* 2001;**344**(2):102–7.
26. Perl J, Unruh ML, Chan CT. Sleep disorders in end-stage renal disease: 'Markers of inadequate dialysis'? *Kidney Int* 2006;**70**(10): 1687–93.

27. Shayamsunder AK, Patel SS, Jain V, Peterson RA, Kimmel PL. Sleepiness, sleeplessness, and pain in end-stage renal disease: distressing symptoms for patients. *Semin Dial* 2005;**18**(2):109–18.
28. Mucsi I, Molnar MZ, Ambrus C, et al. Restless legs syndrome, insomnia and quality of life in patients on maintenance dialysis. *Nephrol Dial Transplant* 2005;**20**(3):571–7.
29. Krishnan AV, Phoon RK, Pussell BA, Charlesworth JA, Bostock H, Kiernan MC. Altered motor nerve excitability in end-stage kidney disease. *Brain* 2005;**128**(Pt 9):2164–74.
30. Krishnan AV, Kiernan MC. Uremic neuropathy: clinical features and new pathophysiological insights. *Muscle Nerve* 2007;**35**(3): 273–90.
31. Bergstrom J. Regulation of appetite in chronic renal failure. *Miner Electrolyte Metab* 1999;**25**(4–6):291–7.
32. Mitch WE. Cachexia in chronic kidney disease: a link to defective central nervous system control of appetite. *J Clin Investig* 2005; **115**(6):1476–8.
33. Cheung W, Yu PX, Little BM, Cone RD, Marks DL, Mak RH. Role of leptin and melanocortin signaling in uremia-associated cachexia. *J Clin Investig* 2005;**115**(6):1659–65.
34. Wynne K, Giannitsopoulou K, Small CJ, et al. Subcutaneous ghrelin enhances acute food intake in malnourished patients who receive maintenance peritoneal dialysis: a randomized, placebo-controlled trial. *J Am Soc Nephrol* 2005;**16**(7):2111–8.
35. Cheung WW, Kuo HJ, Markison S, et al. Peripheral administration of the melanocortin-4 receptor antagonist NBI-12i ameliorates uremia-associated cachexia in mice. *J Am Soc Nephrol* 2007;**18**(9): 2517–24.
36. Griep MI, Van der Niepen P, Sennesael JJ, Mets TF, Massart DL, Verbeelen DL. Odour perception in chronic renal disease. *Nephrol Dial Transplant* 1997;**12**(10):2093–8.
37. Middleton RA, Allman-Farinelli MA. Taste sensitivity is altered in patients with chronic renal failure receiving continuous ambulatory peritoneal dialysis. *J Nutr* 1999;**129**(1):122–5.
38. Raff AC, Lieu S, Melamed ML, et al. Relationship of impaired olfactory function in ESRD to malnutrition and retained uremic molecules. *Am J Kidney Dis* 2008;**52**(1):102–10.
39. Nigwekar SU, Weiser JM, Kalim S, et al. Characterization and correction of olfactory deficits in kidney disease. *J Am Soc Nephrol* 2017;**28**(11):3395–403.
40. Fernstrom A, Hylander B, Rossner S. Taste acuity in patients with chronic renal failure. *Clin Nephrol* 1996;**45**(3):169–74.
41. Welt LG, Sachs JR, McManus TJ. An ion transport defect in erythrocytes from uremic patients. *Trans Assoc Am Phys* 1964;**77**:169–81.
42. Kaji D, Thomas K. Na+-K+ pump in chronic renal failure. *Am J Physiol* 1987;**252**(5 Pt 2):F785–93.
43. Komiyama Y, Dong XH, Nishimura N, et al. A novel endogenous digitalis, telocinobufagin, exhibits elevated plasma levels in patients with terminal renal failure. *Clin Biochem* 2005;**38**(1):36–45.
44. Bagrov AY, Shapiro JI, Fedorova OV. Endogenous cardiotonic steroids: physiology, pharmacology, and novel therapeutic targets. *Pharmacol Rev* 2009;**61**(1):9–38.
45. Kennedy DJ, Vetteth S, Periyasamy SM, et al. Central role for the cardiotonic steroid marinobufagenin in the pathogenesis of experimental uremic cardiomyopathy. *Hypertension* 2006;**47**(3): 488–95.
46. Elkareh J, Kennedy DJ, Yashaswi B, et al. Marinobufagenin stimulates fibroblast collagen production and causes fibrosis in experimental uremic cardiomyopathy. *Hypertension* 2007;**49**(1): 215–24.
47. Cotton JR, Woodard T, Carter NW, Knochel JP. Resting skeletal muscle membrane potential as an index of uremic toxicity. A proposed new method to assess adequacy of hemodialysis. *J Clin Investig* 1979;**63**(3):501–6.
48. Depner TA. Uremic toxicity: urea and beyond. *Semin Dial* 2001; **14**(4):246–51.
49. Johnson WJ, Hagge WW, Wagoner RD, Dinapoli RP, Rosevear JW. Effects of urea loading in patients with far-advanced renal failure. *Mayo Clin Proc* 1972;**47**(1):21–9.
50. Tanaka H, Sirich TL, Plummer NS, Weaver DS, Meyer TW. An enlarged profile of uremic solutes. *PLoS One* 2015;**10**(8):e0135657.
51. Vanholder R, Pletinck A, Schepers E, Glorieux G. Biochemical and clinical impact of organic uremic retention solutes: a comprehensive update. *Toxins* 2018;**10**(1).
52. Rhee EP, Souza A, Farrell L, et al. Metabolite profiling identifies markers of uremia. *J Am Soc Nephrol* 2010;**21**(6):1041–51.
53. Rhee EP. How omics data can be used in nephrology. *Am J Kidney Dis* 2018;**72**(1):129–35.
54. Meyer TW, Sirich TL, Hostetter TH. Dialysis cannot be dosed. *Semin Dial* 2011;**24**(5):471–9.
55. Cheung AK, Rocco MV, Yan G, et al. Serum beta-2 microglobulin levels predict mortality in dialysis patients: results of the HEMO study. *J Am Soc Nephrol* 2006;**17**(2):546–55.
56. Ward RA, Greene T, Hartmann B, Samtleben W. Resistance to intercompartmental mass transfer limits beta2-microglobulin removal by post-dilution hemodiafiltration. *Kidney Int* 2006;**69**(8): 1431–7.
57. Vanholder R, De Smet R, Glorieux G, et al. Review on uremic toxins: classification, concentration, and interindividual variability. *Kidney Int* 2003;**63**(5):1934–43.
58. Grooteman MP, van den Dorpel MA, Bots ML, et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. *J Am Soc Nephrol* 2012;**23**(6):1087–96.
59. Ok E, Asci G, Toz H, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. *Nephrol Dial Transplant* 2013;**28**(1):192–202.
60. Maduell F, Moreso F, Pons M, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *J Am Soc Nephrol* 2013;**24**(3):487–97.
61. Vanholder R, Schepers E, Pletinck A, Neirynck N, Glorieux G. An update on protein-bound uremic retention solutes. *J Ren Nutr* 2012; **22**(1):90–4.
62. Bammens B, Evenepoel P, Verbeke K, Vanrenterghem Y. Removal of middle molecules and protein-bound solutes by peritoneal dialysis and relation with uremic symptoms. *Kidney Int* 2003;**64**(6): 2238–43.
63. Pham NM, Recht NS, Hostetter TH, Meyer TW. Removal of the protein-bound solutes indican and p-cresol sulfate by peritoneal dialysis. *Clin J Am Soc Nephrol* 2008;**3**(1):85–90.
64. Martinez AW, Recht NS, Hostetter TH, Meyer TW. Removal of P-cresol sulfate by hemodialysis. *J Am Soc Nephrol* 2005;**16**(11): 3430–6.
65. Niwa T. Indoxyl sulfate is a nephro-vascular toxin. *J Ren Nutr* 2010; **20**(5 Suppl. l):S2–6.
66. Vanholder R, De Smet R, Lameire N. Protein-bound uremic solutes: the forgotten toxins. *Kidney Int Suppl* 2001;**78**:S266–70.
67. Yu M, Kim YJ, Kang DH. Indoxyl sulfate-induced endothelial dysfunction in patients with chronic kidney disease via an induction of oxidative stress. *Clin J Am Soc Nephrol* 2011;**6**(1):30–9.
68. Adijiang A, Goto S, Uramoto S, Nishijima F, Niwa T. Indoxyl sulphate promotes aortic calcification with expression of osteoblast-specific proteins in hypertensive rats. *Nephrol Dial Transplant* 2008;**23**(6):1892–901.
69. Jourde-Chiche N, Dou L, Cerini C, Dignat-George F, Brunet P. Vascular incompetence in dialysis patients–protein-bound uremic toxins and endothelial dysfunction. *Semin Dial* 2011;**24**(3): 327–37.

70. Meijers BK, Bammens B, De Moor B, Verbeke K, Vanrenterghem Y, Evenepoel P. Free p-cresol is associated with cardiovascular disease in hemodialysis patients. *Kidney Int* 2008;**73**(10):1174–80.
71. Melamed ML, Plantinga L, Shafi T, et al. Retained organic solutes, patient characteristics and all-cause and cardiovascular mortality in hemodialysis: results from the retained organic solutes and clinical outcomes (ROSCO) investigators. *BMC Nephrol* 2013; **14**(1):134.
72. Evenepoel P, Glorieux G, Meijers B. p-cresol sulfate and indoxyl sulfate: some clouds are gathering in the uremic toxin sky. *Kidney Int* 2017;**92**(6):1323–4.
73. Gryp T, Vanholder R, Vaneechoutte M, Glorieux G. p-Cresyl sulfate. *Toxins* 2017;**9**(2).
74. Eloot S, Torremans A, De Smet R, et al. Kinetic behavior of urea is different from that of other water-soluble compounds: the case of the guanidino compounds. *Kidney Int* 2005;**67**(4):1566–75.
75. Cheung AK, Alford MF, Wilson MM, Leypoldt JK, Henderson LW. Urea movement across erythrocyte membrane during artificial kidney treatment. *Kidney Int* 1983;**23**(6):866–9.
76. Lim VS, Flanigan MJ, Fangman J. Effect of hematocrit on solute removal during high efficiency hemodialysis. *Kidney Int* 1990; **37**(6):1557–62.
77. Ponda MP, Quan Z, Melamed ML, Raff A, Meyer TW, Hostetter TH. Methylamine clearance by haemodialysis is low. *Nephrol Dial Transplant* 2010;**25**(5):1608–13.
78. Eloot S, Torremans A, De Smet R, et al. Complex compartmental behavior of small water-soluble uremic retention solutes: evaluation by direct measurements in plasma and erythrocytes. *Am J Kidney Dis* 2007;**50**(2):279–88.
79. Marquez IO, Tambra S, Luo FY, et al. Contribution of residual function to removal of protein-bound solutes in hemodialysis. *Clin J Am Soc Nephrol* 2011;**6**(2):290–6.
80. Shannon JA. Renal tubular excretion. *Phys Rev* 1939;**19**:63–93.
81. Sirich TL, Aronov PA, Plummer NS, Hostetter TH, Meyer TW. Numerous protein-bound solutes are cleared by the kidney with high efficiency. *Kidney Int* 2013;**84**(3):585–90.
82. Kopple JD, Gordon SI, Wang M, Swendseid ME. Factors affecting serum and urinary guanidinosuccinic acid levels in normal and uremic subjects. *J Lab Clin Med* 1977;**90**(2):303–11.
83. Cohen BD. Methyl group deficiency and guanidino production in uremia. *Mol Cell Biochem* 2003;**244**(1–2):31–6.
84. Nakamura K, Ienaga K, Yokozawa T, Fujitsuka N, Oura H. Production of methylguanidine from creatinine via creatol by active oxygen species: analyses of the catabolism in vitro. *Nephron* 1991; **58**(1):42–6.
85. Meyer TW, Hostetter TH. Uremic solutes from colon microbes. *Kidney Int* 2012;**81**(10):949–54.
86. Mair RD, Sirich TL, Plummer NS, Meyer TW. Characteristics of colon-derived uremic solutes. *Clin J Am Soc Nephrol* 2018;**13**(9): 1398–404.
87. Tang WH, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med* 2013;**368**(17):1575–84.
88. Bain MA, Faull R, Fornasini G, Milne RW, Evans AM. Accumulation of trimethylamine and trimethylamine-N-oxide in end-stage renal disease patients undergoing haemodialysis. *Nephrol Dial Transplant* 2006;**21**(5):1300–4.
89. Shafi T, Powe NR, Meyer TW, et al. Trimethylamine N-oxide and cardiovascular events in hemodialysis patients. *J Am Soc Nephrol* 2017;**28**(1):321–31.
90. Sullivan JF, Eisenstein AB. Ascorbic acid depletion in patients undergoing chronic hemodialysis. *Am J Clin Nutr* 1970;**23**(10):1339–46.
91. Leblanc M, Pichette V, Geadah D, Ouimet D. Folic acid and pyridoxal-5′-phosphate losses during high-efficiency hemodialysis in patients without hydrosoluble vitamin supplementation. *J Ren Nutr* 2000;**10**(4):196–201.
92. Ikizler TA, Flakoll PJ, Parker RA, Hakim RM. Amino acid and albumin losses during hemodialysis. *Kidney Int* 1994;**46**(3): 830–7.
93. Barreto FC, Barreto DV, Liabeuf S, et al. Serum indoxyl sulfate is associated with vascular disease and mortality in chronic kidney disease patients. *Clin J Am Soc Nephrol* 2009;**4**(10):1551–8.
94. Meinitzer A, Kielstein JT, Pilz S, et al. Symmetrical and asymmetrical dimethylarginine as predictors for mortality in patients referred for coronary angiography: the Ludwigshafen Risk and Cardiovascular Health study. *Clin Chem* 2011;**57**(1):112–21.
95. Berman N, Lectura M, Thurman JM, et al. A zebrafish model for uremic toxicity: role of the complement pathway. *Blood Purif* 2013;**35**(4):265–9.
96. Sirich TL, Luo FJ, Plummer NS, Hostetter TH, Meyer TW. Selectively increasing the clearance of protein-bound uremic solutes. *Nephrol Dial Transplant* 2012;**27**(4):1574–9.

QUESTIONS AND ANSWERS

Question 1

Uremic patients may present with which of the following signs and symptoms?

A. Anorexia
B. Diminished smell
C. Hypothermia
D. Restless leg syndrome
E. All of the above

Answer: E

Anorexia, diminished sense of smell, hypothermia, and restless leg syndrome are all manifestations of uremic syndrome present in patients with ESRD. Other signs and symptoms of uremia include fatigue, inflammation, insulin resistance, nausea and vomiting, impaired cognition, and pruritus.[4,38]

Question 2

A 75-year-old man with diabetes mellitus for more than 20 years, proteinuria, hypertension, and CKD, presents to the emergency room complaining of chest pain and shortness of breath. He was noncompliant with his medical treatment and was last seen by a physician more than a year ago. The chest pain started suddenly, approximately four hours prior to admission. It was sharp, exacerbated by taking a deep breath and relieved by leaning forward. The patient stated that for the past month he had poor appetite, generalized pruritus, nausea, and vomited several times.

He had a blood pressure of 210/99 mm Hg, heart rate 88 beats/minute, and was afebrile. He had jugular venous distention, bilateral crackles in the lower two-thirds of lung fields, laterally displaced apical impulse, S3 gallop, a friction rub, and lower extremity edema up to the thighs. Approximately 30 minutes after being examined in the emergency department he had a generalized tonic-clonic seizure.

His laboratory findings were hemoglobin 7 mg/dL, sodium 140 mEq/L, potassium 6.5 mEq/L, chloride 101 mEq/L, bicarbonate 12 mEq/L, BUN 160 mg/dL, creatinine 12.5 mg/dL, phosphate 7.9 mg/dL, calcium 8.5 mg/dL, and albumin 3.8 mg/dL. Chest X-ray was consistent with an enlarged heart and increased interstitial markings.

The renal team was consulted and hemodialysis treatment was initiated emergently.

What manifestation of uremia will be completely resolved by the initiation of hemodialysis treatment?

A. Seizures
B. Anemia
C. Hypertension
D. Pruritus
E. Nausea and vomiting

Answer: A

Of the classic manifestations of uremia not attributable to electrolyte disorders, only uremic seizures present in ESRD patients prior to initiation of hemodialysis (Answer A) are completely abrogated by the current renal replacement therapies. Anemia (Answer B), though successfully treated with erythropoietin analogs, is not corrected by dialysis. Hypertension (Answer C) is usually improved by careful removal of the excess extracellular fluid through ultrafiltration, but many patients still remain hypertensive despite the best efforts at fluid management during dialysis. Pruritus (Answer D) is one of the most difficult uremic symptoms to treat and has a poorly understood pathophysiology. Nausea and vomiting (Answer E) in uremic patients are only partially corrected by the available dialysis therapies.

Question 3

A solute with which of the following properties is likely to be removed by hemodialysis to about the same extent as urea?

A. One that is 90% bound to albumin
B. One that has a molecular weight of 8000 D
C. One that is highly concentrated in cells
D. One that has a molecular weight of 100 D

Answer: D

Conventional hemodialysis treatment aims at removing about two-thirds of the accumulated total body urea content during each of three weekly sessions. Hemodialysis also removes other unidentified toxic solutes but removes them as well as urea only if they too are small (Answer D), unbound, and traffic readily across capillaries and cell membranes. Removal of other compounds may be limited due to protein binding (Answer A), large molecular size (Answer B), or sequestration within body compartments (Answer C).[74]

Question 4

Which of the following statements is true?

A. The protein-bound solutes have a high clearance due to the unbound fraction available for diffusion across the dialysis membrane
B. In the normal functioning kidney, the protein-bound solutes are removed through the active process of tubular secretion

C. The protein-bound solute levels in people treated with hemodialysis are generally lower than in normal individuals
D. Plasma levels of p-cresol sulfate and indoxyl sulfate are higher in peritoneal dialysis than in hemodialysis patients
E. Conventional hemodialysis treatment is able to remove a substantial fraction of protein-bound uremic toxins

Answer: B

Protein-bound solutes are removed through the active process of tubular secretion (Answer B). They have a low clearance in dialysis patients (Answer A), because only the unbound fraction is available for diffusion across the dialysis membrane. Therefore, their concentration is high in ESRD patients (Answer C). P-cresol sulfate and indoxyl sulfate, the most studied uremic toxins, are lower in peritoneal dialysis patients, due in part to better preserved residual renal function compared with hemodialysis patients (Answer D). Conventional hemodialysis treatment is able to remove only the unbound fraction of protein-bound uremic toxins (Answer E).[64,66]

Question 5

Which of the following statements is true?

A. Notable reductions in quality of life and well-being appear when GFR falls below 60 mL/min/1.73 m^2
B. The prevalence of depression is similar in patients receiving dialysis and those with a kidney transplant
C. Treatment of anemia in dialysis patients does not improve physical functioning
D. In patients with CKD, fatigue is present only when GFR falls below 15 mL/min/1.73 m^2
E. Middle-aged dialysis patients with good nutrition and no significant comorbidities exhibit the same physical functioning as those of matched controls

Answer: A

Reductions in quality of life and well-being appear when GFR falls below 60 mL/min/1.73 m^2 (Answer A). Transplant recipients have lower rate of depression compared with dialysis patients (Answer B). Physical functioning is improved by treatment of anemia in dialysis (Answer C). It is unclear at what level of GFR uremic symptoms begin to manifest but is likely much higher than 15 mL/min (Answer D). Relatively "healthy" dialysis patients with good nutrition and no significant comorbidities still have decline in physical functioning compared with normal individuals (Answer E).[4–6]

Question 6

All of the following statements regarding anorexia in ESRD are true, except?

A. Loss of appetite is a common uremic symptom and presumably contributes to malnutrition in patients with advanced renal failure
B. Acidosis and inflammatory cytokines including TNF-alpha and various interleukins have been identified as contributing factors
C. Levels of leptin, an anorexigen produced by adipose tissue, are elevated in ESRD
D. ESRD patients have a disproportionate reduction in the intake of protein
E. Anorexia is eliminated by proper dialysis

Answer: E

Anorexia is only alleviated, but not completely eliminated by proper dialysis treatment (Answer E). All the other statements are correct.[32]

CHAPTER

15

Pathophysiology of Proteinuria: Albuminuria as a Target for Treatment

Hiddo J.L. Heerspink[a], *Ton Rabelink*[b], *Dick de Zeeuw*[a]

[a]Department of Clinical Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [b]Department of Nephrology, Leiden University Medical Center, Leiden, Netherlands

Abstract

The presence of albumin in the urine has long been recognized as a hallmark of renal dysfunction. In systemic diseases, such as hypertension or diabetes mellitus, albuminuria is not only a marker of glomerular injury but may also contribute to renal function loss. The development of albuminuria and its adverse consequences is probably a multistep process where, initially, loss of endothelial barrier function may play a role. Endothelial activation within the glomeruli and subsequent shedding of the glycocalyx surface allows albumin to penetrate the subpodocyte space. Podocytes may then take up albumin through scavenger receptors and display actin skeleton rearrangements and injury. In addition, compensatory reabsorption in proximal tubules and the accompanying inflammatory responses may further contribute to the structural interstitial damage that has been associated with albuminuria and may ultimately lead to decreased nephron function.

Further evidence regarding the role of albuminuria in the setting of progressive renal functional loss comes from observational studies demonstrating that the presence of albuminuria is associated with a high risk of renal functional loss over time. This association is found in various diseases such as diabetes mellitus, hypertensive kidney disease, primary renal disease of diverse origins, and even in the general, otherwise healthy, population.

Certain drugs are available that decrease albuminuria, such as renin–angiotensin–aldosterone system inhibitors. More recently, other drugs such as sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists, and endothelin receptor antagonists have been shown to decrease albuminuria as well. It appears that the reduction in albuminuria, observed during the first months of therapy, correlates with the degree of long-term renal protection: the larger the reduction in albuminuria, the slower the rate of renal function decline. Collectively, these data suggest that albuminuria should not only be used to diagnose chronic kidney disease and estimate the risk for increased progressive renal functional loss, but albuminuria can also be used as a target for renoprotective therapy. As such, the level of albumin in urine should be regularly monitored and optimized as with high blood pressure or high cholesterol levels.

This chapter reviews the pathophysiology of albuminuria and clinical studies that support the use of albuminuria as an independent target for renoprotective therapy.

INTRODUCTION

The prevalence of kidney failure is increasing in the US and worldwide and is associated with poor outcomes and high costs.[1] During the last decade, much attention has been paid to early identification of individuals at risk for developing chronic kidney disease (CKD). The presence of albuminuria has emerged as an important risk marker of progressive renal functional loss in various populations. The importance of albuminuria as a diagnostic and prognostic risk marker has been recognized by policy and guideline makers, and albuminuria is currently included in a new CKD classification system in combination with estimated glomerular filtration rate (eGFR) to define the severity of CKD.[2]

The measurement of proteins or albumin in the urine dates to the 18th century, when Domenico Cotugno and Richard Bright noted that after heating and partial evaporation of urine of children with primary kidney diseases "a white mass loosely coagulated like egg albumin" remains.[3–5] The contribution of Hermann Senator, a German physician, further emphasized the importance of albuminuria. In a seminal article, he described that albumin could be present in otherwise healthy individuals, and he provided perspectives on the pathophysiology as well as suggestions for treatment.[6] Based on these early observations, nephrologists became increasingly interested in the measurement of all proteins in the urine

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00015-2

(proteinuria) in patients with primary glomerular diseases. From 1960 to 1980, the standard techniques to measure proteinuria could detect only large quantities of proteins, typically in the range of urinary excretion of grams per day. These increased amounts of urinary proteins predicted faster progression of renal functional loss in patients with CKD.[7] In the 1980s, novel methods were introduced that enabled the measurement of small quantities of albumin in the urine, so-called albuminuria. The introduction of these techniques triggered the attention of diabetologists regarding measurement of urinary albumin in their patients. Clinical studies in the 1980s showed that small increases in urinary albumin excretion (termed microalbuminuria) predicted the development of overt nephropathy and the risk of mortality.[8–10] Over the ensuing years, the measurement of albuminuria was not limited to the CKD or diabetes populations but extended to the hypertensive and general population as well. Even in otherwise healthy persons, microalbuminuria was present in about 5%–10% of the population and predicted the rate of progression of kidney disease.[11]

Important clinical questions are whether interventions are available that decrease albuminuria, and whether the reduction in albuminuria induced by these interventions slow progression of CKD. There are indeed a number of drugs available that decrease albuminuria, such as drugs that intervene in the renin–angiotensin–aldosterone system (RAAS). Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are frequently used when treating high blood pressure in patients with CKD. Interestingly, although the blood pressure lowering effect of RAAS intervention reduces the risk of kidney failure, the albuminuria-lowering effects appears to contribute to this protective effect independent of the blood pressure-lowering effect. Thus, for an effective renoprotective use of RAAS inhibition and its dosing, one can not only use the blood pressure-lowering effect but one also needs other parameters to follow, such as albuminuria. This chapter will discuss the effects of various drugs, not limited to RAAS intervention, on albuminuria, and the use of changes in albuminuria as a target to optimize renoprotection. The use of albuminuria as a cardiovascular risk marker and target for treatment has been reviewed elsewhere and will not be discussed.[12,13]

CRITERIA TO ACCEPT ALBUMINURIA AS A TARGET FOR RENAL PROTECTION TREATMENT

Certain criteria should be met before one may consider albuminuria as a separate target for renal protective treatment in CKD patients:

- The mechanism by which albuminuria causes renal morbidity/mortality should be delineated.
- Different levels of albuminuria should indicate different levels of renal morbidity and mortality, independent of other risk markers and independent of the etiology of renal disease.
- A change in albuminuria (by whatever strategy) should predict a change in renal functional changes, morbidity and mortality, independent of other risk marker changes, independent of the underlying disease and independent of the medication that changes the albuminuria.

PATHOPHYSIOLOGY OF ALBUMINURIA

The glomerulus functions as a size-selective filter for protein filtration. Consequently, tubular fluid contains only proteins of low molecular weight (<60 kD) such as vitamin D-binding protein or free retinol-binding protein, while larger proteins are excluded.[14] Albumin, the most abundant plasma protein, is filtered in very low amounts (1–50 μg/mL). In addition, albumin can be reabsorbed by the tubular epithelium. Consequently, normal total urinary protein excretion in the normal adult should be less than 150 mg/day.[15] Higher rates of urinary protein excretion that persist beyond a single measurement should be evaluated. The increased protein leak can be caused by an increase in the circulating levels of several different proteins. For example, one may observe tubular proteinuria consisting of low molecular weight proteins (less than 25 kD). Such proteinuria usually reflects a systemic disease with overproduction of small peptide fragments that are filtered and may cause tubular damage (such as beta 2-microglobulin, immunoglobulin light chains, and polypeptides derived from the breakdown of albumin). In addition, interference with proximal tubular reabsorption, due to tubulointerstitial diseases or genetic mutations, or overproduction of immunoglobulins, such as occurs in myeloma, can lead to increased excretion of these smaller proteins.[16,17] This chapter will focus on proteinuria in which albumin is the major portion of the excreted urinary protein. Urine albumin excretion less than 30 mg/day is considered normal. Urinary albumin excretion more than 30 mg/day and less than 300 mg/day is called microalbuminuria. Urine albumin excretion greater than 300 mg/day is called macroalbuminuria.[18]

Electron microscopic studies in the 1960s by Farquhar demonstrated that in intact glomeruli only about 0.06% of plasma albumin is filtered, implying that the glomerular filter is capable of retaining macromolecules in the circulation, while allowing a large hydraulic conductivity.[19,20] While tubular reabsorption of albumin may determine whether or not albuminuria finally develops, dysfunction of the glomerular filtration barrier is

assumed to play the key role in initiating the development of albuminuria.

Glomerular Endothelium

The first part of the glomerular barrier that interacts with the flowing blood is the glomerular endothelium (Figure 15.1). The endothelium is highly fenestrated. Its pores are estimated to be around 60–80 nm in diameter.[21] These fenestrae do not contain a diaphragm and thus have to be considered real pores.[22] Although such fenestration greatly facilitates the formation of high volumes of ultrafiltrate, it also implies loss of macromolecules such as albumin, as suggested by some intravital microscopy studies.[23] However, as early as 1976 Ryan and Karnovsky demonstrated that under physiological conditions plasma albumin does not penetrate significantly beyond the endothelial layer of the glomerular capillary wall.[24]

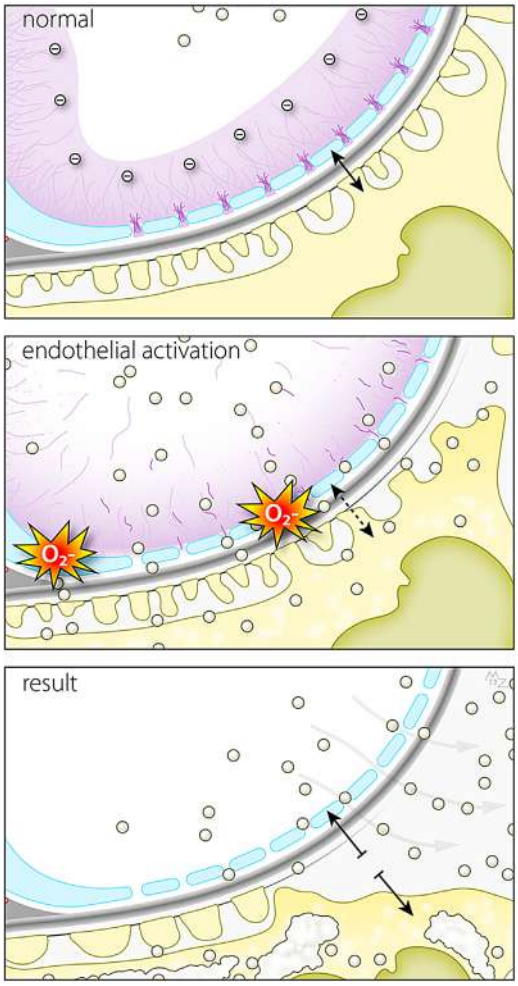


FIGURE 15.1 Proposed mechanism for the development of albuminuria in the setting of endothelial dysfunction and endothelial activation. The top panel shows the normal situation with a negatively charged glycocalyx. The middle panel shows on endothelial cell activation, through redox-sensitive signaling mechanisms, the endothelial glycocalyx is shed and albumin can pass the endothelial layer. Podocytes are subsequently exposed to modified albumin and the normal podocyte-endothelial signaling is disturbed. The lower panel shows podocytes take up albumin and undergo transformational changes that may result in podocyte effacement and podocyte drop-off.

In vivo, the endothelium is covered with a polysaccharide protein gel-like structure, the glycocalyx. This layer actively binds plasma proteins and growth factors and is referred to as the endothelial surface layer (ESL). The composition and biological activity of this surface layer differs in an organ-specific manner. The main constituents of the ESL are protein cores, typically syndecans, with large heparan sulfate side chains (about 60%) or chondroitin sulfate (about 15%).[25] The combination of negatively charged sulfates and the mesh-like structure of the less charged hyaluronan has been proposed to act as a charge-selective barrier against albumin filtration through the fenestrae.[26] Quantitative electron microscopy demonstrated that this glycocalyx acts as an almost perfect barrier against albumin filtration. This finding confirmed those of previous studies: no albumin can pass through the glomerular endothelium unless the glycocalyx is disrupted.[27] Studies in humans and animals have shown that kidney disease is associated with glycocalyx degradation.[28] Sustained endothelial activation, such as accompanies inflammation, results in increased activity of enzymes that degrade the glycocalyx. This direct link between endothelial function and glycocalyx properties may also explain, at least in part, the relationship between cardiovascular risk factors and albuminuria.

Mesangial Cells

Other determinants of the glomerular filtration barrier are the mesangial cells, which are contractile cells that constitute the central stalk of the glomerulus (Figure 15.2). On the capillary lumen side, mesangial cells are in direct contact with the glomerular endothelium without an intervening basement membrane, as one typically can observe with pericytes. Mesangial cells are considered to function as specialized pericytes and are consequently essential to stabilize glomerular endothelial function. The importance of the mesangium for function of the glomerular filtration barrier is shown by experiments where the mesangium is injured by toxins or antibodies.[29] The resulting mesangiolysis invariably results in endothelial injury and proteinuria. In the case of primary endothelial injury, widening of the subendothelial space and deposition of proteinaceous material precedes mesangiolytic changes. In the case of repetitive endothelial injury, this process may

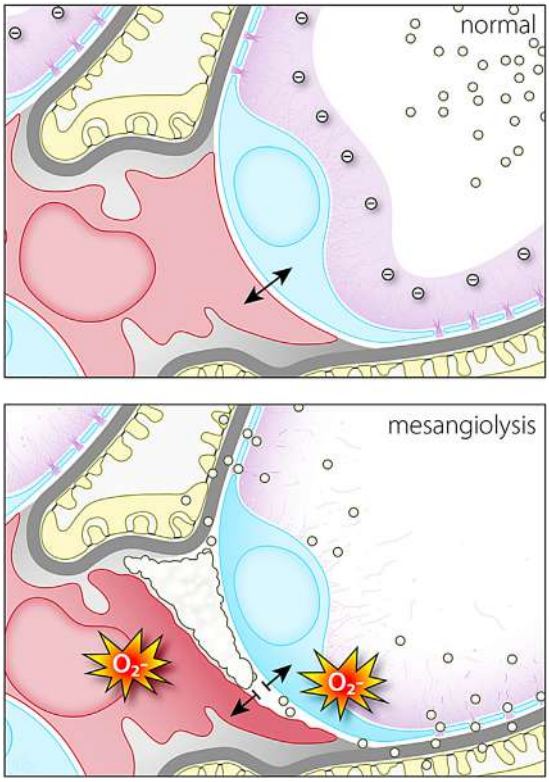


FIGURE 15.2 The proposed mechanism of how endothelial function in diabetes and hypertension may lead to mesangial lesions. The top panel shows the normal situation. Endothelial cells and mesangial cells are in close contact. Mesangial cells function as pericytes for the glomerular endothelium. On endothelial activation, this signaling is disturbed and subendothelial protein deposits may develop. This may result in mesangiolysis and subsequent development of nodular lesions (lower panel).

lead to the development of lamellated mesangial nodules. These phenomena typically can be observed in disease that primarily affects the endothelium, such as diabetes mellitus (Kimmelstiel–Wilson lesion) and thrombotic microangiopathy.

Glomerular Basement Membrane

The glomerular basement membrane (GBM) is the next critical component of the glomerular filtration barrier. It provides a scaffold that supports the physiological function of the glomerular endothelium and podocytes. Severe structural abnormalities of the GBM result in enhanced albumin leakage. Under normal conditions, the GBM probably allows for diffusive albumin transport and does not constitute a major charge barrier. The hydraulic conductance of the GBM accounts, however, for most of the fluid restriction of the intact glomerular barrier.[30] The GBM should therefore be considered an integral and essential component of the glomerular filtration barrier.

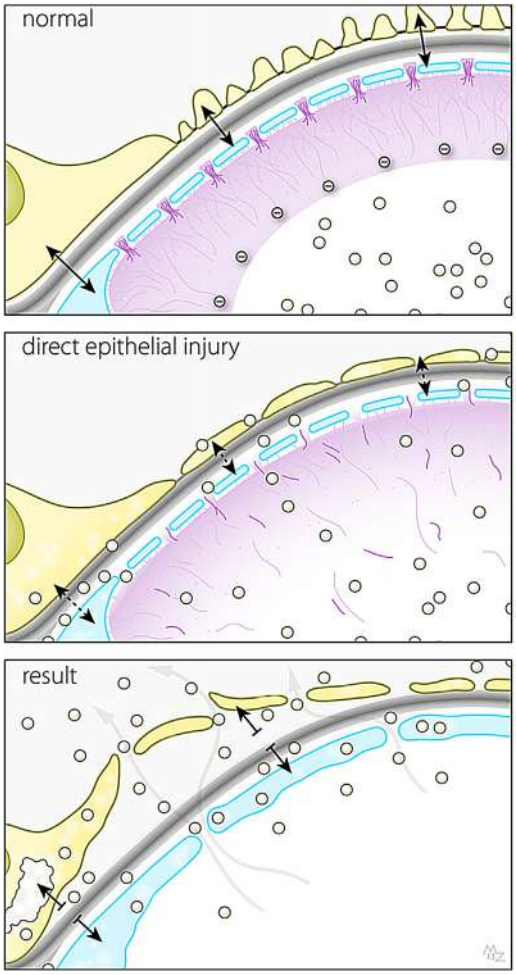


FIGURE 15.3 Proposed mechanisms by which primary epithelial injury leads to proteinuria. Genetic mutations of proteins that are required for podocyte function or direct antibody-mediated injury of podocytes may lead to podocyte effacement and dysfunction of the normal signaling between podocytes and endothelium. Consequently, the endothelium loses its highly specialized phenotype with fenestrations and the covering endothelial surface layer, the glycocalyx. This will result in albumin leakage through endothelium and disturbed slit diaphragm function. Together this results in loss of glomerular integrity (lower panel).

Podocytes

Finally, the glomerular filtration barrier consists of podocytes (Figure 15.3). There are at least two different mechanisms by which podocytes can become involved in, and contribute to, the development and extent of albuminuria. Haraldsson and Deen showed elegantly that the most selective part of a multilayered passive filter cannot be in the last layer (that is, the slit diaphragm), because retention and accumulation of albumin would occur within the filter immediately in front of the slit diaphragm and lead to clogging.[31] As we argued before, the endothelium appears to act as the primary filtration barrier. On endothelial activation,

albumin starts to leak through the GBM, and the podocytes are subsequently exposed to albumin. Interestingly, podocytes are equipped with a megalin-cubilin system,[32] as well as scavenger receptors such as the receptor for advanced glycation end products,[33] suggesting that podocytes may endocytose albumin. In the case of diabetes mellitus, podocytes may also be exposed to chemically modified and glycated albumin. Blocking uptake by these scavenger receptors reduces podocyte injury.

Experimental data suggest that endocytosed albumin induces a mesenchymal transformation in podocytes, with loss of slit diaphragm proteins and induction of desmin.[34,35] From this perspective, changes in podocyte structure can be regarded as a response to injury. Secondly, elegant murine studies have unambiguously demonstrated that normal podocyte function is required for the integrity of the glomerular filtration barrier. Podocyte-specific deletions of genes that control its phenotype lead to loss of the glomerular endothelial phenotype and the development of proteinuria. This has been best demonstrated for the paracrine regulation of components of the vascular endothelial growth factor (VEGF) axis by podocytes. Such gene deletion not only results in podocyte effacement but also in the disappearance of glomerular endothelial fenestration.[36,37] This is clinically exemplified by preeclampsia, a severe proteinuric kidney disease that occurs during pregnancy, where a circulating soluble form of VEGF receptor 1 (sFlt-1, also known as VEGFR-1), scavenges and neutralizes VEGF in the vasculature of the mother. sFlt-1 is secreted from the placenta and binds podocyte-derived VEGF at the glomerular filtration barrier, resulting in the development of albuminuria, severe endothelial damage, and hypertension.[38] Therefore, primary injury of podocytes, either by genetic mutations or immunological injury, results in severe derangement of the integrity of the glomerular filter and the development of macroalbuminuria.

Reabsorption of Albumin

Ultrafiltered albumin, whatever the total amount in the lumen of the initial proximal tubule under physiologic conditions may be, is reabsorbed because normal urine is virtually free of albumin. Albumin reabsorption takes place in the proximal tubule *via* receptor-mediated endocytosis. Two receptors, cubilin and megalin, have been identified as involved in albumin uptake. Under normal circumstances, the tubular concentration of albumin therefore is below the level that saturates this retrieval system. This means that even if some albumin passes through the glomerular filter, only very little albumin is excreted in the urine.

Genetics

With the increased clinical accessibility to whole exome sequencing, more genetic variants are being discovered that may render the glomerular filtration barrier susceptible to injury. One of the most striking examples is the presence of APOL1 gene variants in the African-American population. While evolutionary advantageous to resist trypanosomiasis, the presence of variants is also associated with podocytes more susceptible to injury, such as high blood pressure, perhaps explaining the strong association between blood pressure and proteinuria in this population.[39]

ALBUMINURIA LEVEL PREDICTS RENAL OUTCOMES

In general, the level of albuminuria predicts renal functional loss over time. The higher the concentration of albumin in the urine, the larger the chance of progressive renal functional loss. This is a consistent finding in various populations and diseases. The relationship between albuminuria and the incidence of end-stage renal disease (ESRD) is shown in Figure 15.4. The risk of ESRD starts to increase when the urinary albumin concentration is within the "normal" range. The incidence of ESRD progressively increases with higher urinary albumin concentration in the microalbuminuric or macroalbuminuric range. The association between albuminuria and the development of ESRD runs in parallel in different populations with different conditions (general

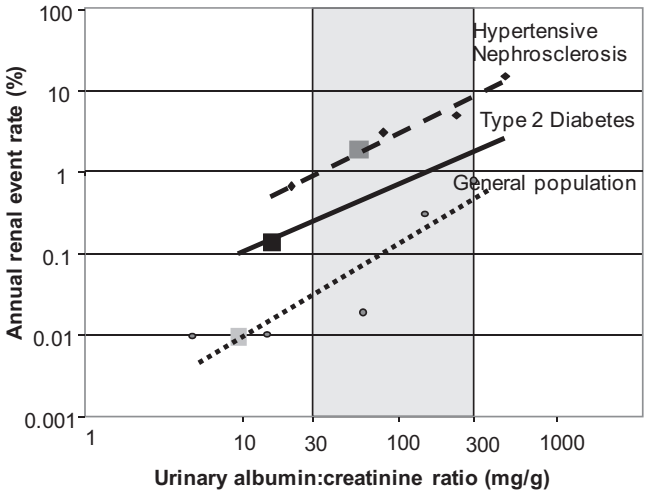


FIGURE 15.4 Level of urine albumin excretion predicts long-term renal function loss (end-stage renal disease (ESRD)). The relation (slope) between the albuminuria level and outcome (ESRD) is very similar for all different studied conditions. However, the level of risk varies per condition. *Adapted with permission from American Journal Nephrology.*[81]

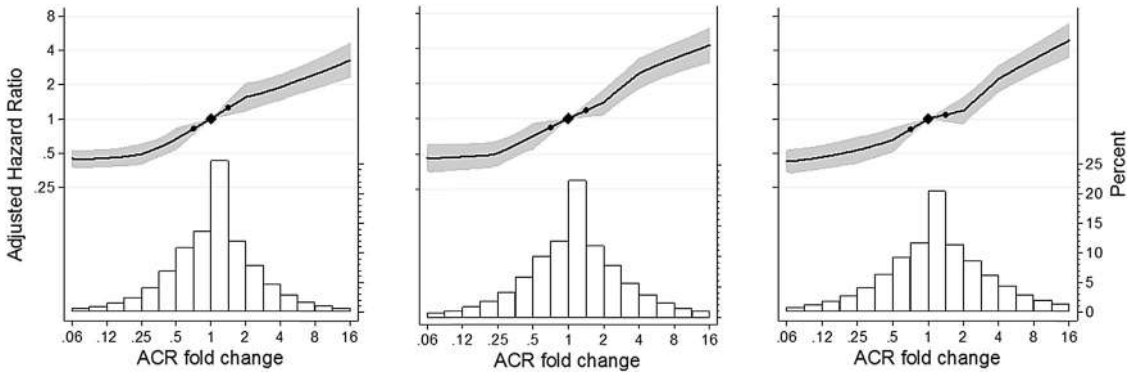


FIGURE 15.5 Adjusted hazard ratio for end-stage renal disease and population distribution of change in albuminuria evaluated over 1 year (a), 2 years (b), and 3 years (c). *Black circles* denote −30% and +43% (equivalent to 30% reduction on log scale) change in albuminuria. *Adapted with permission from Lancet Diabetes and Endocrinology.*

population, hypertension, diabetes) as depicted by the similar slopes of the regression lines in Figure 15.4.

The overall exposure to a certain albumin load over time is an important determinant of progressive renal functional loss, as well as the concentration itself.[40] In other words, a large amount of urinary albumin excretion during a relatively short time frame could well have completely different consequences compared with that associated with low amounts of albumin excretion over a long period of time. This has been illustrated in various studies of patients with glomerular diseases. These studies showed the time-averaged level of proteinuria is a stronger risk predictor of ESRD than the albumin concentration at a single time point. A large Chinese observational study showed patients with immunoglobulin A (IgA) nephropathy with time-averaged urinary protein excretion of more than 1 g/day had a 46-fold increased risk compared with patients with a time-averaged urinary protein excretion of 0.5 g/day.[41] In contrast, when the level of proteinuria at entry into the study was considered, more than 1.0 g/day proteinuria conferred a 4.5-fold increased ESRD risk. Similar findings were reported in patients with IgA nephropathies and diabetic kidney disease.[42,43] Thus, in certain conditions, massive amounts of albumin may pass the glomerulus. If this persists for a short period of time, it does not directly induce visible damage. However, if remission does not occur in a relatively short period of time (spontaneously or through therapy), the exposure to albumin may be sufficient to cause or accelerate renal damage, ultimately leading to the development of ESRD.

CHANGES IN ALBUMINURIA PREDICT CHANGES IN RENAL OUTCOME

Regression or progression of albuminuria frequently occurs, as shown in studies of patients with type 2 diabetes and in the general population.[44,45] Such changes in albuminuria are strongly and consistently associated with the risk of developing ESRD. For example, in a large health care utilization cohort, patients with a fourfold increase in albuminuria showed a threefold higher risk of developing ESRD.[46] These results were confirmed in a meta-analysis of 28 observational studies involving nearly 700,000 individuals.[47] The meta-analysis demonstrated that a 30% decrease in albuminuria over a period of 2 years was independently associated with a 22% reduction of risk of developing ESRD (Figure 15.5). These data imply that albuminuria should be regularly measured to monitor individual renal risk prediction.

SHORT-TERM TREATMENT-INDUCED CHANGE IN ALBUMINURIA INDICATES A TREATMENT-INDUCED CHANGE IN RENAL OUTCOME

According to the third criterion for validation of albuminuria as a target for treatment, the drug effect on albuminuria should correlate with the drug effect on ESRD. To determine whether albuminuria fulfills this criterion, one can analyze within a trial whether a drug-induced change in albuminuria correlates with change in the risk for a renal outcome. Initial relatively small studies demonstrated that the degree of albuminuria reduction in the first weeks of therapy with ACEIs inversely correlated with the degree of renal functional decline during subsequent years of follow-up. The larger the reduction in albuminuria during the first weeks, the slower the rate of subsequent renal functional decline.[48,49] These initial studies were later confirmed in larger clinical trials in different populations, which consistently reported that an early reduction in albuminuria during the first months of treatment with RAAS

inhibitors was independently associated with a lower risk of ESRD.

Is the association between drug-induced changes in albuminuria and renal outcomes only observed with RAAS intervention, since inhibition of angiotensin II protects the kidney and simultaneously reduces albuminuria, without a direct link between albuminuria reduction and renal protection? To answer this one can evaluate studies that used different strategies (drugs or dietary interventions) to lower albuminuria and also monitored renal function. A low protein diet, for example, results in decreased albuminuria, and the magnitude of the reduction in albuminuria correlates with the degree of renoprotection.[50] In addition, glucagon-like peptide 1 (GLP-1) receptor agonists and sodium-glucose transporter 2 inhibitors, both relatively novel oral glucose-lowering agents, have been shown to decrease albuminuria in patients with type 1 and type 2 diabetes.[51–54] Large cardiovascular outcome trials with these drugs have furthermore demonstrated that they slow the progression of renal functional decline. *Post hoc* analyses from these trials demonstrated that the degree of albuminuria reduction is associated with the degree of renal and cardiovascular risk reduction.[55–58] Finally, some statins appear to decrease albuminuria, which seems to be associated with less renal functional decline.[59]

Although these data point to a consistent association between albuminuria reduction and long-term renal protection, independent of the intervention that is used to lower albuminuria, most cited studies are either nonrandomized/open label or *post hoc* analyses of randomized/blinded studies, which are prone to bias. The bias arises from the possibility that patients who show a clear albuminuria response may be a specific population with a lower renal risk.

To address this type of bias, one should analyze multiple randomized controlled trials and correlate the effect of the intervention on albuminuria with its effect on hard renal endpoints across all trials. Such a "trial-level" approach has been recently conducted. A meta-analysis involving 41 studies, including nearly 30,000 individuals and 7 different types of interventions, demonstrated that each 30% reduction in albuminuria during the first 6 months of treatment with these interventions was associated with a 27% lower hazard for the clinical renal endpoint during a median follow-up of 3.4 years (Figure 15.6).[60] Results were consistent when either RAAS inhibitor or non-RAAS inhibitor studies were assessed. This study also reported that in patients with microalbuminuria or macroalbuminuria, an approximately 25% reduction in albuminuria is required to have high confidence that the drug will reduce the risk of a clinical renal endpoint. These data strengthen the notion that albuminuria is an independent target of renoprotective therapy. Most studies to date are not designed to establish that targeting of albuminuria results in additional renoprotection. To prove that targeting of albuminuria confers renal protection, one would need to randomize for the albuminuria response or design a trial to target albuminuria itself. The latter has been done in the ROAD study in nondiabetic patients. Indeed when one aims to achieve a maximal albuminuria response vs. a maximal blood pressure response, the targeting of albuminuria is associated with markedly better renal survival.[61]

The currently available interventions that lower albuminuria are registered for other indications. For

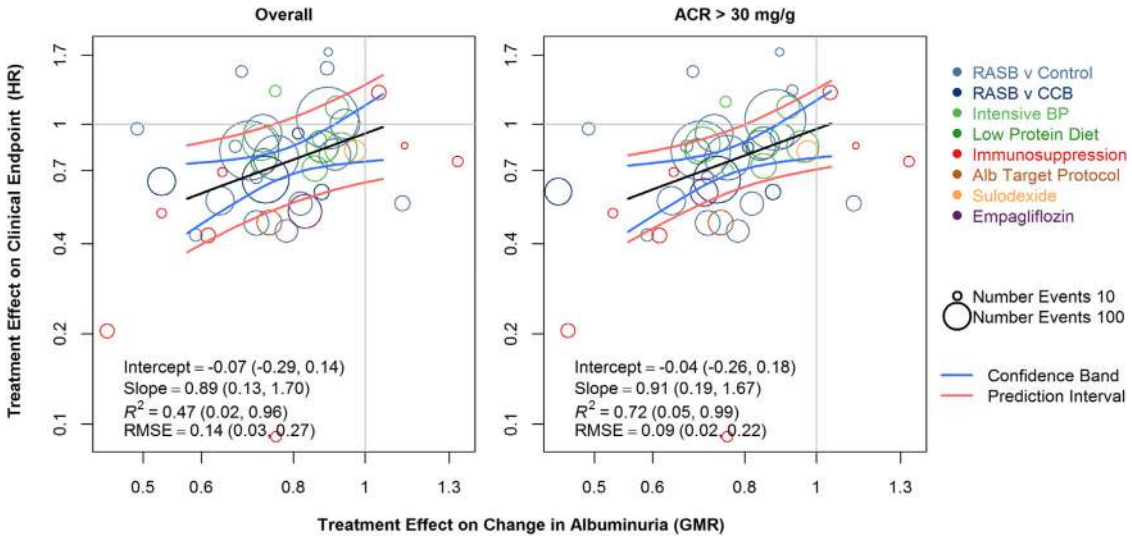


FIGURE 15.6 Meta-analysis of clinical trials showing the association between treatment effects on change in albuminuria and treatment effects on the clinical endpoint. *Adapted with permission from Lancet Diabetes and Endocrinology.*

example, ACEIs are indicated for hypertension and GLP1-RA and SGLT-2 inhibitors are indicated for treatment of hyperglycemia. The albuminuria-lowering properties of these drugs are unintended or off-target effects and are not the only off-target effects. RAAS inhibitors also increase S[K] and decrease hemoglobin levels. SGLT-2 inhibitors increase S[P] and FGF-23.[62] These effects may also determine long-term renal prognosis: higher S[K], S[P], and FGF-23 and low hemoglobin concentration are associated with increased renal risk. The balance of these positive (those leading to protection) and negative (those inducing harm) surrogate effects determine the ultimate efficacy of a drug on renal outcome.[63] This may also explain why some trials failed to demonstrate a reduction in renal risk with the new intervention despite a reduction in albuminuria. For example, clinical trials with dual RAAS intervention showed significant increases in the incidence of hyperkalemia and acute kidney injury during dual RAAS blockade, which may have increased renal risk and outweighed the positive effects of blood pressure and albuminuria lowering. Thus, a drug effect on a single target such as albuminuria should not be evaluated in isolation but considered in the context of all other off-target surrogate effects as well.[63]

OPTIMIZE CONDITIONS IN ALBUMINURIA RESPONSE

If one accepts that albuminuria is a separate target for treatment and one accepts that the risk relationship between albuminuria and renal outcomes is linear, with no lower threshold below which the risk does not decrease, one should pursue the lowest level of albuminuria for each individual. As mentioned, RAAS inhibition is currently the mainstay of therapy to decrease albuminuria. However, the albuminuria response to ACEI and ARB therapy is highly variable, ranging from no response (or even increased albuminuria) to as much as 90% reduction.[64] What options are available to further decrease albuminuria beyond RAAS inhibition? Several possibilities exist. First, the response to RAAS inhibition can be enhanced by optimizing extracellular volume control through either dietary sodium restriction or concomitant diuretic therapy.[65–67] Analysis of long-term follow-up studies suggests that dietary sodium restriction also enhances the long-term effect of RAAS on hard renal and cardiovascular outcomes, highlighting the potential health gain of widespread implementation of reducing dietary sodium consumption.[68,69]

Several drugs are in development that target albuminuria as a means to reduce renal risk beyond RAAS blockade. These drugs are mainly directed toward reducing the renal/vascular "leak" of albumin and or reducing the inflammatory sequelae of the albumin leak. Endothelin receptor antagonists (ERAs) have emerged as potent drugs which decrease albuminuria and reduce renal inflammation.[70–72] Despite potent albuminuria-lowering effects, a trial in patients with type 2 diabetes and nephropathy with the relatively nonselective ERA avosentan was prematurely terminated because of excess congestive heart failure and mortality. The high number of congestive heart failure events may be due to the high doses of avosentan used, which resulted in significant sodium and fluid retention. Newer ERAs, such as sitaxsentan and atrasentan, appear to be more specific for the endothelin A receptor, theoretically rendering them less prone to inducing fluid retention, edema, and heart failure, although caution in interpreting results remains required.[71,73] A study in 211 patients with type 2 diabetes and nephropathy showed that the ERA atrasentan at the low dose of 0.75 mg/day when added to RAAS blockade decreased albuminuria by 35%.[74] A long-term clinical trial (SONAR trial) with atrasentan at a dose of 0.75 mg/day in patients with type 2 diabetes and nephropathy was recently finished. This trial used a unique enrichment design to enhance the selection of patients most likely to benefit.[75] 2648 patients were randomly assigned to atrasentan 0.75 mg orally per day or placebo with median follow-up of 2.2 years. Atrasentan significantly reduced the risk of renal events with no differences seen in hospital admission for heart failure or death.

Novel antiinflammatory drugs decrease albuminuria in various relatively short-term studies.[77–79] The mechanism of the albuminuria-lowering effects of these agents are not completely understood, but they may exert their potential renal protective effects through albuminuria lowering, as well as through their specific antiinflammatory effects. Monocyte chemoattractant protein-1 (MCP-1), a potent cytokine, plays a key role in initiating and sustaining chronic inflammation in renal tissue. Inhibition of MCP-1 or its CCL2 receptor decreases albuminuria in patients with type 2 diabetes and macroalbuminuria.[77,78] Inhibition of the proinflammatory JAK-STAT pathway offers another therapeutic avenue to decrease albuminuria. In a small phase 2 study involving patients with type 2 diabetes and macroalbuminuria, baricitinib, indicated for the treatment of rheumatoid arthritis, decreased albuminuria by 41%.[79] This effect was accompanied by reduction in various proinflammatory biomarkers. Finally, vascular adhesion protein-1 (VAP-1) emerged as another proinflammatory mediator, implicated in various pathophysiological processes that involve oxidative stress and inflammation. VAP-1 inhibition with a potent orally active inhibitor has been shown to be effective in reducing albuminuria and may represent another therapeutic option to slow progression of renal disease.[80]

CONCLUSIONS

A growing body of evidence demonstrates that albuminuria can be considered a separate target for therapy. Emerging experimental data illustrate the importance of the glycocalyx in preventing albumin leakage by glomeruli. When increased amounts of albumin penetrate the subglomerular space, compensatory tubular reabsorption and the accompanying inflammatory responses may further contribute to the structural interstitial damage that has been associated with albuminuria. This may further aggravate progressive renal functional loss. Numerous large clinical studies showed that the level of albuminuria is associated with ultimate renal outcomes. Clinical trial analyses consistently show that drug-induced changes in albuminuria correlate with the long-term drug effects on renal outcomes. This association appears to be independent of the mechanism of action of the drug, and consistent in populations with different types of CKD. Collectively, these studies provide evidence that albuminuria can be viewed as a separate target for therapy.

Abbreviations of Clinical Trial Acronyms

AASK African-American Study of Kidney Diseases
ALTITUDE The Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints
ASCEND Avosentan on time to doubling of Serum Creatinine, ENd stage renal disease or Death
PREVEND Prevention of REnal and Vascular ENdstage Disease
RENAAL Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
ROAD Renoprotection of Optimal Antiproteinuric Doses
SONAR Study Of diabetic Nephropathy with AtRasentan

References

1. Collins AJ, Foley RN, Herzog C, Chavers B, Gilbertson D, Herzog C, Ishani A, Johansen K, Kasiske B, Kutner N, Liu J, St Peter W, Ding S, Guo H, Kats A, Lamb K, Li S, Li S, Roberts T, Skeans M, Snyder J, Solid C, Thompson B, Weinhandl E, Xiong H, Yusuf A, Zaun D, Arko C, Chen SC, Daniels F, Ebben J, Frazier E, Hanzlik C, Johnson R, Sheets D, Wang X, Forrest B, Constantini E, Everson S, Eggers P, Agodoa L. US renal data system 2012 annual data report. *Am J Kidney Dis* 2013;**61**(A7):e1−476.
2. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int* 2011;**80**:17−28.
3. Cotugno D. Sic etiam urina inventa particeps coaguli. *De Ischiade Nervosa* 1970:28−9.
4. Bright R. Reports of medical cases selected with a view to illustrating the symptoms and cure of diseases by a reference to morbid anatomy. In: Greene L, editor; 1827. London, UK.
5. Gansevoort RT, Ritz E. Hermann Senator and albuminuria–forgotten pioneering work in the 19th century. *Nephrol Dial Transplant* 2009;**24**:1057−62.
6. Senator H. *Die albuminuria in gesunden und kranken Zustande*. 1882.
7. Williams PS, Fass G, Bone JM. Renal pathology and proteinuria determine progression in untreated mild/moderate chronic renal failure. *Q J Med* 1988;**67**:343−54.
8. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* 1982;**1**:1430−2.
9. Svendsen PA, Oxenboll B, Christiansen JS. Microalbuminuria in diabetic patients–a longitudinal study. *Acta Endocrinol Suppl* 1981; **242**:53−4.
10. Mogensen CE, Christensen CK. Predicting diabetic nephropathy in insulin-dependent patients. *N Engl J Med* 1984;**311**:89−93.
11. Hillege HL, Janssen WM, Bak AA, Diercks GF, Grobbee DE, Crijns HJ, Van Gilst WH, De Zeeuw D, De Jong PE. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J Intern Med* 2001;**249**:519−26.
12. de Zeeuw D. Albuminuria: a target for treatment of type 2 diabetic nephropathy. *Semin Nephrol* 2007;**27**:172−81.
13. Stehouwer CD, Smulders YM. Microalbuminuria and risk for cardiovascular disease: analysis of potential mechanisms. *J Am Soc Nephrol* 2006;**17**:2106−11.
14. Christensen EI, Verroust PJ, Nielsen R. Receptor-mediated endocytosis in renal proximal tubule. *Pflügers Archiv* 2009;**458**:1039−48.
15. Maack T, Park CH, Camargo MJF. Renal filtration, transport and metabolism of proteins. In: Seldin DW, Giebisch G, editors. *The kidney*. New York: Raven Press; 1992. p. 3005−38.
16. Amer H, Lieske JC, Rule AD, Kremers WK, Larson TS, Franco Palacios CR, Stegall MD, Cosio FG. Urine high and low molecular weight proteins one-year post-kidney transplant: relationship to histology and graft survival. *Am J Transplant* 2013;**13**:676−84.
17. Sanders PW. Light chain-mediated tubulopathies. *Contrib Nephrol* 2011;**169**:262−9.
18. National Kidney F. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**:S1−266.
19. Farquhar MG, Wissig SL, Palade GE. Glomerular permeability. I. Ferritin transfer across the normal glomerular capillary wall. *J Exp Med* 1961;**113**:47−66.
20. Farquhar MG, Palade GE. Glomerular permeability. II. Ferritin transfer across the glomerular capillary wall in nephrotic rats. *J Exp Med* 1961;**114**:699−716.
21. Deen WM, Lazzara MJ, Myers BD. Structural determinants of glomerular permeability. *Am J Physiol Renal Physiol* 2001;**281**: F579−96.
22. Lea PJ, Silverman M, Hegele R, Hollenberg MJ. Tridimensional ultrastructure of glomerular capillary endothelium revealed by high-resolution scanning electron microscopy. *Microvasc Res* 1989;**38**: 296−308.
23. Comper WD, Russo LM. The glomerular filter: an imperfect barrier is required for perfect renal function. *Curr Opin Nephrol Hypertens* 2009;**18**:336−42.
24. Ryan GB, Karnovsky MJ. Distribution of endogenous albumin in the rat glomerulus: role of hemodynamic factors in glomerular barrier function. *Kidney Int* 1976;**9**:36−45.
25. Weinbaum S, Tarbell JM, Damiano ER. The structure and function of the endothelial glycocalyx layer. *Annu Rev Biomed Eng* 2007;**9**: 121−67.
26. Henry CB, Duling BR. Permeation of the luminal capillary glycocalyx is determined by hyaluronan. *Am J Physiol* 1999;**277**:H508−14.
27. Dane MJ, van den Berg BM, Lee DH, Boels MG, Tiemeier GL, Avramut MC, van Zonneveld AJ, van der Vlag J, Vink H, Rabelink TJ. A microscopic view on the renal endothelial glycocalyx. *Am J Physiol Renal Physiol* 2015;**308**:F956−66.
28. Rabelink TJ, de Zeeuw D. The glycocalyx–linking albuminuria with renal and cardiovascular disease. *Nat Rev Nephrol* 2015;**11**: 667−76.

29. Morita T, Yamamoto T, Churg J. Mesangiolysis: an update. *Am J Kidney Dis* 1998;**31**:559–73.
30. Daniels BS, Hauser EB, Deen WM, Hostetter TH. Glomerular basement membrane: in vitro studies of water and protein permeability. *Am J Physiol* 1992;**262**:F919–26.
31. Haraldsson B, Nystrom J, Deen WM. Properties of the glomerular barrier and mechanisms of proteinuria. *Physiol Rev* 2008;**88**:451–87.
32. Prabakaran T, Christensen EI, Nielsen R, Verroust PJ. Cubilin is expressed in rat and human glomerular podocytes. *Nephrol Dial Transplant* 2012;**27**:3156–9.
33. Guo J, Ananthakrishnan R, Qu W, Lu Y, Reiniger N, Zeng S, Ma W, Rosario R, Yan SF, Ramasamy R, D'Agati V, Schmidt AM. RAGE mediates podocyte injury in adriamycin-induced glomerulosclerosis. *J Am Soc Nephrol* 2008;**19**:961–72.
34. Dane MJ, van den Berg BM, Avramut MC, Faas FG, van der Vlag J, Rops AL, Ravelli RB, Koster BJ, van Zonneveld AJ, Vink H, Rabelink TJ. Glomerular endothelial surface layer acts as a barrier against albumin filtration. *Am J Pathol* 2013;**182**:1532–40.
35. Morigi M, Buelli S, Angioletti S, Zanchi C, Longaretti L, Zoja C, Galbusera M, Gastoldi S, Mundel P, Remuzzi G, Benigni A. In response to protein load podocytes reorganize cytoskeleton and modulate endothelin-1 gene: implication for permselective dysfunction of chronic nephropathies. *Am J Pathol* 2005;**166**: 1309–20.
36. Eremina V, Sood M, Haigh J, Nagy A, Lajoie G, Ferrara N, Gerber HP, Kikkawa Y, Miner JH, Quaggin SE. Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases. *J Clin Investig* 2003;**111**:707–16.
37. Jin J, Sison K, Li C, Tian R, Wnuk M, Sung HK, Jeansson M, Zhang C, Tucholska M, Jones N, Kerjaschki D, Shibuya M, Fantus IG, Nagy A, Gerber HP, Ferrara N, Pawson T, Quaggin SE. Soluble FLT1 binds lipid microdomains in podocytes to control cell morphology and glomerular barrier function. *Cell* 2012;**151**:384–99.
38. Levick JR, Michel CC. Microvascular fluid exchange and the revised Starling principle. *Cardiovasc Res* 2010;**87**:198–210.
39. Beckerman P, Susztak K. APOL1: the balance imposed by infection, selection, and kidney disease. *Trends Mol Med* 2018;**24**:682–95.
40. Cattran DC, Pei Y, Greenwood CM, Ponticelli C, Passerini P, Honkanen E. Validation of a predictive model of idiopathic membranous nephropathy: its clinical and research implications. *Kidney Int* 1997;**51**:901–7.
41. Le W, Liang S, Hu Y, Deng K, Bao H, Zeng C, Liu Z. Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population. *Nephrol Dial Transplant* 2012;**27**:1479–85.
42. Reich HN, Troyanov S, Scholey JW, Cattran DC. Remission of proteinuria improves prognosis in IgA nephropathy. *J Am Soc Nephrol* 2007;**18**:3177–83.
43. Hebert LA, Bain RP, Verme D, Cattran D, Whittier FC, Tolchin N, Rohde RD, Lewis EJ. Remission of nephrotic range proteinuria in type I diabetes. Collaborative Study Group. *Kidney Int* 1994;**46**: 1688–93.
44. Brantsma AH, Atthobari J, Bakker SJ, de Zeeuw D, de Jong PE, Gansevoort RT. What predicts progression and regression of urinary albumin excretion in the nondiabetic population? *J Am Soc Nephrol* 2007;**18**:637–45.
45. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int* 2003;**63**:225–32.
46. Carrero JJ, Grams ME, Sang Y, Arnlov J, Gasparini A, Matsushita K, Qureshi AR, Evans M, Barany P, Lindholm B, Ballew SH, Levey AS, Gansevoort RT, Elinder CG, Coresh J. Albuminuria changes are associated with subsequent risk of end-stage renal disease and mortality. *Kidney Int* 2017;**91**:244–51.
47. Coresh J, Heerspink HJ, Sang Y, Matsushita K, Arnlov J, Astor BC. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual-level consortium meta-analysis. *Lancet Diabetes Endocrinol* 2019;**7**(2):115–27.
48. Rossing P, Hommel E, Smidt UM, Parving HH. Reduction in albuminuria predicts a beneficial effect on diminishing the progression of human diabetic nephropathy during antihypertensive treatment. *Diabetologia* 1994;**37**:511–6.
49. Apperloo AJ, de Zeeuw D, de Jong PE. Short-term antiproteinuric response to antihypertensive treatment predicts long-term GFR decline in patients with non-diabetic renal disease. *Kidney Int Suppl* 1994;**45**:S174–8.
50. Levey AS, Greene T, Beck GJ, Caggiula AW, Kusek JW, Hunsicker LG, Klahr S. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? Modification of Diet in Renal Disease Study group. *J Am Soc Nephrol* 1999;**10**:2426–39.
51. Petrykiv SI, Laverman GD, Zeeuw D, Heerspink HJ. The albuminuria lowering response to dapagliflozin is variable and reproducible between individual patients. *Diabetes Obes Metab* 2017;**19**(10): 1363–70.
52. Cherney DZI, Zinman B, Inzucchi SE, Koitka-Weber A, Mattheus M, von Eynatten M, Wanner C. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2017;**5**:610–21.
53. von Scholten BJ, Persson F, Rosenlund S, Hovind P, Faber J, Hansen TW, Rossing P. The effect of liraglutide on renal function: a randomized clinical trial. *Diabetes Obes Metab* 2017;**19**: 239–47.
54. Muskiet MHA, Tonneijck L, Huang Y, Liu M, Saremi A, Heerspink HJL, van Raalte DH. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2018;**6**:859–69.
55. Wanner C, Lachin JM, Inzucchi SE, Fitchett D, Mattheus M, George JT, Woerle HJ, Broedl UC, von Eynatten M, Zinman B, investigators E-RO. Empagliflozin and clinical outcomes in patients with type 2 diabetes, established cardiovascular disease and chronic kidney disease. *Circulation* 2018;**137**(2):119–29.
56. Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Erondu N, Shaw W, Barrett TD, Weidner-Wells M, Deng H, Matthews DR, Neal B. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS program randomised clinical trials. *Lancet Diabetes Endocrinol* 2018;**6**:691–704.
57. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS, Investigators D-T. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**(4):347–57.
58. Mann JFE, Orsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, Tornoe K, Zinman B, Buse JB, Committee LS, Investigators. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017;**377**:839–48.
59. de Zeeuw D, Anzalone D, Cain V, Cressman M, Molitoris B, Monyak J, Parving HH. *Different renal protective effects of atorvastatin and rosuvastatin in patients with proteinuric diabetic and non-diabetic renal disease; result from the PLANET trials*. 2010.
60. Heerspink HJ, Greene T, tighiouart H, Gansevoort R, Coresh J, Simon AW, Chan TM, Hou FF, Lewis JB, Locatelli E, Praga M, Schena P, Levey AS, Inker LA. Change in albuminuria as a surrogate end point for kidney disease progression in clinical trials: a meta-analysis of treatment effects of 41 randomized trials. *Lancet Diabetes Endocrinol* 2019;**7**(2):128–39.

61. Hou FF, Xie D, Zhang X, Chen PY, Zhang WR, Liang M, Guo ZJ, Jiang JP. Renoprotection of Optimal Antiproteinuric Doses (ROAD) Study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. *J Am Soc Nephrol* 2007;**18**: 1889–98.
62. de Jong MA, Petrykiv SI, Laverman GD, van Herwaarden AE, de Zeeuw D, Bakker SJL, Heerspink HJL, de Borst MH. Effects of dapagliflozin on circulating markers of phosphate homeostasis. *Clin J Am Soc Nephrol* 2019;**14**(1):66–73.
63. Heerspink HJ, Grobbee DE, de Zeeuw D. A novel approach for establishing cardiovascular drug efficacy. *Nat Rev Drug Discov* 2014;**13**:942.
64. Laverman GD, de Zeeuw D, Navis G. Between-patient differences in the renal response to renin-angiotensin system intervention: clue to optimising renoprotective therapy? *J Renin-Angiotensin-Aldosterone Syst* 2002;**3**:205–13.
65. Slagman MC, Waanders F, Hemmelder MH, Woittiez AJ, Janssen WM, Lambers Heerspink HJ, Navis G, Laverman GD. Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. *Br Med J* 2011;**343**:d4366.
66. Ekinci EI, Thomas G, Thomas D, Johnson C, Macisaac RJ, Houlihan CA, Finch S, Panagiotopoulos S, O'Callaghan C, Jerums G. Effects of salt supplementation on the albuminuric response to telmisartan with or without hydrochlorothiazide therapy in hypertensive patients with type 2 diabetes are modulated by habitual dietary salt intake. *Diabetes Care* 2009;**32**: 1398–403.
67. Vogt L, Waanders F, Boomsma F, de Zeeuw D, Navis G. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. *J Am Soc Nephrol* 2008;**19**:999–1007.
68. Heerspink HJ, Holtkamp FA, Parving HH, Navis GJ, Lewis JB, Ritz E, de Graeff PA, de Zeeuw D. Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers. *Kidney Int* 2012;**82**:330–7.
69. Vegter S, Perna A, Postma MJ, Navis G, Remuzzi G, Ruggenenti P. Sodium intake, ACE inhibition, and progression to ESRD. *J Am Soc Nephrol* 2011;**23**:165–73.
70. Wenzel RR, Littke T, Kuranoff S, Jurgens C, Bruck H, Ritz E, Philipp T, Mitchell A. Avosentan reduces albumin excretion in diabetics with macroalbuminuria. *J Am Soc Nephrol* 2009;**20**: 655–64.
71. Kohan DE, Pritchett Y, Molitch M, Wen S, Garimella T, Audhya P, Andress DL. Addition of atrasentan to renin-angiotensin system blockade reduces albuminuria in diabetic nephropathy. *J Am Soc Nephrol* 2011;**22**:763–72.
72. Dhaun N, MacIntyre IM, Kerr D, Melville V, Johnston NR, Haughie S, Goddard J, Webb DJ. Selective endothelin-A receptor antagonism reduces proteinuria, blood pressure, and arterial stiffness in chronic proteinuric kidney disease. *Hypertension* 2011;**57**:772–9.
73. Dhaun N, Melville V, Blackwell S, Talwar DK, Johnston NR, Goddard J, Webb DJ. Endothelin-a receptor antagonism modifies cardiovascular risk factors in CKD. *J Am Soc Nephrol* 2013;**24**:31–6.
74. Heerspink HL, Parving HH, Andress DL, et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. *Lancet* 2019 [Epub ahead of print] PMID: 30995972.
75. Heerspink HJL, Andress DL, Bakris G, Brennan JJ, Correa-Rotter R, Dey J, Hou FF, Kitzman DW, Kohan D, Makino H, McMurray J, Perkovic V, Tobe S, Wigderson M, Parving HH, de Zeeuw D. Rationale and protocol of the Study Of diabetic Nephropathy with AtRasentan (SONAR) trial: a clinical trial design novel to diabetic nephropathy. *Diabetes Obes Metab* 2018;**20**:1369–76.
76. Heerspink HJL, Andress DL, Bakris G, Brennan JJ, Correa-Rotter R, Hou FF, Kitzman DW, Kohan D, Makino H, McMurray J, Perkovic V, Tobe S, Wigderson M, Yi T, Parving HH, de Zeeuw D. Baseline characteristics and enrichment results from the SONAR trial. *Diabetes Obes Metab* 2018;**20**:1829–35.
77. de Zeeuw D, Bekker P, Henkel E, Hasslacher C, Gouni-Berthold I, Mehling H, Potarca A, Tesar V, Heerspink HJ, Schall TJ. The effect of CCR2 inhibitor CCX140-B on residual albuminuria in patients with type 2 diabetes and nephropathy: a randomised trial. *Lancet Diabetes Endocrinol* 2015;**3**:687–96.
78. Menne J, Eulberg D, Beyer D, Baumann M, Saudek F, Valkusz Z, Wiecek A, Haller H, Empaticap Study G. C-C motif-ligand 2 inhibition with emapticap pegol (NOX-E36) in type 2 diabetic patients with albuminuria. *Nephrol Dial Transplant* 2017;**32**:307–15.
79. Tuttle KR, Brosius 3rd FC, Adler SG, Kretzler M, Mehta RL, Tumlin JA, Tanaka Y, Haneda M, Liu J, Silk ME, Cardillo TE, Duffin KL, Haas JV, Macias WL, Nunes FP, Janes JM. JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: results from a phase 2 randomized controlled clinical trial. *Nephrol Dial Transplant* 2018;**33**:1950–9.
80. de Zeeuw D, Renfurm RW, Bakris G, Rossing P, Perkovic V, Hou FF, Nangaku M, Sharma K, Heerspink HJL, Garcia-Hernandez A, Larsson TE. Efficacy of a novel inhibitor of vascular adhesion protein-1 in reducing albuminuria in patients with diabetic kidney disease (ALBUM): a randomised, placebo-controlled, phase 2 trial. *Lancet Diabetes Endocrinol* 2018;**6**:925–33.
81. Lambers Heerspink HJ, de Zeeuw D. Debate: PRO position. Should microalbuminuria ever be considered as a renal endpoint in any clinical trial? *Am J Nephrol* 2010;**31**:458–61. discussion 468.
82. Standards of medical care in diabetes 2013. *Diabetes Care* 2013; **36**(Suppl. 1):S11–63.
83. KDIGO clinical practice guideline for evaluation and management of chronic kidney disease. http://www.kdigo.org/home/guidelines.
84. Standaard Nederlands Huisartsen Genootschap: type 2 diabetes mellitus https://www.nhg.org/standaarden/samenvatting/diabetes-mellitus-type-2.
85. Kidney Disease: Improving Global Outcome (KDIGO) clinical practice guideline for the management of blood pressure in chronic kidney disease. http://www.kdigo.org/home/guidelines/blood-pressure-in-ckd/.
86. Vogt L, Waanders F, Boomsma F, et al. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. *J Am Soc Nephrol* 2008;**19**(5):999–1007.
87. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**(12):861–9.
88. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**(12): 851–60.
89. Perkovic V, Jardine MJ, Neal B, et al. CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019 [Epub ahead of print] PMID: 30990260.

QUESTIONS AND ANSWERS

Question 1

Type 2 diabetes mellitus is diagnosed in your patient. Her blood pressure is 143/81 mm Hg. Her last albuminuria measurement was done 1.5 year ago. What do you do?

A. Base your future steps on the urinary albumin level recorded 1.5 year ago
B. Ask the patient to collect a 24-hour urine for measurement of albumin excretion
C. No further action is required. Albuminuria should only be assessed 6 months after diagnosis of type 2 diabetes
D. Ask your patient to collect a first morning void and measure the albumin:creatinine ratio (ACR)

Answer: D

According to American Diabetes Association (ADA) guidelines, albuminuria should be measured in every patient starting at diagnosis and annually thereafter. 24-hour urinary albumin excretion is the "gold standard" measurement because albumin excretion follows a circadian rhythm. However, as 24-hour urine collections are impractical, an easier alternative is the measurement of the ACR in a first morning void urine. The best answer is D.[82]

Question 2

You decide to ask the patient to collect a first morning void. The lab results show an ACR of 85 mg/g. What do you do?

A. Start treatment with ramipril 10 mg/day
B. Ask the patient to collect another first morning void for confirmation
C. No further action is required as the ACR is below 300 mg/g
D. Start treatment with amlodipine 10 mg/day because the ACR is below 300 mg/g and the systolic blood pressure is above 140 mm Hg

Answer: B

Several guidelines recommend performing a repeat test to confirm the presence of microalbuminuria or macroalbuminuria.[83,84] Answer B is thus correct. However, it should be noted that not all guidelines are in agreement. For example, the ADA guideline does not mention the need for a confirmatory laboratory test. Guidelines do not provide clear recommendations in case the patient is already being treated with ACEI or ARB and a sustained high albuminuria level is present. However, one can consider increasing the dose of the ACEI or ARB, starting diuretic therapy, or recommending decreased dietary sodium intake.[82]

Question 3

A 63-year-old women presents for a routine visit. She has CKD and hypertension. On physical examination, her blood pressure is 139/88 mm Hg and body weight is 72 kg.

The following labs are obtained:

- Hba1c 6.1%
- Total cholesterol 165 mg/dL
- eGFR 46 mL/min/1.73 m^2
- Urinary albumin:creatinine ratio (UACR) 160 mg/g

Her medication consists of hydrochlorothiazide 25 mg/day.

Which of the following is correct?

A. No additional antihypertensive medication is required
B. An ACEI or ARB should be added to control blood pressure and albuminuria
C. A combination of ACEI and ARB should be started as the patient has abnormal albuminuria
D. ACEIs are always preferred over ARBs
E. Hydrochlorothiazide should be discontinued

Answer: B

According the Kidney Disease: Improving Global Outcome (KDIGO) guideline, all patients with nondiabetic kidney disease whose blood pressure is above 130/80 mm Hg should be treated with blood pressure lowering medication.[85] First-line therapies are ACEIs or ARBs. The right answer is thus B. Combination therapy with ACEI and ARBs is not recommended on the basis of the ONTARGET and ALTITUDE trials, which showed no benefit with combination therapy and more adverse events. The guideline does not differentiate between ACEI and ARBs, making Answer D incorrect. Combination of ACEI or ARB with diuretics enhances the effects of the combination vs. the single treatments on both blood pressure lowering and albuminuria lowering.[86]

Question 4

A 45-year-old man has type 2 diabetes mellitus and CKD. You have asked him to collect a first morning void urine for albuminuria measurement. In the past, his urinary albumin levels were always below 30 mg/g, but last month the ACR was 410 mg/g. You have asked the patient to return to your clinic to confirm

this finding. At physical examination, his blood pressure is 138/92 mm Hg and his body weight is 96 kg.

The following labs are obtained:

- Hba1c 7.9%
- Total cholesterol 200 mg/dL
- eGFR 38 mL/min/1.73 m^2
- UACR 680 mg/g

His medications consist of metformin 1500 mg/day, simvastatin 40 mg/day, amlodipine 5 mg/day, and venlafaxine 150 mg/day.

Which of the following is true?

A. No changes in medication are required
B. Any ACEI or ARB should be started
C. Increase the dosage of amlodipine to 10/day
D. Start treatment with atenolol 50 mg/day
E. A patient with type 2 diabetes mellitus and nephropathy should always be treated with an ACEI

Answer: B

According to the KDIGO guideline, all patients with type 2 diabetes mellitus and CKD whose blood pressure is above 130/80 mm Hg with macroalbuminuria should be treated with an ACEI or ARB. The guideline does not differentiate between ACEIs and ARBs, and their effectiveness is likely equivalent. Answer B is therefore the correct answer. Of note, the only two ARBs that have received an indication for the treatment of nephropathy in patients with type 2 diabetes and hypertension are losartan and irbesartan, on the basis of the RENAAL and IDNT trials. Thus, if one follows evidence-based medicine answers, one should start treatment with one of these drugs. Neither increasing the dosage of amlodipine nor starting treatment with atenolol is the best next step.[85,87,88]

Question 5

A 58-year-old man has type 2 diabetes mellitus and CKD. You have asked him to collect a 24-hour urine for measurement of albumin and sodium excretion. In the past, his urinary albumin levels were 900 mg/g (~900 mg/24 h), and you have started treatment with losartan 100 mg/day. Since then, his urinary albumin levels dropped to 600 mg/g. He does not receive other blood pressure-lowering medications. His blood pressure is 141/86 mm Hg.

The following laboratory values are obtained:

- eGFR 33 mL/min/1.73 m^2
- Urinary albumin excretion 630 mg/24 h
- Urinary 24-hour urinary sodium excretion 180 mmol/24 hr

You aim to improve albuminuria control. Which option is preferred?

A. Start treatment with amlodipine 5 mg/day
B. Add an ACEI to the therapeutic regimen
C. Instruct the patient to adhere to a moderately low salt diet of 5–6 g/day
D. Start treatment with atenolol
E. Start treatment with monoxidine

Answer: C

The patient's salt intake (as assessed by 24-hour urinary sodium excretion) is around 10 gram per day. World Health Organization guidelines recommend sodium intake of 5–6 gram of salt per day. Small studies and *post hoc* analyses of randomized controlled trials have shown that dietary sodium restriction and treatment with diuretics potentiate the antialbuminuric effect of ACEIs and ARBs. Thus, although hard evidence is lacking, from a clinical perspective sodium restriction or treatment with diuretics seems to be a rationale choice making Answer C correct.

Question 6

A 63-year-old woman has type 2 diabetes mellitus and CKD. You have asked her to collect a 24-hour urine for measurement of albumin and sodium excretion. In the past, her urinary albumin levels were 400 mg/g, and you started treatment with losartan 100 mg/day. Since then, her urinary albumin levels decreased to 200 mg/g. She also takes hydrochlorothiazide 25 mg/day and adheres to a low sodium diet. Her blood pressure is 135/83 mm Hg.

The following labs are obtained:

- HbA1c 7.3%
- eGFR 48 mL/min/1.73 m^2
- Urinary albumin excretion 630 mg/24 h
- Urinary 24-hour urinary sodium excretion 95 mmol/24 h

You aim to improve albuminuria control. Which option is preferred?

A. Start treatment with a calcium channel blocker
B. Add an ACEI to the therapeutic regimen
C. Start treatment with a sodium-glucose co-transporter inhibitor
D. Start treatment with a GLP-1 receptor agonist

Answer: C

Sodium-glucose co-transporter inhibitors and glucagon-like peptide receptor agonists have been shown to decrease albuminuria in patients with type 2 diabetes. In clinical trials of patients with type 2

diabetes and high cardiovascular risk, SGLT-2 inhibitors also slow progression of renal function decline. A dedicated renal outcome trial with an SGLT-2 inhibitor (canagliflozin) demonstrated a 30% lower risk for developing the primary composite outcome of time to dialysis or kidney transplantation, doubling of S[Cr], and renal or CV death with canaglifozin.[89] Based on this trial, it is expected that SGLT-2 inhibitors will be part of guideline recommended treatment in 2019 or 2020. Therefore, Answer C should be correct.

CHAPTER

16

Protein Energy Metabolism in Chronic Kidney Disease

Manuel T. Velasquez, Sarah C. Andrews, Dominic S. Raj

Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States

Abstract

Chronic kidney disease (CKD) patients with protein energy wasting (PEW) have increased morbidity, mortality, and diminished quality of life. This dysfunctional metabolic state is characterized by anorexia, ineffective utilization of nutrients, and augmented muscle protein catabolism, which leads to loss of lean body mass. A multitude of factors contribute to PEW, including inflammation, oxidative stress, hormonal dysregulation, resistance to the actions of insulin and growth hormone (GH), and metabolic acidosis. These factors trigger muscle breakdown through activation of the ubiquitin-proteasome system, oxidation of branched-chain amino acids, and apoptosis. Several treatments for PEW have been proposed in the KDOQI guidelines, including nutritional goals to maintain protein stores. Potentially relevant treatments that have yielded controversial results so far include aerobic and resistance exercise, treatment with human GH, and bicarbonate supplementation. Other potential treatments requiring additional study for safety and efficacy in humans include ghrelin administration and testosterone treatment. Understanding the etiology of this maladaptive metabolic state is important for the development of new therapies for treatment of PEW. The current pathophysiology of PEW remains elusive, and treatment of PEW in the CKD population remains difficult.

SCOPE OF THE PROBLEM

Protein energy wasting (PEW) is a maladaptive metabolic state, well defined in end-stage renal disease (ESRD) patients. The International Society of Renal Nutrition and Metabolism (ISRNM) expert panel recommends use of the term "protein energy wasting" for loss of body protein mass and fuel reserves in patients with chronic kidney disease (CKD) and ESRD.[1] PEW should be distinguished from malnutrition. The latter is due to inadequate intake of nutrients with intact adaptive metabolic responses. PEW, or its extreme form, cachexia, is a dysfunctional state common in inflammatory conditions, which is resistant to nutritional supplementation.[1,2] PEW occurs in 20–70% of adults treated with dialysis. Its prevalence is affected by type of dialysis, the population studied, and the assessment tool used to estimate nutritional status.[3] Recently, a meta-analysis of Contemporary Observational Studies from the ISRNM reported the prevalence of PEW ranged from 11 to 54% in patients with CKD stages 3–5 and 28–54% in dialysis patients.[4] The prevalence of PEW and inflammatory markers increases with decline in glomerular filtration rate (GFR). Results from the National Health and Nutrition Examination Survey (NHANES) III confirm that renal function is independently associated with PEW.[5] Muscle wasting can also be caused by factors that may or may not be related to kidney disease. Quality of life is significantly affected by PEW, which is associated with increased frailty, decreased mobility, and psychological effects.[6] PEW is caused by a multitude of factors (Figure 16.1 and Table 16.1).

PATHOPHYSIOLOGY OF PEW

Anorexia and Nutrient Insufficiency

Insufficient nutrient intake is an integral component in the development and maintenance of PEW. The pathophysiology of PEW in CKD patients is multifactorial and includes anorexia, accumulation of uremic retention solutes or "toxins," increase in inflammatory cytokines, changes in taste, and disruption of appetite sensing molecules, such as ghrelin and leptin.[7,8] Most studies of

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00016-4

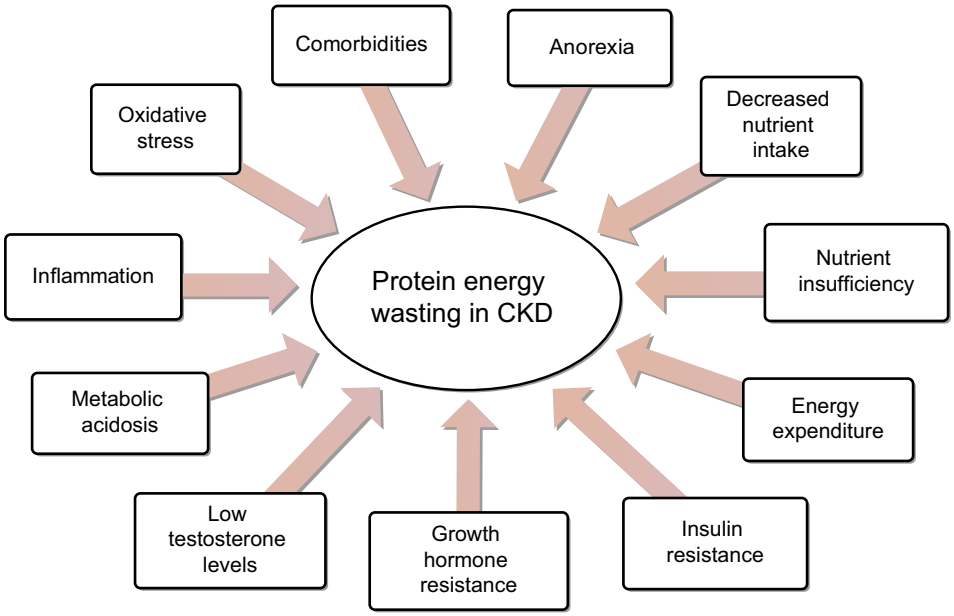


FIGURE 16.1 Pathophysiology of protein energy wasting in chronic kidney disease (CKD).

TABLE 16.1 Etiology of Protein Energy Wasting (PEW) in Chronic Kidney Disease (CKD)

Contributors to PEW	Causes of Contribution to PEW	Organism	References
Anorexia	CKD patients have increased levels of inflammatory cytokines, changes in taste, disruption of appetite sensing molecules, and increased levels of des-acyl ghrelin in the plasma.	Humans	Mak et al. 2012,[7] Bonanni et al. 2011,[8] Kalantar-Zadeh et al. 2004[9]
Decreased nutrient intake	Intraperitoneal injection of uremic plasma ultrafiltrate, urine fraction, and middle molecule fraction (300–2000 daltons) decreased carbohydrate intake.	Rats	Anderstam et al. 1996,[11] Mamoun et al. 1999[12]
	Decreased GFR is associated with spontaneous decrease in energy and protein intake. Individuals with the lowest GFR levels have smallest consumption of food and lowest anthropometric measures.	Humans	Duenhas et al. 2003[13]
Nutrient insufficiency	ESRD patients have gastric hypomotility, impaired gastric myoelectrical activity, and delayed gastric emptying.	Humans	Hirako et al. 2005[16]
	ESRD patients have dysregulation of key gastric hormones including peptide YY and cholecystokinin.	Humans	Mak et al. 2007,[40] Pappas et al. 1985,[38] Aguilera et al. 2003.[183]
Energy expenditure	CKD patients have decreased resting energy expenditure potentially due to loss of kidney function, decreased glucose oxidation, and dysfunctional skeletal muscle energy utilization.	Humans	Cuppari 2010[19]
	ESRD patients have increased resting energy expenditure.	Humans	Neyra et al. 2003,[21] Wang et al. 2004[22]
	Uremic mice have increased levels of resting energy expenditure and uncoupling proteins (UCP-1 and UCP-3).	Mice	Cheung et al. 2007[30]
Insulin resistance	Studies in rats showed reduced phosphorylation of Akt in the IRS/PI3K/Akt pathway. This leads to activation of the	Rats	Bailey et al. 2006[47]

TABLE 16.1 Etiology of Protein Energy Wasting (PEW) in Chronic Kidney Disease (CKD)—cont'd

Contributors to PEW	Causes of Contribution to PEW	Organism	References
	E3 ubiquitin conjugating enzymes, atrogin-1 and MuRF1, and muscle breakdown. Diabetic ESRD patients have enhanced rate of muscle wasting compared with nondiabetic ESRD individuals.	Humans	Pupim et al. 2005[44]
	Mice have increased levels of inflammatory cytokines due to increased glucocorticoid levels and insulin and insulin-like growth factor resistance in muscle.	Mice	Hu 2009[43]
Growth hormone resistance	There are mixed results on levels of GH in CKD patients. Decreased activation of the JAK/STAT pathway leads to decreased IGF-1 expression. Inflammation antagonizes positive effects GH has on protein metabolism in ESRD patients.	Humans	Rabkin et al. 2005,[53] Garibotto et al. 2008[62]
Low testosterone	Men with low testosterone levels and CKD stages 3 through 5 had twofold higher mortality. In men with CKD stages 2 through 4, testosterone levels are an independent predictor of muscle strength and fat-free mass, potentially caused by increased expression of myostatin and altered IGF-1 signaling.	Humans	Cigarran et al. 2013,[65] Haring et al. 2011[67]
Metabolic acidosis	Rats with renal failure and metabolic acidosis had preferential degradation of muscle protein through the ubiquitin-proteasome pathway.	Rats	May et al. 1987[69]
	Metabolic acidosis leads to a decrease in serum levels of essential branched-chain amino acid levels in muscle. Metabolic acidosis also activates ATP-dependent pathway involving ubiquitin and proteasomes.	Humans	Carrero et al. 2013,[68] Mitch 1998[70]
Inflammation	Inflammation indicators were associated with GFR and cystatin C in CRIC Study participants.	Humans	Gupta et al. 2012[78]
	In ESRD patients, IL-6 expression in muscle intensifies muscle protein catabolism and amino acid release that results in acute phase protein synthesis. Inflammation also induces expression of protein catabolism genes in ESRD patients.	Humans	Raj et al. 2008,[84] Raj et al. 2003[85]
	NFκβ pathway activation decreases protein synthesis, inhibits differentiation of myocytes, and decreases MyoD expression.	Humans	Mak et al. 2012,[7] Guttridge 2000[87]
Muscle biology dysfunction	Patients and rats with CKD have increased expression of myostatin, FOXO, atrogin-1, MuRF1, ubiquitin, and the 26SW proteasome subunits as well as decreased expression of IGF-1.	Humans and Rats	Sun et al. 2006,[88] Verzola et al. 2011,[90] Xu et al. 2012[92]
	ESRD patients have increased levels of 14-kDa actin fragment, which is characteristic of muscle degradation.	Humans	Rajan and Mitch 2008[48]
Oxidative stress	Oxidative stress increases inflammation through the NFκβ pathway. Protein structure is modified to resist ubiquitination and breakdown, which leads to increased generation of reactive oxygen species.	Humans	Bonanni et al. 2011,[8] Grune et al. 2003,[101] Dounousi et al. 2006[102]
Comorbidities	Diabetic ESRD patients have higher rates of muscle catabolism and increased atherosclerotic CVD due to increased levels of proinflammatory cytokines. Diabetic ESRD patients also have increased CRP levels and chronic heart failure associated with pathways contributing to PEW.	Humans	Pupim et al. 2005,[44] Stenvinkel 1999,[104] Panichi et al. 2002[105]

Abbreviations: *CKD*, chronic kidney disease; *CRIC*, Chronic Renal Insufficiency Cohort; *CRP*, C-reactive protein; *CVD*, cardiovascular disease; *ESRD*, end-stage renal disease; *FOXO*, forkhead family of transcription factors; *GFR*, glomerular filtration rate; *GH*, growth hormone; *IGF-1*, insulin-like growth factor-1; *IL*, interleukin; *IRS/PI3K/Akt*, insulin receptor signaling/phosphatidylinositol 3-kinase/Akt; *JAK/STAT*, Janus-activated kinase/signal transducers and activator; *MuRF1*, muscle ring finger-1; *NFκβ*, nuclear factor κβ; *UCP*, uncoupling proteins.

PEW have focused on the dialysis population, where anorexia is present in 30–40% of patients, associated with increased mortality, poor quality of life, and an increased inflammatory state with high levels of proinflammatory cytokines.[9] In progressive CKD, increased uremic toxins are associated with nausea, vomiting, and anorexia.[8]

Nutrient insufficiency in CKD may be caused by factors that lead to decreased ingestion of nutrients due to anorexia, as well as inhibition of uptake of nutrients due to changes in gastric motility. HD patients were first noted to have problems with nutrition in a case report from 1960.[10] Uremic toxins influence nutritional absorption in rats after intraperitoneal injection of uremic plasma ultrafiltrate, and uremic toxins inhibit carbohydrate intake.[11,12] In CKD patients, a decrease in estimated glomerular filtration rate (eGFR) was associated with a spontaneous decrease in energy and protein intake.[13] Individuals with the lowest kidney function (GFR $<19.9\ \text{mL/min/1.73 m}^2$) had the smallest consumption of food, as well as the lowest values for body mass index (BMI), triceps skinfold thickness, and mid-arm muscle circumference. Children with CKD have stunted growth, which is present even when GFR levels are as high as $70\ \text{mL/min/1.73 m}^2$, which is associated with an increase in uremic toxins.[14] Growth rates in children were significantly diminished when normal nutritional intake decreased to less than 80% of recommended levels.[15] In addition, studies have shown impairment of gastric motility in patients with CKD. Hirako et al. demonstrated that patients with CKD prior to initiation of dialysis had gastric hypomotility, impaired gastric myoelectrical activity, and delayed gastric emptying.[16] Other factors that can influence nutrient intake in CKD patients include depression, socioeconomic status, and altered mental status.[6]

Energy Balance

Disruption of energy balance contributes to PEW, both through lack of nutritional intake and energy expenditure changes. Individuals with CKD potentially have changes in total energy expenditure through changes in resting energy expenditure (REE), physical activity, and thermoregulation. Contrary to expectation, after adjusting for lean body mass (LBM), ESRD patients treated with dialysis have normal REE.[17] CKD patients have a lower REE compared with individuals with normal kidney function.[18] In CKD, the lower REE can potentially be explained by decreased energy expenditure of the kidney due to loss of function, decreased glucose oxidation, and dysfunctional skeletal muscle energy utilization.[19] Lower REE in CKD is surprising, because chronic diseases such as diabetes, hyperparathyroidism, and increased inflammation lead to higher REE.[19,20] Indeed, a study in nondialysis CKD patients illustrated that increased REE was associated with inflammation.[20]

Not all studies of energy balance in ESRD patients have shown consistent results. Neyra et al. showed ESRD patients have increased REE.[21] Dialysis also affects energy balance. Patients treated with continuous ambulatory PD with higher REE had increased all-cause and cardiovascular mortality.[22] Uncoupling proteins could also play a role in increased REE, with their increased activity leading to increased energy expenditure. Uncoupling protein 1 (UCP-1) and uncoupling protein 3 (UCP-3) release energy in the form of heat *via* thermogenesis in humans and mice. Cheung et al. illustrated that mice with uremia had increased levels of UCP-1 mRNA and protein and UCP-3 protein in brown adipose tissue, which was associated with a 10% increased REE, compared with normal controls.[23]

Hormonal Dysfunction

A variety of hormones, including ghrelin, leptin, peptide YY (PYY), and cholecystokinin (CCK), modulate appetite, nutrient intake, nutritional status, and energy expenditure, which may be involved in PEW in patients with CKD. Neuropeptides function to maintain energy homeostasis by responding to changes in hormone levels that dictate satiety and hunger, such as leptin and ghrelin.[24] Leptin is a hormone secreted from adipocytes that modulates appetite and increases energy expenditure. CKD patients have increased circulating levels of leptin, possibly due to lack of breakdown of the hormone by the kidneys.[25] ESRD patients also have hyperleptinemia due to increased release of the hormone, as demonstrated when visceral adipocytes are exposed to plasma from ESRD patients.[26] Leptin has two concurrent effects within the arcuate nucleus in the hypothalamus that lead to satiety and an increase in energy expenditure. Leptin activates the melanocortin receptor-4 (MC4-R), causing increased energy expenditure and inhibition of food intake. Simultaneously, leptin inhibits the activity of the neuropeptide Y/agouti-related peptide (AgRP) neurons, which prevents the secretion of AgRP, a natural antagonist of MC4-R that stimulates food intake and increases both lean mass and fat mass.[27] Castaneda-Sceppa et al. showed that higher leptin levels were associated with lower muscle mass in patients with stage 3 and 4 CKD.[28] However, further evidence of increased leptin contributing to muscle wasting is lacking in humans. Hyperleptinemia is not associated with worse appetite in dialysis patients.[29]

Mak et al. demonstrated that blocking the activity of leptin using genetic and pharmacological interventions in rats attenuates PEW by decreasing energy expenditure and increasing muscle and fat mass.[30,31] AgRP

administration in CKD mice also normalized protein levels of the inflammatory biomarkers interleukin (IL)-6 and tumor necrosis factor-α (TNF-α), and expression levels of molecules involved in muscle mass turnover, such as myostatin and insulin-like growth factor-1 (IGF-1). Cheung et al. demonstrated that intraperitoneal administration of NBI-12i to uremic mice was associated with increased food intake, weight gain, lower basal metabolic rate, and gains in LBM and fat mass.[30] The oral MC4-R antagonist BL-6020/979 diminished cachexia-like symptoms in a murine C26 adenocarcinoma model, and increased energy intake and decreased energy expenditure in normal mice.[32] Future studies are necessary to evaluate whether MC4-R antagonists could be used as an effective and safe treatment for PEW in clinical settings.

Ghrelin is a peptide hormone released from the stomach that has a number of functions relevant to PEW, including appetite stimulation through orexigenic signaling to the hypothalamus and effects on gastric motility and food intake. Studies of ghrelin in dialysis patients have yielded conflicting results. A report in children with ESRD showed that plasma ghrelin levels were no different in children treated with PD, children receiving conservative treatment, and children of similar BMI with normal kidney function.[33] Pérez-Fontán et al. showed an increase in plasma ghrelin levels in HD and PD patients compared with controls.[34] Another study showed that HD and control patients had normal plasma ghrelin levels, but PD patients had decreased levels of ghrelin.[35]

The type of ghrelin measured in these studies may be a confounding factor, leading to the differences in these reports. There are two major types of ghrelin, with opposite functions. Acylated ghrelin stimulates food intake, whereas des-acyl ghrelin promotes negative energy balance. Des-acyl ghrelin plasma levels are elevated in CKD patients, with higher levels in those patients with worse renal function.[36] Muscaritoli et al. also showed des-acyl levels are higher in HD patients, suggesting that des-acyl ghrelin may contribute to the pathogenesis of anorexia.[37]

PYY is a gut hormone released during feeding, which suppresses gastric motility and appetite. Administration of PYY_{3-36} lowers total daily food intake in humans.[38] PYY and other gastric hormones are dysregulated and are present in higher levels in ESRD patients compared with patients with normal renal function, suggesting that these hormones may be involved in gastric dysregulation and its associated symptoms in CKD patients.[39] Further studies and better assay technologies are needed to determine if these gut hormones are potential targets to develop therapies to improve nutritional intake and appetite in this population.

CCK suppresses energy intake and satiety and slows gastric emptying when released from peripheral and central receptors from the intestine.[40] CCK has synergistic effects with leptin, suppressing food intake after a meal begins. ESRD patients have higher plasma levels of CCK compared with patients with normal renal function. Peripheral administration of CCK has been associated with a decrease in short-term food intake in humans.[41] However, CCK administration does not decrease body weight or influence changes in daily caloric intake due to compensation by eating more frequent meals. Blocking the action of CCK could be a potential way to influence decreased food intake, anorexia, nausea, and vomiting in CKD and ESRD patients.[40]

Insulin Resistance

Insulin resistance contributes to PEW by influencing pathways that control regulation of muscle regeneration and breakdown. In CKD, there are at least two major pathways that can cause insulin resistance in muscles that dysregulates protein breakdown: metabolic acidosis and an increase in glucocorticoids.[42] Inflammatory cytokines also contribute to insulin resistance by increasing glucocorticoid levels and promoting insulin and IGF-1 resistance in muscle.[43] The significant role insulin resistance plays in PEW is demonstrated by comparing individuals with diabetes and ESRD with their nondiabetic counterparts. Diabetic ESRD patients had enhanced muscle wasting compared with nondiabetic ESRD patients.[44]

Insulin and IGF-1 stimulate and act through specific pathways to prevent muscle degradation. The insulin receptor signaling (IRS)/phosphatidylinositol 3-kinase (PI3K)/Akt pathway regulates the metabolic activities of insulin and is involved in muscle maintenance.[45] The forkhead transcription factor (FOXO) family members are key regulators of the downstream catabolic effects of insulin resistance. FOXO activates muscle E3 ubiquitin conjugating enzymes atrogin-1 and muscle ring finger-1 (MuRF1), two key proteins functioning in muscle proteolysis by tagging proteins for degradation.[46] Activation of the IRS/PI3K/Akt pathway by insulin phosphorylates Akt, which suppresses the activity of FOXO and prevents activation of atrogin-1 and MuRF1. Rats with chronic renal failure have reduced phosphorylation of Akt, pointing to suppression of the IRS-1/PI3K/Akt signaling as a potential pathway leading to muscle breakdown.[47] Metabolic acidosis can also cause insulin resistance by inducing the ubiquitin signaling pathway.[48] Treating chronic renal failure rats with bicarbonate reversed muscle proteolysis and

recovered the function of the IRS/PI3K signaling pathway. The signal regulatory protein-α (SIRP-α) glycoprotein was identified as being involved in insulin signaling that contributes to PEW in mice with CKD.[45] Mice with overexpressed SIRP-α had insulin resistance and increased muscle breakdown.[45] Blocking SIRP-α expression led to phosphorylation of the insulin receptor and IRS-1, activating phosphorylated Akt, and preventing protein breakdown.[45]

Glucocorticoids and insulin have antagonistic roles in muscle degradation. Glucocorticoids can block PI3K from binding to the insulin receptor, either by binding to specific subunits of PI3K (such as p85) or stopping its activity by modifying the structure of its subunits.[43] Whichever modification occurs, the direct result is activation of atrogin-1 and MuRF1 by FOXO. Increase in circulating glucocorticoid levels also stimulates the glucocorticoid receptor, leading to binding of PI3K and suppression of Akt phosphorylation.[43] Glucocorticoids activate ubiquitin through the MEK/ERK signaling pathway and also cause expression of atrogin-1 and MuRF1, increasing muscle breakdown.[42]

Low vitamin D levels have been associated with insulin resistance. A NHANES III study demonstrated that individuals with the lowest eGFR (15−29 mL/min/1.73 m^3) had the lowest levels of 25-hydroxyvitamin D. CKD patients with eGFR between 30 and 59 mL/min/1.73 m^3 had vitamin D levels similar to those with normal kidney function.[49] Vitamin D levels and kidney function were inversely associated with insulin resistance measured by HOMA-IR. $1,25(OH)_2D_3$ functions in the pancreas by inducing insulin release from islet cells.[50] Increasing vitamin D levels by injection of vitamin D_3 was associated with a decrease in insulin resistance and induced insulin secretion in animals with low levels of $1,25(OH)_2D_3$ and in patients with ESRD.[51,52]

Growth Hormone Resistance

Growth hormone (GH) resistance is a major issue in patients with CKD that leads to stunted growth in children and PEW in adults. GH secretion from the pituitary gland is influenced by several factors, including ghrelin, PYY, and leptin.[53] The results of studies in CKD patients have not been consistent. Some studies report decreased, normal, or even increased production levels of the hormone. Studies in late prepubertal and early pubertal patients show low or normal levels of pulsatile secretion of GH, whereas prepubertal children and adults with ESRD have increased secretion of GH.[54] GH levels tend to be increased in patients with CKD, most likely due to decreased renal metabolic clearance rate (MCR) of GH. Haffner et al. showed the MCR of GH is decreased by 50% in patients with CKD or ESRD compared with healthy controls, and that the relationship between the MCR of GH and GFR is linear.[55]

The role of GH in PEW is thought to be due to defects in the GH and IGF-1 signaling pathways.[53] Studies in uremic rats reported low levels of the growth hormone receptor (GHR), documented by measuring hepatic GHR mRNA levels and growth plate GHR protein levels.[56,57] However, other studies in animals have found no difference in GHR levels between uremic rats and pair-fed controls.[58,59] In humans, GHR levels have been measured using GH-binding protein (GHBP) levels as a surrogate. This protein is enzymatically cleaved from the GHR receptor and released into the circulation. Most studies show low levels of GHBP in patients with CKD.[53] Powell et al., however, showed children with CKD had similar levels of GHBP at baseline, 3 months, and 12 months after treatment with GH.[60] Rabkin et al. also suggested that GHBP may not be the most accurate measure of GHR levels. In adult ESRD patients, GHBP levels were low, whereas levels of GHR from peripheral blood mononuclear cells were normal.[61] Further studies are necessary to determine what level of GHR is normal in specific tissues, and whether GHR levels influence GH resistance.

Muscle degradation in PEW may be the result of depressed IGF-1 expression due to decreased GH activation of the Janus kinase 2-signal transducer and activator of transcription pathway.[53] Garibotto et al. demonstrated GH response decreases with increasing age and inflammation, and that inflammation directly antagonizes the positive effect GH has on potassium and protein metabolism in the skeletal muscle of ESRD patients.[62]

Testosterone

Testosterone is an important hormone in muscle maintenance. Testosterone increases the efficiency of amino acid reuse in skeletal muscle, preserves nitrogen to facilitate skeletal muscle growth, causes myoblast differentiation, and increases fractional muscle protein synthesis.[63] Testosterone levels decrease with age and are further decreased in diseases such as hypertension, diabetes, CKD, and ESRD.[64] In addition, endogenous testosterone levels are associated with muscle strength and fat-free mass in men with CKD.[65] Low testosterone levels were associated with increased all-cause and cardiovascular disease (CVD)-related mortality in men treated with dialysis.[66] Haring et al. showed men with both total testosterone levels below the 10th percentile by age and kidney dysfunction (eGFR <60 mL/min/1.73 m^2) had more than a twofold higher all-cause mortality compared with men with kidney dysfunction

and total testosterone greater than the 10th percentile.[67] Both women and men with CKD have low testosterone levels.[63,68] A study in patients with stage 2−4 CKD demonstrated that endogenous testosterone is an independent predictor of muscle strength, measured by handgrip strength, as well as fat-free mass measured by bioelectrical impedance (BIA).[65] Men with CKD in the lower third of testosterone distribution had lower fat-free mass and handgrip strength of 31.9 ± 10.1 kg, compared with men in the upper third of testosterone distribution who had an average handgrip strength of 38.3 ± 8.8 kg.[65] Possible causes of low testosterone influencing PEW include increased expression of myostatin and altered IGF-1 signaling. Studies in humans and rats indicate that males are more affected by inflammation-induced anorexia compared with females, with appetite loss associated with gender.[42,68]

Metabolic Acidosis

Metabolic acidosis is an important contributor to PEW in CKD. Metabolic acidosis exacerbates muscle wasting through various mechanisms. In classic experimental studies, May et al. demonstrated that rats with renal failure and metabolic acidosis had preferential degradation of muscle protein.[69] This protein breakdown occurs even at moderate levels of acidosis (20 mmol/L bicarbonate).[70,71] Protein breakdown is mediated by activation of the adenosine triphosphate-dependent pathway involving ubiquitin and proteasomes.[72,73] Metabolic acidosis also causes a decrease in serum levels of essential branched-chain amino acid levels in muscle, contributing to muscle wasting.[68] Abnormal muscle signaling, inflammation, and dysregulation of IGF-1 signaling may also contribute to muscle wasting seen in patients with metabolic acidosis.[74] Metabolic acidosis induces insulin resistance.[75] Bailey et al. showed that acidosis in CKD leads to accelerated proteolysis through the IRS/PI3K/Akt pathway.[47] Correction of metabolic acidosis in rats decreased muscle catabolism through increasing IRS-associated PI3K activity, illustrating the importance of insulin and IGF-1 signaling in modulating muscle protein catabolism.[47]

Inflammation

There is considerable evidence that inflammation is intimately involved in the pathogenesis of PEW in CKD. CKD leads to a state of inflammation associated with increased morbidity and mortality.[76,77] Gupta et al. demonstrated that markers of inflammation were significantly associated with eGFR and cystatin C in Chronic Renal Insufficiency Cohort Study participants.[78] Increased cytokine levels in patients with CKD may be due to increased production or decreased renal clearance. Inflammation in patients with CKD could also be caused by volume overload,[79] chronic subclinical infections,[80] dysbiosis of the gut leading to endotoxin production,[81] oxidative stress,[82] and poor nutrition.

Inflammatory cytokines are involved in the pathways affecting PEW and contribute to anorexia and increased energy expenditure. Increased expression of proinflammatory cytokines contributes to GH, insulin, and IGF-1 resistance (Figure 16.2). In animal studies, infusion of inflammatory markers IL-6, IL-1β, TNF-α, and interferon (IFN)-γ leads to muscle catabolism, whereas blocking the action of these markers mitigates muscle breakdown.[83] When secreted from the muscle, IL-6 acts as a hormone, signaling and affecting the liver and adipose tissue. Raj et al. showed that IL-6 expression in skeletal muscle intensifies muscle protein catabolism and results in acute phase protein synthesis from the released amino acids rather than muscle protein synthesis in ESRD patients (Figure 16.2).[84] The expression of IL-6 also induces the expression of genes involved in protein catabolism.[85] Subclinical endotoxemia has been implicated as a key mediator of inflammation in CKD. Soluble CD14, a receptor through which endotoxin mediates its action, has been shown to be associated with PEW in ESRD patients, where it acts through the stimulation of inflammatory cytokines.[86]

Most of the inflammatory cytokines contributing to PEW induce muscle catabolism through the nuclear factor κβ (NFκβ) pathway, which regulates expression of downstream targets involved in the inflammatory response. The upregulation of TNF-α leads to activation of NFκβ, leading to inhibition of differentiation of myocytes and decreased protein synthesis induced by insulin signaling.[7] NFκβ signaling causes attenuation of MyoD expression, preventing muscle repair and differentiation.[87] Inflammation can also lead to increased production of glucocorticoids, which leads to increased muscle catabolism.[43] Activation of caspase 3 and the ubiquitin-proteasome pathway are the key mechanisms responsible for muscle wasting *via* inflammation.

Muscle Biology Dysfunction

Muscle catabolism in PEW occurs due to disruption in the balance of molecules involved in maintenance of muscle mass, especially myostatin and IGF-1.[88] These molecules have antagonistic roles in muscle. Myostatin expression increases muscle breakdown, whereas IGF-1 stimulates muscle protein synthesis and development.[89] Patients with stage 5 CKD before dialysis treatment have increased levels of myostatin mRNA, IL-6, and apoptosis in skeletal muscle, as well as decreased

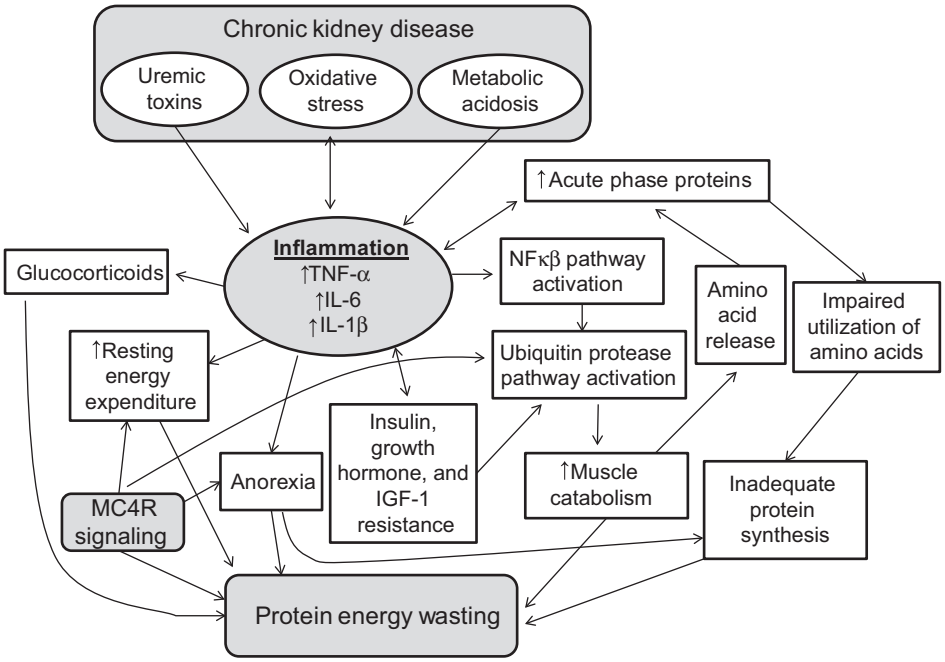


FIGURE 16.2 Interaction of different etiologies leading to protein energy wasting in chronic kidney disease (CKD). Uremic toxins, oxidative stress, and metabolic acidosis are present in CKD, leading to increased levels of proinflammatory cytokines (TNF-α, IL-6, IL-1β). Inflammation causes increased glucocorticoid production, increased resting energy expenditure, anorexia, insulin resistance, GH resistance, IGF-1 resistance, and activation of the NFκβ pathway. The ubiquitin-protease pathway is activated by NFκβ signaling, MC4-R signaling, and insulin and IGF-1 resistance, leading to increased muscle catabolism. Subsequently, muscle catabolism causes increased amino acid release, triggering release of acute phase proteins. These proteins cause impaired utilization of amino acids, leading to inadequate protein synthesis, and ultimately protein energy wasting. In addition, MC4-R signaling increases resting energy expenditure in end-stage renal disease patients and causes anorexia, both leading to protein energy wasting. Abbreviations: *IGF-1*, insulin-like growth factor-1; *IL*, interleukin; *NFκβ*, nuclear factor κβ; *MC4-R*, melanocortin; *TNF-α*, tumor necrosis factor-α.

levels of IGF-1.[90] Cheung et al. found AgRP antagonism of MC4-R in CKD mice reversed altered myostatin and IGF-1 gene expression, compared with untreated CKD mice.[30,31]

Modified muscle protein kinetics in PEW is responsible, at least in part, for increased muscle catabolism and decreased myogenesis.[91] The ubiquitin-proteasome system is the major pathway contributing to muscle breakdown, which is regulated by expression of FOXO transcription factors. Muscle-specific FOXO1 deletion in mice prevented muscle mass degradation compared with CKD control mice.[92] In addition, microRNA-486 inhibition of FOXO1 prevents loss of LBM.[92] Levels of ubiquitin, 26SW proteasome subunits, atrogin-1, and MuRF1 are increased in animal models of CKD,[48] and in patients with ESRD with muscle degradation.[93] In addition, caspase 3 degrades actomyosin to produce a 14-kDa actin fragment, a characteristic measure of muscle degradation. ESRD patients have increased levels of this 14-kDa actin fragment, along with increased rates of apoptosis in skeletal muscle. Studies by Workeneh and Mitch show the density of the 14-kDa actin fragment is significantly correlated with the rate of protein breakdown.[94]

Maintenance of cellular energy and metabolic balance during periods of decreased nutrient intake is fundamental to the structural and functional integrity of all cells. The main regulator of cellular energy homeostasis in virtually all eukaryotic cells is the AMP-activated protein kinase (AMPK).[95] AMPK is a serine/threonine protein kinase that acts as an energy sensor to regulate growth and metabolism at both the cellular and whole body levels.[96] An AMPK activator, A-769662, attenuated fibrosis and improved energy status in the kidneys in a murine model of CKD.[97] These findings suggest that a failure to sense AMP is a key mechanism underlying energy depletion and CKD progression.

Another protein kinase that mediates muscle protein loss in CKD is Rho-associated coiled-coil containing kinase 1 (ROCK 1). Peng et al. showed ROCK 1 enhances the activity of phosphatase and tensin homolog and reduces Akt activity.[98] A novel nuclear phosphatase, the small C-terminal domain phosphatase (SCP) 4, is another regulator of skeletal muscle protein synthesis and degradation implicated in muscle wasting. SCP4 expression was upregulated in the skeletal muscle of mice with CKD, as well as in the skeletal muscle of CKD patients.[99] Deletion of SCP4 significantly

suppressed FOXO1/3a-mediated expression of atrogin-1 and MuRF1 and prevented muscle wasting in mice with CKD. Thus, targeting SCP4 may prevent muscle wasting in CKD.

Dysfunction of satellite cells also contributes to the muscle degeneration seen in CKD. Satellite cells are located below the basal lamina of myofibers and are involved in repair and maintenance of muscle mass.[94] Satellite cells are induced after injury, and, once activated, they proliferate and differentiate to repair muscle. In CKD, breakdown of muscle occurs by decreasing the size of the muscle myofibers and inhibiting muscle regeneration by stopping satellite or stem cells from binding to myofibers.[68] Dysregulation of IGF-1 signaling in CKD prevents satellite cells from repairing muscle.[69]

Oxidative Stress

Oxidative stress can induce the NFκβ pathway, increasing levels of inflammation.[8] The opposite can also occur, where chronic inflammation causes oxidative stress. Both oxidative stress and inflammation can activate pathways contributing to muscle protein degradation and PEW. Oxidative stress modifies proteins, making them resistant to ubiquitination.[100] In addition, heavily oxidized proteins form covalent bonds with each other to severely inhibit proteolysis, in turn leading to buildup of protein aggregates in the cell.[101] A study in patients with CKD stages 1−4 showed oxidative stress increased with worsening kidney function, and oxidative stress significantly inversely correlated with GFR.[102] Studies in dialysis patients also show that overall secretion of malonaldehyde and carbonyl protein from the muscle acts as a marker of increased generation of reactive oxygen species.[103]

Comorbidities

CKD is associated with several comorbidities, such as diabetes mellitus, inflammation, chronic heart failure, hypertension, infection, and psychological changes, which may contribute to PEW. Diabetes affects muscle breakdown through insulin resistance. Diabetic ESRD patients have higher rates of muscle catabolism than their nondiabetic counterparts, illustrating that diabetes exacerbates PEW and the rate of protein breakdown.[44] CVD is a common comorbidity in CKD, with changes in the vasculature increasing the risk of myocardial infarction and stroke. In addition, malnutrition or PEW, along with increased levels of proinflammatory cytokines, is associated with atherosclerotic CVD.[104] One of the most used biomarkers in CVD is the C-reactive protein (CRP), which is a potent CVD risk factor. Panichi et al. illustrated that levels of CRP and IL-6 increase with decreasing GFR.[105] In addition, chronic heart failure is associated with low cardiac output, inducing glucocorticoids, increased angiotensin II, and sympathetic nerve activity,[68] pathways contributing to PEW. Finally, inflammation and proinflammatory cytokines can play roles in the pathogenesis of depression due to their effect on neurotransmitters and neurohormones in the brain.[106] These psychological changes can cause lack of appetite, fatigue, and physical inactivity, contributing to PEW.

DIAGNOSIS OF PEW IN CKD

The guidelines for diagnosis of PEW by the ISRNM establish standard nomenclature and definitions for PEW in CKD.[107] Diagnosis of PEW in CKD patients is determined by four key categories: (1) changes in biochemical indicators, (2) weight loss, decrease in total body fat, and low body weight, (3) decrease in muscle mass, and (4) low protein or energy intake (Figure 16.3). At least three out of these four categories, with at least one criterion from each of these categories, should be satisfied to establish the diagnosis of PEW in CKD patients. Fulfillment of these criteria should be observed at least three times at intervals of 2−4 weeks.

The ISRNM recommends that at least one of the diagnostic criteria includes a biochemical indicator, such as S[Alb]. Circulating levels of albumin and prealbumin are strong predictors of mortality in CKD and dialysis patients,[77,108] but can be affected by inflammation. In addition, hypoalbuminemia may reflect low levels of nutrition or inflammation. Kaysen et al., however, determined that after controlling for inflammation, hypoalbuminemia may not predict mortality in ESRD patients.[109] A biochemical indicator of PEW includes S[Alb] less than 3.8 g/dL. Low levels of serum prealbumin, or transthyretin, can also be a measure used for diagnosis in dialysis patients, but they vary in patients with CKD stages 2−5.[109] Serum cholesterol level less than 100 mg/dL is also a biochemical indicator of PEW.

A recent study of participants in the general and moderate CKD populations from the 1999−2004 NHANES showed the presence of all three nondietary categories was associated with significantly lower LBM and fat mass and very strongly associated with increased mortality.[110] The presence of dietary category in addition to two nondietary categories was also associated with significantly lower LBM and fat mass and mortality. However, when the dietary category alone was considered, the presence of any one of the categories was surprisingly associated with higher LBM and higher fat mass. Inclusion of dietary category undermines the face validity of the PEW criteria as a measure of protein or energy wasting. Thus, a modified

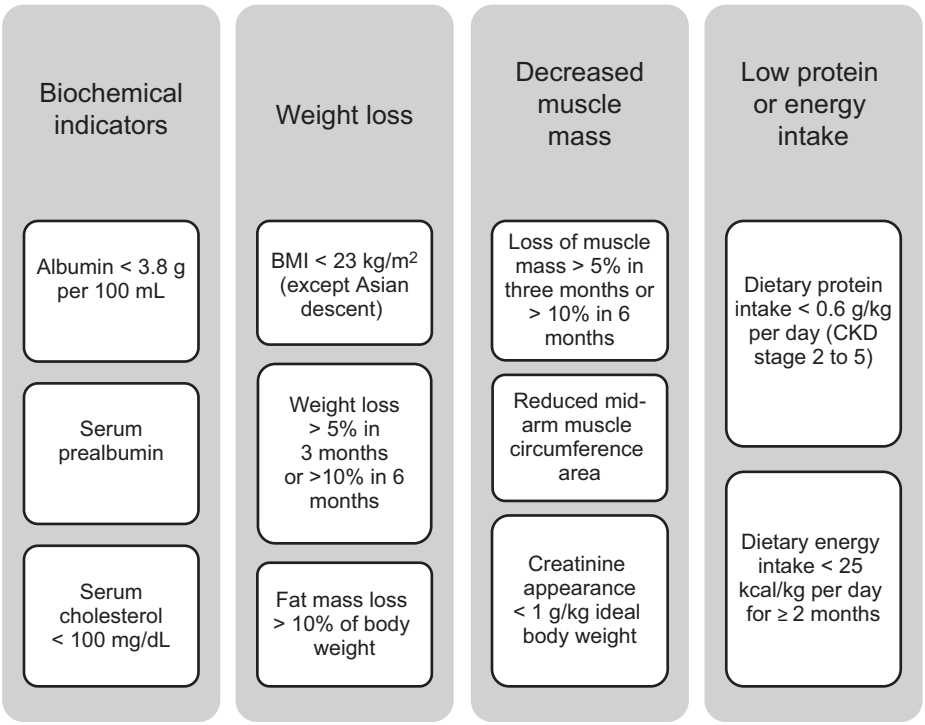


FIGURE 16.3 Diagnosis of protein energy wasting (PEW) in chronic kidney disease. At least three of these four categories must be met, with at least one criterion from each category satisfied for diagnosis of PEW. Fulfillment of these criteria should be confirmed at least three times at intervals of 2–4 weeks.

definition of PEW without dietary variables is likely a better indicator of protein or energy wasting. Similarly, in ESRD patients treated with hemodialysis, low protein or energy intake was not associated with PEW. Paradoxically, high dietary intake was associated with increased risk of the PEW.[111]

Decrease in body mass is also used to diagnosis PEW, with BMI being the most commonly used measure. Although BMI is heavily influenced by body fat and hydration status, BMI levels less than 23 kg/m^2 are an indicator of PEW in CKD and ESRD patients.[107] This threshold may not be suitable for individuals of Asian descent, where low BMI levels do not necessarily indicate chronic disease.[112] Unintended weight loss over a short amount of time is also used to diagnose PEW, independent of BMI. This includes more than a 5% loss of weight over 3 months and more than a 10% decrease over 6 months. Finally, loss of fat mass greater than 10% of an individual's body weight is an indicator of wasting. Decrease in body fat mass in dialysis patients is associated with increased mortality.[113]

Loss of muscle mass is the most consistent criterion for PEW in ESRD.[114] Although fat and muscle stores are both lost in PEW, the loss of LBM is thought to be more detrimental. This has been demonstrated by studies in dialysis patients, where the protective advantage of individuals with higher BMI is associated with the amount of lean muscle mass rather than fat mass.[115] Kalantar-Zadeh et al., however, have shown that fat mass is associated with an independent survival advantage in patients treated with dialysis.[116] Investigators have used several methods to estimate LBM, including dual X-ray absorptiometry (DEXA), near-infrared interactance (NIR), and BIA.[91,117] However, there is no good reproducible clinical measure that gives an accurate representation of muscle loss or protein catabolism.[118] Similarly to fat mass, a reduction in 5% of muscle mass over 3 months or 10% over 6 months is an indicator of PEW. Reduced mid-arm muscle circumference area measured by a trained anthropometrist can also be used in diagnosis. Creatinine appearance is an indirect clinical measurement that can be used to assess muscle mass, but it is influenced by meat intake and amount of muscle mass.[107] Creatinine appearance is a measure of the total creatinine generated after degradation and can be identified through 24-hour urine collection in patients with CKD. Levels of creatinine appearance less than 1 g/kg ideal body weight (IBW) can be used in the diagnosis of PEW.[119]

Low protein and energy intake is another key component of the rate of PEW, especially the amounts of dietary protein intake (DPI) and dietary energy intake (DEI). DEI can be measured using interviews or dietary diaries. DPI is measured as the normalized protein

equivalent of the total nitrogen appearance. DPI can be measured by urea kinetics to estimate the net protein degradation and protein intake. Levels of DPI unintentionally less than 0.6 g/kg/per day for patients with CKD stages 2–5 and DEI less than 25 kcal/kg per day for at least 2 months are both diagnostic criteria for PEW. The recommended DEI for CKD patients is 30–35 kcal/kg IBW per day to maintain protein stores.[120,121]

The ISRNM also identified several other measures of body composition, laboratory markers, nutritional scoring systems, and food intake and expenditure that are recognized as important indicators, but not diagnostic tools, for PEW. Measures of body composition that are used to measure body fat and muscle mass include CT or MRI of muscle mass, energy beaming technologies (DEXA, NIR, BIA), air or underwater displacement weighing, muscle measures (muscle fiber size, proportion of muscle fiber types, muscle alkaline soluble protein, and the 14-kDa fragment of actomyosin), total body nitrogen, and total body potassium.[107] The 14-kDa actomyosin fragment serves as a strong indicator of muscle breakdown. Its levels have been shown to be elevated in catabolic states, such as ESRD.[118] In patients with ESRD, the amount of the fragment increases before HD treatment and is further elevated after completion of dialysis.[122] Laboratory measures can also be used as indicators of PEW, including urea, triglycerides, and IGF-1. Transferrin and nutritional scoring systems, such as Subjective Global Assessment of Nutrition questionnaires,[123] can be used to estimate nutritional intake. Additional research is needed to see if these measures could potentially be used in the diagnosis of PEW in CKD patients in the future.

TREATMENT OF PEW IN CKD

Treatment of PEW begins with early identification of the etiologic factors causing nutrient insufficiency and muscle catabolism.[124] Once diagnostic criteria are met, specific therapies should be targeted to the address the presumed causes and the underlying pathophysiology. These therapies will hopefully prevent further muscle breakdown and circumvent worsening of function and perception of quality of life. Treatment of PEW includes changing diet, adding nutritional supplements, incorporating both aerobic and resistance exercise, and pharmacological therapy for metabolic acidosis, insulin, and GH resistance, as well as administration of anabolic steroids (Table 16.2). The treatment of PEW in CKD patients is a balancing act, requiring lifestyle changes and the correct pharmacological dosing to maintain muscle mass and prevent subsequent PEW.[125] Treatments for PEW target specific causes of muscle wasting, from the most experimental to the safest and most effective.

Ghrelin

Ghrelin is a sensor for appetite that may be a potential target for anorectic patients with PEW or cachexia. In 51 CKD and 15 HD patients, des-acyl ghrelin levels increased with decreasing eGFR.[126] Short-term clinical trials in anorexic ESRD patients demonstrated subcutaneous administration of ghrelin enhances appetite and energy intake without side effects.[127,128] Although ghrelin does have some benefits in the short term, it is unknown whether there will be long-term benefits, as appetite-regulating centers may become tolerant.[91] Further studies are needed before ghrelin can be used as a treatment for PEW in CKD patients.

Insulin Resistance and Sensitivity

Insulin resistance in muscle leads to PEW in ESRD patients.[129] Insulin-sensitizing medications, such as rosiglitazone, can improve mortality and suppress breakdown of muscle. Treatment with rosiglitazone, a peroxisome proliferator-activated receptor-γ agonist, suppressed breakdown of muscle in insulin resistant *db/db* mice.[130] In addition, mice treated with rosiglitazone had decreased expression of proteins in the ubiquitin-proteasome proteolytic pathway, including atrogin-1 and MuRF1. Diabetic HD patients treated with thiazolidinedione had improvement of both S [Alb] and 47% lower all-cause mortality at 1 year, compared with patients who did not receive thiazolidinedione.[131] These treatments demonstrate that increasing insulin sensitivity may decrease muscle breakdown by suppressing the ubiquitin-proteasome proteolytic pathway and decrease mortality. Additional studies are necessary to determine whether these treatments are safe and effective in patients with CKD.

Testosterone

Testosterone is an important anabolic hormone that maintains skeletal muscle mass. Male patients with ESRD have low testosterone levels, associated with inflammation and mortality.[132] Johansen et al. performed two clinical trials to investigate the effect of androgen therapy on body composition and muscle function in patients treated with dialysis. Patients treated with nandrolone decanoate, an anabolic steroid, had significant increases in LBM, along with decreased time to complete walking, stair climbing, and treadmill activities compared with a placebo group.[133] The other

TABLE 16.2 Types of Treatment for Protein Energy Wasting in Chronic Kidney Disease

Etiology	Treatment	Benefits	Organism	Reference
Nutrient insufficiency	Low protein diet and nutritional supplements	Suplena (low protein/high caloric) supplement slows progression of CKD and improves nutritional parameters	CKD patients	Montes-Delgado et al. 1998[170]
	Ketoanalogue supplements	Sustains kidney function and maintains S[Alb] and total protein levels	CKD patients	Prakash et al. 2004,[174] Kalantar-Zadeh et al. 2011[159]
Growth hormone resistance	Recombinant human growth hormone	Increases growth rate and catch-up growth to almost normal height (1.6±1.2 SD below normal)	Children with CKD	Fine et al. 1994,[137] Haffner et al. 2000[140]
	Super-agonist of human GHRH (AKL-0707)	Increases fat mass and decreases serum urea	CKD patients	Niemczyk et al. 2010[142]
Low testosterone	Nandrolone decanoate injections	Increases percentage of lean body mass	CKD patients	Eiam-Ong et al. 2007[135]
Metabolic acidosis	Oral bicarbonate	Increases lean body mass, improves dietary protein intake, and slows progression of CKD to ESRD	CKD patients	de Brito-Ashurst et al. 2009[154]
Muscle biology dysfunction	Resistance exercise	Increases muscle mass and mitochondrial DNA copy number, increases muscle strength and protein utilization, and lowers inflammation	CKD patients	Balakrishnan et al. 2010,[144] Castaneda et al. 2004[145]
Inflammation	Pentoxifylline infusion	Decreases whole body proteolysis	CKD patients	Biolo et al. 2002[146]

Abbreviations: *CKD*, chronic kidney disease; *GHRH*, growth hormone-releasing hormone; *S[Alb]*, serum albumin concentration.

clinical trial investigated the effects of resistance exercise along with nandrolone decanoate treatment on change in LBM measured by DEXA and quadriceps muscle cross-sectional area measured by MRI. Sixty-eight dialysis patients were randomized using a 2-by-2 factorial design, with 17 patients receiving nandrolone decanoate injections (women: 100 mg; men 200 mg), 16 patients receiving placebo injections, 19 patients participating in low extremity resistance exercise training (ankle weights), and 16 patients receiving nandrolone decanoate injections and participating in resistance exercise for 12 weeks.[134] LBM was significantly increased in the nandrolone decanoate group (3.1 ± 2.2 kg; $p < 0.0001$), but not in the exercise group. There was no significant additional increase in LBM for patients in the nandrolone decanoate with exercise group. However, there was an increase in quadriceps muscle cross-sectional area in the exercise group. These results indicate that androgen therapy is associated with an increase in LBM and may be a beneficial treatment to prevent muscle catabolism in patients with ESRD and PEW.

Preliminary evidence in patients with CKD shows testosterone treatment improves LBM. Sixteen patients were randomized to receive an intramuscular injection of 100 mg of nandrolone decanoate for 3 months, while 13 patients served as the control group, receiving conventional care.[135] The treatment group had increased LBM compared with the control group ($4.2\% \pm 1.5\%$, $CI = 2-8$; $p < 0.05$). Further studies are warranted in patients with CKD, but must take into account the potential side effects of testosterone treatment.

Recombinant Human Growth Hormone

Recombinant human growth hormone (rhGH) stimulates anabolic effects in patients with malnutrition and has been investigated as a treatment for PEW in children and adults treated with HD and PD.[136] Results are well established in children, where a randomized double-blind, placebo-controlled study showed that children with CKD treated with rhGH had significantly increased growth rate.[137] In the first year, children with CKD treated with rhGH grew 10.7 ± 3.1 cm compared with the placebo group who grew 6.5 ± 2.6 cm. Second-year growth was also significantly higher in children treated with rhGH, with a growth of 7.8 ± 2.1 cm vs. a growth of 5.5 ± 1.9 cm in children given placebo. These results provided the evidence necessary for allowing the use of rhGH as a treatment for growth failure in children with CKD.[138,139] Children with CKD treated with

rhGH have sustained catch-up growth compared with untreated CKD children. The mean final adult height of pediatric CKD patients treated with rhGH is only 1.6 ± 1.2 SD below normal, which is 1.4 SD above their standardized height at baseline ($p < 0.001$).[140] Untreated children with CKD had a final height of 2.1 ± 1.2 SD below normal, which is 0.6 SD below their standardized height at baseline.[140]

GH administration has been studied in ESRD patients.[136] A randomized controlled trial of 139 HD patients concluded that rhGH treatment was associated with a 2.5 kg increase in LBM compared with HD patients taking placebo, who had a decrease in LBM of 0.4 kg ($p < 0.001$).[141] The OPPORTUNITY™ trial, a randomized double-blinded clinical trial, attempted to investigate the use of rhGH in 2500 adult HD patients and its effects on mortality, morbidity, markers of body protein mass, inflammation, and exercise capacity.[136] However, the trial was stopped prematurely due to slow recruitment rates, and the resulting study ($n = 695$) was underpowered to accurately determine whether rhGH treatment improves clinical outcomes or mortality in HD patients.

There is limited support for the use of rhGH in adult patients with CKD. Niemczyk et al. completed a placebo-controlled, randomized clinical trial studying a super-agonist of human GH-releasing hormone (GHRH), AKL-0707, in 28 patients with CKD stages 4 and 5.[142] Treatment with AKL-0707 for 28 days was associated with increased fat-free mass, measured by DEXA, and decreased serum urea concentrations. Additional long-term studies using GH treatment in patients with CKD are warranted.

Exercise and Resistance Training

Few studies have been done to determine whether exercise improves health outcomes in CKD in relation to PEW. Forty patients with CKD stages 4 and 5 completed 6 months of walking exercise, which showed short-term improvement in body composition at 1 month. Fat mass was reduced by 0.71 ± 0.62 kg ($p = 0.001$), while lean mass increased 0.56 ± 0.98 kg ($p = 0.060$).[143] However, there was no improvement in anthropometric measures at 6 months. This study has several limitations. The study sample was quite small, and patients were not randomized to participate in the walking exercise, but assigned to the intervention.

Resistance training may be an effective treatment to improve muscle maintenance and repair in patients with CKD. A randomized controlled trial in patients with stages 3 and 4 CKD showed that 12-week high-intensity resistance exercise training was associated with increased mitochondrial DNA copy number, which was correlated with changes in types I and II muscle fiber cross-sectional area, both indicating increase in muscle mass.[144] Patients who performed resistance exercise also had increased muscle strength, as shown by improvement in protein utilization and muscle hypertrophy. However, these are surrogate measures of muscle strength, illustrating that more evidence is needed to determine if resistance exercise in patients with CKD actually improves muscle strength. A study by Castaneda et al. investigated the role of resistance training in CKD patients on a low protein diet (LPD) (about 0.6 g/kg/day). Patients in the training group had lower levels of the inflammatory biomarkers IL-6 and CRP, as well as increased types I and II muscle fiber cross-sectional area and muscle strength.[145] Additional studies are needed to determine how much and what type of exercise is needed for muscle preservation and prevention of PEW in patients with CKD, and whether exercise improves survival outcomes in such patients.

Inflammation

Inflammation contributes to PEW through a number of mechanisms including GH, insulin, and IGF-1 resistance, as well as activation of genes involved in protein catabolism. Targeting treatments for inflammation may alleviate or slow muscle wasting. Pentoxifylline, a xanthine-derived phosphodiesterase inhibitor, can suppress TNF gene expression and decrease circulating levels of TNF-α and TNF-α soluble receptor. Biolo et al. showed that pentoxifylline treatment was associated with decreased whole body proteolysis in patients with CKD (mean eGFR 17 mL/min/1.73 m^2) by suppressing the TNF-α system.[146] Studies are warranted to determine whether pentoxifylline and other antiinflammatory treatments may attenuate PEW in patients with CKD.

Metabolic Acidosis

There is both experimental and clinical evidence that correction of metabolic acidosis in CKD may improve PEW.[73] There are many studies of bicarbonate supplementation that have been completed in dialysis patients, with some showing increases in anthropometric measures of LBM,[147,148] while others do not.[149–151] Early studies indicated that sodium bicarbonate treatment in CKD patients before initiation of dialysis was associated with decreased protein degradation, amino acid oxidation, and plasma urea levels.[152,153] A short-term study in 20 patients with CKD (eGFR 15–45 mL/min/1.73 m^2) taking increasing doses of oral bicarbonate (0.3, 0.6, and 1.0 mEq/kg/day) studied the effect on functional status measured by sit-to-stand tests and handgrip strength.[74] The investigators showed that

sit-to-stand time for 10 repetitions decreased after 6 weeks of treatment, improving from 23.8 ± 1.4 seconds to 22.2±1.6 seconds ($p = 0.002$). However, handgrip strength was not statistically different after treatment, with average handgrip strength of 29.5 ± 9.6 kg before treatment and 28.4 ± 9.4 kg after treatment.

Only one long-term clinical trial has investigated the use of oral bicarbonate treatment on rate of creatinine clearance (CrCL) decline and progression to ESRD, as well as DPI, S[Alb], and mid-arm muscle circumference in CKD patients.[154] A total of 134 patients with CKD and low serum bicarbonate concentration (16−20 mmol/L) were randomized to oral sodium bicarbonate treatment vs. placebo and standard of care treatment. The investigators found that patients treated with bicarbonate supplementation had a lower decline in CrCL of 1.88 mL/min/1.73 m^2 compared with controls, who had a decline of 5.93 mL/min/1.73 m^2 ($p < 0.0001$). Only four patients treated with bicarbonate supplementation progressed to ESRD (6.5%) compared with 22 patients who did not receive bicarbonate treatment (33%; $p < 0.001$). Treatment was associated with slowing progression of CKD, with nine patients having fast progression vs. 45% of patients having fast progression receiving standard of care ($p < 0.0001$). In addition, patients with bicarbonate supplementation had improved DPI, decreased normalized protein nitrogen appearance, and increased LBM measured by arm circumference compared with patients receiving standard of care. In a single-center, open-label, randomized, prospective parallel-group study, 188 patients with CKD stages 3 and 4 and with venous bicarbonate levels <22 mEq/L were randomized to receive oral sodium bicarbonate supplementation to maintain venous bicarbonate levels at 24−26 mEq/L or to standard care alone. Individuals in the intervention arm had higher LBM and mid-arm circumference compared with the control group.[155]

Two additional studies, the Correction of Metabolic Acidosis with Use of Bicarbonate in Chronic Renal Insufficiency (UBI) Study ($n = 600$; 36 months) and the SoBic-Study ($n = 200$; 2 years), have been proposed to investigate bicarbonate treatment in patients with CKD stages 3 and 4.[156,157] Preliminary data from the UBI study showed that the largest HOMA-IR reduction was noted for serum bicarbonate concentrations between 24 and 28 mmol/L.[158]

Diet and Nutritional Supplements

A healthy diet and sufficient nutrient intake are essential for maintenance of muscle mass in patients with PEW. A plethora of studies evaluating the effectiveness of nutritional supplementation have been completed in patients treated with HD and PD.[159−166] Most studies,[161−164] but not all,[160,165,166] showed improved nutritional status as measured by S[Alb] levels.[159] For example, intradialytic parenteral nutrition (IDPN) has been shown to be an effective way to promote protein synthesis and decrease muscle protein breakdown in malnourished chronic HD patients.[164] However, patients who received oral supplementation had persistent anabolic benefits after dialysis treatment, whereas patients receiving IDPN did not have such benefits.[167] Cano et al. demonstrated that IDPN did not improve 2-year mortality compared with malnourished HD patients who received oral nutritional supplements.[168] Nutritional supplementation overall did improve prealbumin levels. Nutritional supplementation is associated with increased survival rates in those malnourished HD patients who had prealbumin levels that increased by more than 3 mg/dL after 3 months.[168] A recent study showed partial replacement of meat and fish with egg whites induced a significant decrease in S[P] without causing protein malnutrition. This intervention could represent a useful instrument to control S[P] in hemodialysis patients.[169]

The most significant reason for negative results in studies of oral supplementation may relate to intolerance and/or nonadherence, which is as high as 50% in some studies. Many patients experience nausea and other side effects.[159,160,165] However, this intolerance may be worse in sicker patients with more severe kidney disease, which may account for these negative results. Such findings support the notion that nutritional supplementation may not be effective in patients with more severe CKD. Teixido-Planas et al. showed that compliant patients taking the oral protein-energy supplement Protenplus had significantly improved LBM ($p < 0.002$), body weight ($p < 0.03$), tricep skinfold thickness ($p < 0.01$), and mid-arm circumference ($p < 0.025$).[166] However, in their intent to treat analysis, which included noncompliant patients, there was no significant improvement in these measures. Heaf et al. found no improvement in S[Alb] after 10 weeks of treatment with protein supplements, with a decrease in S[Alb] of 26 ± 108 μmol/L in noncompliant patients.[160] In addition, there was no significant improvement in compliant patients, with a decrease in S[Alb] of 16 ± 24 μmol/L.[160] Overall, most studies have shown improvement in nutritional markers when DPI and DEI levels are met in compliant patients, but further research is necessary to generate firm treatment recommendations.

Montes-Delgado et al. investigated the use of diet and/or nutritional supplements in patients with CKD before they progress to ESRD.[170] The study used Suplena, a low protein and hypercaloric supplement, in patients with CKD and compared them with patients

with CKD on a 0.6 g/kg/day LPD.[170] After months, patients in the supplement group had better retention of renal function measured by CrCL (smaller decrease in renal function compared with LPD control group), better nutritional parameters, and better compliance with the LPD and with therapy overall. However, this study is limited by the fact there were only 33 patients in the study and by a short treatment time (6 months). In addition, there is a possibility that changes in nutrition alter creatinine metabolism. This raises the question of the utility of CrCL as an endpoint measurement in CKD nutritional trials.

It has also been suggested that an LPD, by itself, may provide metabolic benefits in patients with CKD and slow progression of the disease.[171] However, the Modification of Diet in Renal Disease (MDRD) study showed that an LPD did not improve survival in CKD patients compared with patients ingesting a normal protein diet (1.3 g/kg/day).[172] Additional studies are necessary to determine whether there is long-term benefit to LPDs in preserving renal function, improving mortality, quality of life of patients, and other important nutritional outcomes.[124]

Ketoanalogues (KAs) of essential amino acids are another type of supplement that may provide nutritional benefit to CKD patients. Mitch et al. first showed that an LPD and KAs slowed progression of CKD.[173] 10 of the 17 patients treated with KAs had slower rise in S[Cr] than expected during 20 months of treatment. This study had several limitations, as it was not a randomized controlled trial and used historical controls. The use of KAs along with an LPD was investigated in CKD patients to determine if such an intervention slows the progression of CKD and maintains nutritional status.[174] Patients given the KA supplement and LPD for 9 months maintained S[Alb] and total protein levels and sustained kidney function based on GFR levels measured by the 99mTc-DTPA (99 m technetium diethylenetriaminepenta-acetic acid) plasma sample method.[174] The ketodiet patients had an average GFR of 28.1 ± 8.8 mL/min/1.73 m^2 at baseline, with an average GFR of 27.6 ± 10.1 mL/min/1.73 m^2 at the end of the study ($p = 0.72$). Patients taking placebo had an average GFR of 28.6 ± 17.6 mL/min/1.73 m^2 at baseline and an average GFR of 22.5 ± 15.9 mL/min/1.73 m^2 at study completion ($p = 0.015$). The MDRD study showed that it was the LPD of 0.5–1 g/kg/day rather than KAs that slowed progression of CKD.[175] Additional studies and randomized controlled trials are needed before KA supplementation becomes a valid treatment for patients along with nutritional supplementation specific for the CKD population.[159,176]

CKD patients are often advised to limit or avoid protein foods that are plant-based due to their potassium and phosphate content, implying that protein foods that are animal-based should be the primary protein food source.[177] However, those consuming a higher proportion of protein from plant foods had significantly higher bicarbonate concentrations.[124,178] Furthermore, animal protein intake may generate toxins such as trimethylamine N-oxide which is proatherogenic.[124,179] In a prospective, randomized, controlled trial, a KA–supplemented vegetarian very low–protein diet was shown to be nutritionally safe. The diet could defer dialysis initiation by ameliorating CKD–associated metabolic disturbances compared with a conventional low–protein diet.[180] This study suggests that the source of the protein (animal protein vs. plant based), not just the protein content of the diet, may be important.

RECOMMENDATIONS AND GUIDELINES

Several prospective, experimental, and clinical studies have investigated potential treatments for PEW in patients with CKD (Table 16.2). Overall, there are a very limited number of studies in CKD patients before ESRD, pointing to the need for more research in this population. Recommendations and guidelines for the treatment of PEW in patients with CKD have been published (Figure 16.4).

Nutritional supplementation has shown some promising results in HD and PD patients.[159] The use of supplements in patients with earlier stage CKD is not so definitive, with limited results available for evaluation of the effects of nutrition supplementation. Patients taking Suplena with an LPD had preserved renal function measured by CrCL. Additional studies are needed before nutritional supplementation can be prescribed as an intervention for PEW in CKD patients, especially investigating if there are long-term benefits maintaining muscle stores and determining whether supplements reduce morbidity and/or mortality.

A baseline nutritional evaluation by a renal dietitian is recommended for patients with PEW. Patients with PEW should undergo nutritional screening regularly at outpatient clinic visits, including 24-hour urine collections and measuring S[Alb], weight, and BMI.[124,181] Follow-up dietary consultations should be performed as required as dictated by change in clinical status.[124] The ISRNM also suggests the following mineral intake levels be met: potassium levels less than 1 mmol/kg if S[K] is elevated, 80–100 mmol/day of sodium, 800–1000 mg of phosphorus, and binders if S[P] levels are elevated (Figure 16.4).[181]

Stable uremic patients adapt well to an LPD and maintain energy stores.[121] KDOQI recommendations state a DPI of 0.6–0.8 g/kg IBW and energy intake of 30–35 kcal/kg IBW/day preserve protein stores in patients with CKD and reduce the generation of toxic

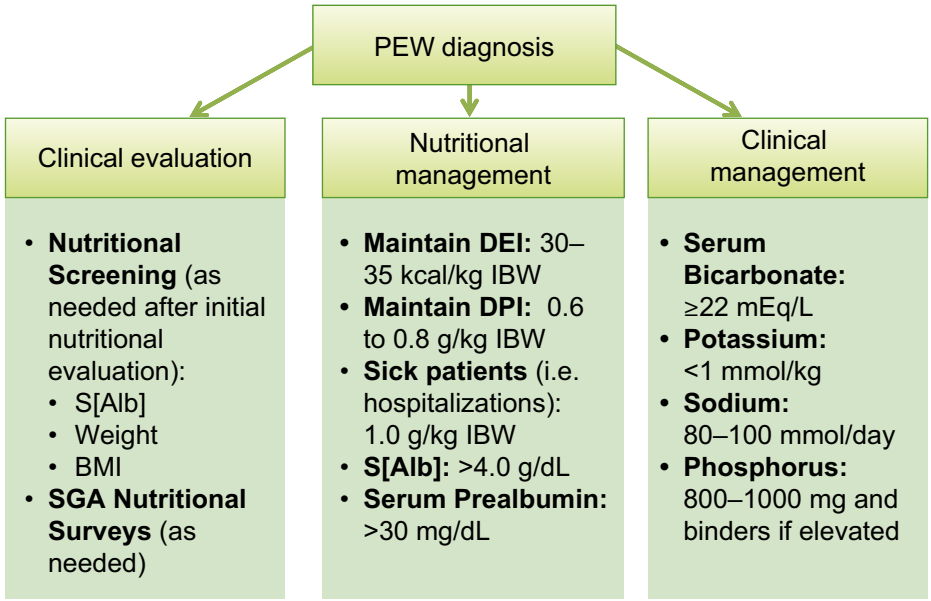


FIGURE 16.4 Recommendations and guidelines for treatment of patients with protein energy wasting (PEW) in chronic kidney disease (CKD). After diagnosis of PEW in CKD patients, they should have follow-up appointments in the clinic to undergo nutritional screening. This includes measurement of S[Alb], weight, BMI, DPI, and DEI. Patients should have nutritional surveys, such as Subjective Global Assessment, completed as needed. Patients should also have nutritional management, with intake levels described to maintain protein stores. Clinical management includes maintaining levels of important minerals as well as serum bicarbonate levels to maintain muscle mass. Abbreviations: *BMI*, body mass index; *DEI*, daily energy intake; *DPI*, daily protein intake; *IBW*, ideal body weight; *S[Alb]*, serum albumin concentration.

nitrogenous metabolites.[120,121,182] However, with catabolic conditions, such as metabolic acidosis and inflammation, nutritional supplementation with oral supplements does not maintain protein stores.[121] For patients with catabolic conditions, KDOQI recommends increasing the DPI to 0.75 g/kg IBW. This DPI may not only be beneficial and lead to an increase in nutritional intake but may also increase the rate of progression of CKD.[121] Those patients with illness or hospitalizations should have their DPI increased to 1.0 g/kg IBW/day.[181] Although these recommendations are extant, mixed results in the literature indicate that nutritional supplementation and LPD may not provide benefit or prevent PEW from occurring in CKD patients. Additional studies are needed to determine what dietary recommendation is best for preserving renal function and whether these diets are effective in delaying PEW and its comorbidities.

Resistance exercise has shown some promise as a potential way to increase muscle mass and decrease inflammation,[144,145] but specific guidelines and demonstration of long-term benefits from these interventions are lacking. There are no current recommendations that patients with CKD and muscle wasting should participate in resistance exercise to improve PEW.

Treatment with bicarbonate has been shown to be effective in decreasing progression to ESRD, slowing the rate of progression of CKD, and improving LBM in limited studies.[154] However, two additional large and long-term clinical trials have investigated the use of bicarbonate in patients with CKD, pointing to bicarbonate supplementation as a potentially effective treatment for PEW.[156,157] For now, KDOQI guidelines recommend that serum bicarbonate levels be maintained at 22 mEq/L or greater in CKD patients. Current research suggests that bicarbonate supplementation is a safe and effective way of improving serum bicarbonate levels,[71] but additional studies are needed before definitive recommendations can be made.

Additional research, especially long-term, randomized controlled clinical trials, is necessary before ghrelin, testosterone, and recombinant human GH can be used as treatments for PEW in CKD patients. Ghrelin has been investigated in very small and short-term studies in patients with ESRD, where it was associated with increased appetite and energy intake.[127,128] However, ghrelin administration to improve PEW has not been studied in CKD patients. rhGH treatment improves LBM in ESRD patients,[141] whereas administration of the super-agonist of GHRH AKL-0707 improves fat mass in CKD patients.[142] Preliminary evidence shows that testosterone treatment was associated with improvement in LBM in ESRD[133,134] and in CKD patients.[135] However, this increase in LBM must be balanced against possible adverse side effects of testosterone treatment, such as toxicity and potential for liver damage and prostate cancer.[132]

Additional pathways, such as neuroendocrine signaling cascades, are being pursued as targets for treatment of PEW. Preliminary evidence in animal studies shows that blocking the activity of leptin through pharmacological and genetic interventions increases muscle and fat mass, decreases inflammation, and increases energy intake.[30–32] This type of treatment is still far from being applied in clinical studies but represents a new field of research that should be investigated in the future as a potential treatment for patients with CKD.

CONCLUSIONS

PEW is a common problem in patients with CKD, and if undiagnosed or improperly treated, PEW leads to increased morbidity, mortality, and lower quality of life. The causes of PEW are multiple and include anorexia, increased energy expenditure, ineffective ingestion and utilization of nutrients, and increased muscle protein catabolism. In addition, understanding the factors or mediators contributing to enhanced muscle protein catabolism, namely, insulin resistance, inflammation, oxidative stress, hormone dysregulation, and metabolic acidosis, is of critical importance for management of PEW in the setting of CKD.

Both nonpharmacological and pharmacological approaches to prevent or reverse PEW have been recommended and used that specifically target the etiologic factors of PEW in CKD patients. These include dietary changes and nutritional supplementation to improve nutrient intake. Other studies have pointed to some clinical benefit of pharmacologic treatment with human GH, anabolic steroids, and insulin-sensitizing agents to treat hormonal deficiencies and insulin resistance. Bicarbonate administration and RRT to correct metabolic acidosis and reduce associated inflammation have also been considered potential treatments for PEW in CKD patients. Other potential therapeutic strategies to prevent or reduce protein catabolism by stimulating appetite, such as MC4-R antagonists and ghrelin administration, have also been suggested, but their safety and efficacy in CKD patients need further study. Other interventions, such as resistance exercise, antioxidants, and antiinflammatory or anticytokine agents, which indirectly or directly target the oxidative and inflammatory responses in PEW, have also been considered but their effects in CKD have not been adequately studied.

Additional studies focused on patients with CKD, before they progress to ESRD, are necessary to elucidate the mechanisms underlying PEW in this population and to identify therapeutic targets and develop potential therapies to prevent and potentially reverse muscle catabolism.

References

1. Loprinzi CL, Michalak JC, Schaid DJ, Mailliard JA, Athmann LM, Goldberg RM, Tschetter LK, Hatfield AK, Morton RF. Phase III evaluation of four doses of megestrol acetate as therapy for patients with cancer anorexia and/or cachexia. *J Clin Oncol* 1993;**11**:762–7.
2. Streat SJ, Beddoe AH, Hill GL. Aggressive nutritional support does not prevent protein loss despite fat gain in septic intensive care patients. *J Trauma* 1987;**27**:262–6.
3. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. *Am J Kidney Dis* 2003;**42**: 864–81.
4. Carrero JJ, Thomas F, Nagy K, Arogundade F, Avesani CM, Chan M, Chmielewski M, Cordeiro AC, Espinosa-Cuevas A, Fiaccadori E, Guebre-Egziabher F, Hand RK, Hung AM, Ikizler TA, Johansson LR, Kalantar-Zadeh K, Karupaiah T, Lindholm B, Marckmann P, Mafra D, Parekh RS, Park J, Russo S, Saxena A, Sezer S, Teta D, Ter Wee PM, Verseput C, Wang AYM, Xu H, Lu Y, Molnar MZ, Kovesdy CP. Global prevalence of protein-energy wasting in kidney disease: a meta-analysis of contemporary observational studies from the International Society of Renal Nutrition and Metabolism. *J Ren Nutr* 2018;**28**: 380–92.
5. Garg AX, Blake PG, Clark WF, Clase CM, Haynes RB, Moist LM. Association between renal insufficiency and malnutrition in older adults: results from the NHANES III. *Kidney Int* 2001;**60**: 1867–74.
6. Cohen SD, Kimmel PL. Nutritional status, psychological issues and survival in hemodialysis patients. *Contrib Nephrol* 2007;**155**: 1–17.
7. Mak RH, Cheung WW, Zhan JY, Shen Q, Foster BJ. Cachexia and protein-energy wasting in children with chronic kidney disease. *Pediatr Nephrol* 2012;**27**:173–81.
8. Bonanni A, Mannucci I, Verzola D, Sofia A, Saffioti S, Gianetta E, Garibotto G. Protein-energy wasting and mortality in chronic kidney disease. *Int J Environ Res Public Health* 2011;**8**:1631–54.
9. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. *Am J Clin Nutr* 2004; **80**:299–307.
10. Scribner BH, Buri R, Caner JE, Hegstrom R, Burnell JM. The treatment of chronic uremia by means of intermittent hemodialysis: a preliminary report. 1960. *J Am Soc Nephrol* 1998;**9**:719–26.
11. Anderstam B, Mamoun AH, Sodersten P, Bergstrom J. Middle-sized molecule fractions isolated from uremic ultrafiltrate and normal urine inhibit ingestive behavior in the rat. *J Am Soc Nephrol* 1996;**7**:2453–60.
12. Mamoun AH, Sodersten P, Anderstam B, Bergstrom J. Evidence of splanchnic-brain signaling in inhibition of ingestive behavior by middle molecules. *J Am Soc Nephrol* 1999;**10**:309–14.
13. Duenhas MR, Draibe SA, Avesani CM, Sesso R, Cuppari L. Influence of renal function on spontaneous dietary intake and on nutritional status of chronic renal insufficiency patients. *Eur J Clin Nutr* 2003;**57**:1473–8.
14. Abitbol CL, Zilleruelo G, Montane B, Strauss J. Growth of uremic infants on forced feeding regimens. *Pediatr Nephrol* 1993; **7**:173–7.
15. Betts PR, Magrath G. Growth pattern and dietary intake of children with chronic renal insufficiency. *Br Med J* 1974;**2**: 189–93.
16. Hirako M, Kamiya T, Misu N, Kobayashi Y, Adachi H, Shikano M, Matsuhisa E, Kimura G. Impaired gastric motility and its relationship to gastrointestinal symptoms in patients with chronic renal failure. *J Gastroenterol* 2005;**40**:1116–22.

17. Kamimura MA, Draibe SA, Avesani CM, Canziani ME, Colugnati FA, Cuppari L. Resting energy expenditure and its determinants in hemodialysis patients. *Eur J Clin Nutr* 2007;**61**: 362–7.
18. Avesani CM, Draibe SA, Kamimura MA, Dalboni MA, Colugnati FA, Cuppari L. Decreased resting energy expenditure in non-dialysed chronic kidney disease patients. *Nephrol Dial Transplant* 2004;**19**:3091–7.
19. Cuppari L, Ikizler TA. Energy balance in advanced chronic kidney disease and end-stage renal disease. *Semin Dial* 2010;**23**: 373–7.
20. Utaka S, Avesani CM, Draibe SA, Kamimura MA, Andreoni S, Cuppari L. Inflammation is associated with increased energy expenditure in patients with chronic kidney disease. *Am J Clin Nutr* 2005;**82**:801–5.
21. Neyra R, Chen KY, Sun M, Shyr Y, Hakim RM, Ikizler TA. Increased resting energy expenditure in patients with end-stage renal disease. *J Parenter Enter Nutr* 2003;**27**:36–42.
22. Wang AY, Sea MM, Tang N, Sanderson JE, Lui SF, Li PK, Woo J. Resting energy expenditure and subsequent mortality risk in peritoneal dialysis patients. *J Am Soc Nephrol* 2004;**15**:3134–43.
23. Cheung AK, Parker CJ, Wilcox LA, Janatova J. Activation of complement by hemodialysis membranes: polyacrylonitrile binds more C3a than cuprophan. *Kidney Int* 1990;**37**:1055–9.
24. Nasrallah MP, Ziyadeh FN. Overview of the physiology and pathophysiology of leptin with special emphasis on its role in the kidney. *Semin Nephrol* 2013;**33**:54–65.
25. Daschner M, Tonshoff B, Blum WF, Englaro P, Wingen AM, Schaefer F, Wuhl E, Rascher W, Mehls O. Inappropriate elevation of serum leptin levels in children with chronic renal failure. European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. *J Am Soc Nephrol* 1998;**9**:1074–9.
26. Aminzadeh MA, Pahl MV, Barton CH, Doctor NS, Vaziri ND. Human uraemic plasma stimulates release of leptin and uptake of tumour necrosis factor-alpha in visceral adipocytes. *Nephrol Dial Transplant* 2009;**24**:3626–31.
27. Pinto S, Roseberry AG, Liu H, Diano S, Shanabrough M, Cai X, Friedman JM, Horvath TL. Rapid rewiring of arcuate nucleus feeding circuits by leptin. *Science* 2004;**304**:110–5.
28. Castaneda-Sceppa C, Sarnak MJ, Wang X, Greene T, Madero M, Kusek JW, Beck G, Kopple JD, Levey AS, Menon V. Role of adipose tissue in determining muscle mass in patients with chronic kidney disease. *J Ren Nutr* 2007;**17**:314–22.
29. Rodriguez-Carmona A, Perez FM, Cordido F, Garcia FT, Garcia-Buela J. Hyperleptinemia is not correlated with markers of protein malnutrition in chronic renal failure. A cross-sectional study in predialysis, peritoneal dialysis and hemodialysis patients. *Nephron* 2000;**86**:274–80.
30. Cheung WW, Kuo HJ, Markison S, Chen C, Foster AC, Marks DL, Mak RH. Peripheral administration of the melanocortin-4 receptor antagonist NBI-12i ameliorates uremia-associated cachexia in mice. *J Am Soc Nephrol* 2007;**18**:2517–24.
31. Cheung W, Yu PX, Little BM, Cone RD, Marks DL, Mak RH. Role of leptin and melanocortin signaling in uremia-associated cachexia. *J Clin Investig* 2005;**115**:1659–65.
32. Dallmann R, Weyermann P, Anklin C, Boroff M, Bray-French K, Cardel B, Courdier-Fruh I, Deppe H, Dubach-Powell J, Erb M, Haefeli RH, Hennebohle M, Herzner H, Hufschmid M, Marks DL, Nordhoff S, Papp M, Rummey C, Santos G, Scharer F, Siendt H, Soeberdt M, Sumanovski LT, Terinek M, Mondadori C, Guven N, Feurer A. The orally active melanocortin-4 receptor antagonist BL-6020/979: a promising candidate for the treatment of cancer cachexia. *J Cachexia Sarcopenia Muscle* 2011;**2**:163–74.
33. Szczepanska M, Szprynger K, Mazur B, Zwolinska D, Kilis-Pstrusinska K, Makulska I. Plasma ghrelin levels in children with chronic renal failure on peritoneal dialysis. *Perit Dial Int* 2007;**27**:61–6.
34. Perez-Fontan M, Cordido F, Rodriguez-Carmona A, Peteiro J, Garcia-Naveiro R, Garcia-Buela J. Plasma ghrelin levels in patients undergoing haemodialysis and peritoneal dialysis. *Nephrol Dial Transplant* 2004;**19**:2095–100.
35. Iglesias P, Diez JJ, Fernandez-Reyes MJ, Codoceo R, Alvarez-Fidalgo P, Bajo MA, Aguilera A, Selgas R. Serum ghrelin concentrations in patients with chronic renal failure undergoing dialysis. *Clin Endocrinol* 2006;**64**:68–73.
36. Yoshimoto A, Mori K, Sugawara A, Mukoyama M, Yahata K, Suganami T, Takaya K, Hosoda H, Kojima M, Kangawa K, Nakao K. Plasma ghrelin and desacyl ghrelin concentrations in renal failure. *J Am Soc Nephrol* 2002;**13**:2748–52.
37. Muscaritoli M, Molfino A, Chiappini MG, Laviano A, Ammann T, Spinsanti P, Melchiorri D, Inui A, Alegiani F, Rossi FF. Anorexia in hemodialysis patients: the possible role of des-acyl ghrelin. *Am J Nephrol* 2007;**27**:360–5.
38. Pappas TN, Debas HT, Goto Y, Taylor IL. Peptide YY inhibits meal-stimulated pancreatic and gastric secretion. *Am J Physiol* 1985;**248**:G118–23.
39. Hegbrant J, Thysell H, Ekman R. Plasma levels of vasoactive regulatory peptides in patients receiving regular hemodialysis treatment. *Scand J Urol Nephrol* 1992;**26**:169–76.
40. Mak RH, Cheung W. Adipokines and gut hormones in end-stage renal disease. *Perit Dial Int* 2007;**27**(Suppl. 2):S298–302.
41. Greenough A, Cole G, Lewis J, Lockton A, Blundell J. Untangling the effects of hunger, anxiety, and nausea on energy intake during intravenous cholecystokinin octapeptide (CCK-8) infusion. *Physiol Behav* 1998;**65**:303–10.
42. Price SR, Gooch JL, Donaldson SK, Roberts-Wilson TK. Muscle atrophy in chronic kidney disease results from abnormalities in insulin signaling. *J Ren Nutr* 2010;**20**:S24–8.
43. Hu Z, Wang H, Lee IH, Du J, Mitch WE. Endogenous glucocorticoids and impaired insulin signaling are both required to stimulate muscle wasting under pathophysiological conditions in mice. *J Clin Investig* 2009;**119**:3059–69.
44. Pupim LB, Flakoll PJ, Majchrzak KM, Aftab Guy DL, Stenvinkel P, Ikizler TA. Increased muscle protein breakdown in chronic hemodialysis patients with type 2 diabetes mellitus. *Kidney Int* 2005;**68**: 1857–65.
45. Thomas SS, Dong Y, Zhang L, Mitch WE. Signal regulatory protein-alpha interacts with the insulin receptor contributing to muscle wasting in chronic kidney disease. *Kidney Int* 2013;**84**: 308–16.
46. Stitt TN, Drujan D, Clarke BA, Panaro F, Timofeyva Y, Kline WO, Gonzalez M, Yancopoulos GD, Glass DJ. The IGF-1/PI3K/Akt pathway prevents expression of muscle atrophy-induced ubiquitin ligases by inhibiting FOXO transcription factors. *Mol Cell* 2004; **14**:395–403.
47. Bailey JL, Zheng B, Hu Z, Price SR, Mitch WE. Chronic kidney disease causes defects in signaling through the insulin receptor substrate/phosphatidylinositol 3-kinase/Akt pathway: implications for muscle atrophy. *J Am Soc Nephrol* 2006;**17**:1388–94.
48. Rajan VR, Mitch WE. Muscle wasting in chronic kidney disease: the role of the ubiquitin proteasome system and its clinical impact. *Pediatr Nephrol* 2008;**23**:527–35.
49. Chonchol M, Scragg R. 25-Hydroxyvitamin D, insulin resistance, and kidney function in the Third National Health and Nutrition Examination Survey. *Kidney Int* 2007;**71**:134–9.
50. Norman AW, Frankel JB, Heldt AM, Grodsky GM. Vitamin D deficiency inhibits pancreatic secretion of insulin. *Science* 1980;**209**: 823–5.
51. Cade C, Norman AW. Vitamin D3 improves impaired glucose tolerance and insulin secretion in the vitamin D-deficient rat in vivo. *Endocrinology* 1986;**119**:84–90.

52. Mak RH. 1,25-Dihydroxyvitamin D3 corrects insulin and lipid abnormalities in uremia. *Kidney Int* 1998;**53**:1353–7.
53. Rabkin R, Sun DF, Chen Y, Tan J, Schaefer F. Growth hormone resistance in uremia, a role for impaired JAK/STAT signaling. *Pediatr Nephrol* 2005;**20**:313–8.
54. Feneberg R, Schaefer F, Veldhuis JD. Neuroendocrine adaptations in renal disease. *Pediatr Nephrol* 2003;**18**:492–7.
55. Haffner D, Schaefer F, Girard J, Ritz E, Mehls O. Metabolic clearance of recombinant human growth hormone in health and chronic renal failure. *J Clin Investig* 1994;**93**:1163–71.
56. Tonshoff B, Eden S, Weiser E, Carlsson B, Robinson IC, Blum WF, Mehls O. Reduced hepatic growth hormone (GH) receptor gene expression and increased plasma GH binding protein in experimental uremia. *Kidney Int* 1994;**45**:1085–92.
57. Edmondson SR, Baker NL, Oh J, Kovacs G, Werther GA, Mehls O. Growth hormone receptor abundance in tibial growth plates of uremic rats: GH/IGF-I treatment. *Kidney Int* 2000;**58**: 62–70.
58. Schaefer F, Chen Y, Tsao T, Nouri P, Rabkin R. Impaired JAK-STAT signal transduction contributes to growth hormone resistance in chronic uremia. *J Clin Investig* 2001;**108**:467–75.
59. Sun DF, Zheng Z, Tummala P, Oh J, Schaefer F, Rabkin R. Chronic uremia attenuates growth hormone-induced signal transduction in skeletal muscle. *J Am Soc Nephrol* 2004;**15**:2630–6.
60. Powell DR, Liu F, Baker BK, Hintz RL, Lee PD, Durham SK, Brewer ED, Frane JW, Watkins SL, Hogg RJ. Modulation of growth factors by growth hormone in children with chronic renal failure. The Southwest Pediatric Nephrology Study Group. *Kidney Int* 1997;**51**:1970–9.
61. Greenstein J, Guest S, Tan JC, Tummala P, Busque S, Rabkin R. Circulating growth hormone binding protein levels and mononuclear cell growth hormone receptor expression in uremia. *J Ren Nutr* 2006;**16**:141–9.
62. Garibotto G, Russo R, Sofia A, Ferone D, Fiorini F, Cappelli V, Tarroni A, Gandolfo MT, Vigo E, Valli A, Arvigo M, Verzola D, Ravera G, Minuto F. Effects of uremia and inflammation on growth hormone resistance in patients with chronic kidney diseases. *Kidney Int* 2008;**74**:937–45.
63. Herbst KL, Bhasin S. Testosterone action on skeletal muscle. *Curr Opin Clin Nutr Metab Care* 2004;**7**:271–7.
64. Reckelhoff JF, Yanes LL, Iliescu R, Fortepiani LA, Granger JP. Testosterone supplementation in aging men and women: possible impact on cardiovascular-renal disease. *Am J Physiol Renal Physiol* 2005;**289**:F941–8.
65. Cigarran S, Pousa M, Castro MJ, Gonzalez B, Martinez A, Barril G, Aguilera A, Coronel F, Stenvinkel P, Carrero JJ. Endogenous testosterone, muscle strength, and fat-free mass in men with chronic kidney disease. *J Ren Nutr* 2013;**23**:e89–95.
66. Carrero JJ, Qureshi AR, Parini P, Arver S, Lindholm B, Barany P, Heimburger O, Stenvinkel P. Low serum testosterone increases mortality risk among male dialysis patients. *J Am Soc Nephrol* 2009;**20**:613–20.
67. Haring R, Nauck M, Volzke H, Endlich K, Lendeckel U, Friedrich N, Dorr M, Rettig R, Kroemer HK, Wallaschofski H. Low serum testosterone is associated with increased mortality in men with stage 3 or greater nephropathy. *Am J Nephrol* 2011; **33**:209–17.
68. Carrero JJ, Stenvinkel P, Cuppari L, Ikizler TA, Kalantar-Zadeh K, Kaysen G, Mitch WE, Price SR, Wanner C, Wang AY, ter WP, Franch HA. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). *J Ren Nutr* 2013;**23**:77–90.
69. May RC, Kelly RA, Mitch WE. Mechanisms for defects in muscle protein metabolism in rats with chronic uremia. Influence of metabolic acidosis. *J Clin Investig* 1987;**79**:1099–103.
70. Mitch WE. Robert H Herman Memorial Award in Clinical Nutrition Lecture, 1997. Mechanisms causing loss of lean body mass in kidney disease. *Am J Clin Nutr* 1998;**67**:359–66.
71. Mitch WE, Price SR. Mechanisms activating proteolysis to cause muscle atrophy in catabolic conditions. *J Ren Nutr* 2003;**13**:149–52.
72. Chiu YW, Kopple JD, Mehrotra R. Correction of metabolic acidosis to ameliorate wasting in chronic kidney disease: goals and strategies. *Semin Nephrol* 2009;**29**:67–74.
73. Mitch WE, Medina R, Grieber S, May RC, England BK, Price SR, Bailey JL, Goldberg AL. Metabolic acidosis stimulates muscle protein degradation by activating the adenosine triphosphate-dependent pathway involving ubiquitin and proteasomes. *J Clin Investig* 1994;**93**:2127–33.
74. Abramowitz MK, Melamed ML, Bauer C, Raff AC, Hostetter TH. Effects of oral sodium bicarbonate in patients with CKD. *Clin J Am Soc Nephrol* 2013;**8**:714–20.
75. Mak RH. Insulin and its role in chronic kidney disease. *Pediatr Nephrol* 2008;**23**:355–62.
76. Barreto DV, Barreto FC, Liabeuf S, Temmar M, Lemke HD, Tribouilloy C, Choukroun G, Vanholder R, Massy ZA. Plasma interleukin-6 is independently associated with mortality in both hemodialysis and pre-dialysis patients with chronic kidney disease. *Kidney Int* 2010;**77**:550–6.
77. Menon V, Greene T, Wang X, Pereira AA, Marcovina SM, Beck GJ, Kusek JW, Collins AJ, Levey AS, Sarnak MJ. C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. *Kidney Int* 2005;**68**:766–72.
78. Gupta J, Mitra N, Kanetsky PA, Devaney J, Wing MR, Reilly M, Shah VO, Balakrishnan VS, Guzman NJ, Girndt M, Periera BG, Feldman HI, Kusek JW, Joffe MM, Raj DS. Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. *Clin J Am Soc Nephrol* 2012;**7**:1938–46.
79. Goncalves S, Pecoits-Filho R, Perreto S, Barberato SH, Stinghen AE, Lima EG, Fuerbringer R, Sauthier SM, Riella MC. Associations between renal function, volume status and endotoxaemia in chronic kidney disease patients. *Nephrol Dial Transplant* 2006;**21**:2788–94.
80. Ioannidou E, Swede H, Dongari-Bagtzoglou A. Periodontitis predicts elevated C-reactive protein levels in chronic kidney disease. *J Dent Res* 2011;**90**:1411–5.
81. Anders HJ, Andersen K, Stecher B. The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease. *Kidney Int* 2013;**83**:1010–6.
82. Ramos LF, Shintani A, Ikizler TA, Himmelfarb J. Oxidative stress and inflammation are associated with adiposity in moderate to severe CKD. *J Am Soc Nephrol* 2008;**19**:593–9.
83. Cheung WW, Paik KH, Mak RH. Inflammation and cachexia in chronic kidney disease. *Pediatr Nephrol* 2010;**25**:711–24.
84. Raj DS, Moseley P, Dominic EA, Onime A, Tzamaloukas AH, Boyd A, Shah VO, Glew R, Wolfe R, Ferrando A. Interleukin-6 modulates hepatic and muscle protein synthesis during hemodialysis. *Kidney Int* 2008;**73**:1054–61.
85. Raj DS, Shah H, Shah VO, Ferrando A, Bankhurst A, Wolfe R, Zager PG. Markers of inflammation, proteolysis, and apoptosis in ESRD. *Am J Kidney Dis* 2003;**42**:1212–20.
86. Raj DS, Carrero JJ, Shah VO, Qureshi AR, Barany P, Heimburger O, Lindholm B, Ferguson J, Moseley PL, Stenvinkel P. Soluble CD14 levels, interleukin 6, and mortality among prevalent hemodialysis patients. *Am J Kidney Dis* 2009; **54**:1072–80.
87. Guttridge DC, Mayo MW, Madrid LV, Wang CY, Baldwin Jr AS. NF-kappaB-induced loss of MyoD messenger RNA: possible role in muscle decay and cachexia. *Science* 2000;**289**:2363–6.
88. Sun DF, Chen Y, Rabkin R. Work-induced changes in skeletal muscle IGF-1 and myostatin gene expression in uremia. *Kidney Int* 2006;**70**:453–9.

89. Heszele MF, Price SR. Insulin-like growth factor I: the yin and yang of muscle atrophy. *Endocrinology* 2004;**145**:4803–5.
90. Verzola D, Procopio V, Sofia A, Villaggio B, Tarroni A, Bonanni A, Mannucci I, De CF, Gianetta E, Saffioti S, Garibotto G. Apoptosis and myostatin mRNA are upregulated in the skeletal muscle of patients with chronic kidney disease. *Kidney Int* 2011;**79**:773–82.
91. Mak RH, Ikizler AT, Kovesdy CP, Raj DS, Stenvinkel P, Kalantar-Zadeh K. Wasting in chronic kidney disease. *J Cachexia Sarcopenia Muscle* 2011;**2**:9–25.
92. Xu J, Li R, Workeneh B, Dong Y, Wang X, Hu Z. Transcription factor FoxO1, the dominant mediator of muscle wasting in chronic kidney disease, is inhibited by microRNA-486. *Kidney Int* 2012; **82**:401–11.
93. Pickering WP, Price SR, Bircher G, Marinovic AC, Mitch WE. Walls J: nutrition in CAPD: serum bicarbonate and the ubiquitin-proteasome system in muscle. *Kidney Int* 2002;**61**:1286–92.
94. Workeneh BT, Mitch WE. Review of muscle wasting associated with chronic kidney disease. *Am J Clin Nutr* 2010;**91**:1128S–32S.
95. Garcia D, Shaw RJ. AMPK: mechanisms of cellular energy sensing and restoration of metabolic balance. *Mol Cell* 2017;**66**:789–800.
96. Rodriguez FJ, Ligon AH, Horkayne-Szakaly I, Rushing EJ, Ligon KL, Vena N, Garcia DI, Cameron JD, Eberhart CG. BRAF duplications and MAPK pathway activation are frequent in gliomas of the optic nerve proper. *J Neuropathol Exp Neurol* 2012; **71**:789–94.
97. Kikuchi H, Sasaki E, Nomura N, Mori T, Minamishima YA, Yoshizaki Y, Takahashi N, Furusho T, Arai Y, Mandai S, Yamashita T, Ando F, Maejima Y, Isobe K, Okado T, Rai T, Uchida S, Sohara E. Failure to sense energy depletion may be a novel therapeutic target in chronic kidney disease. *Kidney Int* 2019;**95**:123–37.
98. Peng H, Cao J, Yu R, Danesh F, Wang Y, Mitch WE, Xu J, Hu Z. CKD stimulates muscle protein loss via Rho-associated protein kinase 1 activation. *J Am Soc Nephrol* 2016;**27**:509–19.
99. Liu X, Yu R, Sun L, Garibotto G, Lin X, Wang Y, Thomas SS, Li R, Hu Z. The nuclear phosphatase SCP4 regulates FoxO transcription factors during muscle wasting in chronic kidney disease. *Kidney Int* 2017;**92**:336–48.
100. Grune T, Reinheckel T, Davies KJ. Degradation of oxidized proteins in mammalian cells. *FASEB J* 1997;**11**:526–34.
101. Grune T, Merker K, Sandig G, Davies KJ. Selective degradation of oxidatively modified protein substrates by the proteasome. *Biochem Biophys Res Commun* 2003;**305**:709–18.
102. Dounousi E, Papavasiliou E, Makedou A, Ioannou K, Katopodis KP, Tselepis A, Siamopoulos KC, Tsakiris D. Oxidative stress is progressively enhanced with advancing stages of CKD. *Am J Kidney Dis* 2006;**48**:752–60.
103. Raj DS, Dominic EA, Pai A, Osman F, Morgan M, Pickett G, Shah VO, Ferrando A, Moseley P. Skeletal muscle, cytokines, and oxidative stress in end-stage renal disease. *Kidney Int* 2005; **68**:2338–44.
104. Stenvinkel P, Heimburger O, Paultre F, Diczfalusy U, Wang T, Berglund L, Jogestrand T. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 1999;**55**:1899–911.
105. Panichi V, Migliori M, De PS, Taccola D, Bianchi AM, Giovannini L, Norpoth M, Metelli MR, Cristofani R, Bertelli AA, Sbragia G, Tetta C, Palla R, Colombo R. C-reactive protein and interleukin-6 levels are related to renal function in predialytic chronic renal failure. *Nephron* 2002;**91**:594–600.
106. Cukor D, Cohen SD, Peterson RA, Kimmel PL. Psychosocial aspects of chronic disease: ESRD as a paradigmatic illness. *J Am Soc Nephrol* 2007;**18**:3042–55.
107. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Trevino-Becerra A, Wanner C. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int* 2008;**73**:391–8.
108. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, McAllister CJ, Alcorn Jr H, Kopple JD, Greenland S. Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction. *Nephrol Dial Transplant* 2005;**20**:1880–8.
109. Kaysen GA. Malnutrition and the acute-phase reaction in dialysis patients-how to measure and how to distinguish. *Nephrol Dial Transplant* 2000;**15**:1521–4.
110. Beddhu S, Chen X, Wei G, Raj D, Raphael KL, Boucher R, Chonchol MB, Murtaugh MA, Greene T. Associations of protein-energy wasting syndrome criteria with body composition and mortality in the general and moderate chronic kidney disease populations in the United States. *Kidney Int Rep* 2017;**2**: 390–9.
111. Beddhu S, Wei G, Chen X, Boucher R, Kiani R, Raj D, Chonchol M, Greene T, Murtaugh MA. Associations of dietary protein and energy intakes with protein-energy wasting syndrome in hemodialysis patients. *Kidney Int Rep* 2017;**2**:821–30.
112. Stevens J, Nowicki EM. Body mass index and mortality in asian populations: implications for obesity cut-points. *Nutr Rev* 2003; **61**:104–7.
113. Kakiya R, Shoji T, Tsujimoto Y, Tatsumi N, Hatsuda S, Shinohara K, Kimoto E, Tahara H, Koyama H, Emoto M, Ishimura E, Miki T, Tabata T, Nishizawa Y. Body fat mass and lean mass as predictors of survival in hemodialysis patients. *Kidney Int* 2006;**70**:549–56.
114. Axelsson J, Qureshi AR, Divino-Filho JC, Barany P, Heimburger O, Lindholm B, Stenvinkel P. Are insulin-like growth factor and its binding proteins 1 and 3 clinically useful as markers of malnutrition, sarcopenia and inflammation in end-stage renal disease? *Eur J Clin Nutr* 2006;**60**:718–26.
115. Beddhu S, Pappas LM, Ramkumar N, Samore M. Effects of body size and body composition on survival in hemodialysis patients. *J Am Soc Nephrol* 2003;**14**:2366–72.
116. Kalantar-Zadeh K, Kuwae N, Wu DY, Shantouf RS, Fouque D, Anker SD, Block G, Kopple JD. Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. *Am J Clin Nutr* 2006;**83**:202–10.
117. Chertow GM, Lowrie EG, Wilmore DW, Gonzalez J, Lew NL, Ling J, Leboff MS, Gottlieb MN, Huang W, Zebrowski B. Nutritional assessment with bioelectrical impedance analysis in maintenance hemodialysis patients. *J Am Soc Nephrol* 1995;**6**: 75–81.
118. Workeneh BT, Rondon-Berrios H, Zhang L, Hu Z, Ayehu G, Ferrando A, Kopple JD, Wang H, Storer T, Fournier M, Lee SW, Du J, Mitch WE. Development of a diagnostic method for detecting increased muscle protein degradation in patients with catabolic conditions. *J Am Soc Nephrol* 2006;**17**:3233–9.
119. Ikizler TA. A patient with CKD and poor nutritional status. *Clin J Am Soc Nephrol* 2013;**8**:2174–82.
120. Cano NJ, Aparicio M, Brunori G, Carrero JJ, Cianciaruso B, Fiaccadori E, Lindholm B, Teplan V, Fouque D, Guarnieri G. ESPEN guidelines on parenteral nutrition: adult renal failure. *Clin Nutr* 2009;**28**:401–14.
121. Kopple JD. National kidney foundation K/DOQI clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis* 2001;**37**:S66–70.

122. Boivin MA, Battah SI, Dominic EA, Kalantar-Zadeh K, Ferrando A, Tzamaloukas AH, Dwivedi R, Ma TA, Moseley P, Raj DS. Activation of caspase-3 in the skeletal muscle during haemodialysis. *Eur J Clin Investig* 2010;**40**:903–10.
123. Steiber AL, Kalantar-Zadeh K, Secker D, McCarthy M, Sehgal A, McCann L. Subjective Global Assessment in chronic kidney disease: a review. *J Ren Nutr* 2004;**14**:191–200.
124. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. *N Engl J Med* 2017;**377**:1765–76.
125. Wing MR, Raj DS. A balancing act: protein-energy wasting in chronic kidney disease. *Am J Physiol Renal Physiol* 2012;**303**: F1608–9.
126. Gupta RK, Kuppusamy T, Patrie JT, Gaylinn B, Liu J, Thorner MO, Bolton WK. Association of plasma des-acyl ghrelin levels with CKD. *Clin J Am Soc Nephrol* 2013;**8**:1098–105.
127. Ashby DR, Ford HE, Wynne KJ, Wren AM, Murphy KG, Busbridge M, Brown EA, Taube DH, Ghatei MA, Tam FW, Bloom SR, Choi P. Sustained appetite improvement in malnourished dialysis patients by daily ghrelin treatment. *Kidney Int* 2009;**76**:199–206.
128. Wynne K, Giannitsopoulou K, Small CJ, Patterson M, Frost G, Ghatei MA, Brown EA, Bloom SR, Choi P. Subcutaneous ghrelin enhances acute food intake in malnourished patients who receive maintenance peritoneal dialysis: a randomized, placebo-controlled trial. *J Am Soc Nephrol* 2005;**16**:2111–8.
129. Siew ED, Ikizler TA. Insulin resistance and protein energy metabolism in patients with advanced chronic kidney disease. *Semin Dial* 2010;**23**:378–82.
130. Wang X, Hu Z, Hu J, Du J, Mitch WE. Insulin resistance accelerates muscle protein degradation: activation of the ubiquitin-proteasome pathway by defects in muscle cell signaling. *Endocrinology* 2006;**147**:4160–8.
131. Brunelli SM, Thadhani R, Ikizler TA, Feldman HI. Thiazolidinedione use is associated with better survival in hemodialysis patients with non-insulin dependent diabetes. *Kidney Int* 2009; **75**:961–8.
132. Carrero JJ, Qureshi AR, Nakashima A, Arver S, Parini P, Lindholm B, Barany P, Heimburger O, Stenvinkel P. Prevalence and clinical implications of testosterone deficiency in men with end-stage renal disease. *Nephrol Dial Transplant* 2011;**26**:184–90.
133. Johansen KL, Mulligan K, Schambelan M. Anabolic effects of nandrolone decanoate in patients receiving dialysis: a randomized controlled trial. *J Am Med Assoc* 1999;**281**:1275–81.
134. Johansen KL, Painter PL, Sakkas GK, Gordon P, Doyle J, Shubert T. Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: a randomized, controlled trial. *J Am Soc Nephrol* 2006;**17**:2307–14.
135. Eiam-Ong S, Buranaosot S, Eiam-Ong S, Wathanavaha A, Pansin P. Nutritional effect of nandrolone decanoate in predialysis patients with chronic kidney disease. *J Ren Nutr* 2007;**17**:173–8.
136. Kopple JD, Cheung AK, Christiansen JS, Djurhuus CB, El NM, Feldt-Rasmussen B, Lange M, Mitch WE, Wanner C, Wiedemann J, Ikizler TA. OPPORTUNITY: a randomized clinical trial of growth hormone on outcome in hemodialysis patients. *Clin J Am Soc Nephrol* 2008;**3**:1741–51.
137. Fine RN, Kohaut EC, Brown D, Perlman AJ. Growth after recombinant human growth hormone treatment in children with chronic renal failure: report of a multicenter randomized double-blind placebo-controlled study. Genentech Cooperative Study Group. *J Pediatr* 1994;**124**:374–82.
138. Hardin DS. Treatment of short stature and growth hormone deficiency in children with somatotropin (rDNA origin). *Biologics* 2008;**2**:655–61.
139. Mehls O, Schaefer F. Missed OPPORTUNITY: growth hormone therapy in adults with CKD. *Nephrol Dial Transplant* 2011;**26**: 3835–7.
140. Haffner D, Schaefer F, Nissel R, Wuhl E, Tonshoff B, Mehls O. Effect of growth hormone treatment on the adult height of children with chronic renal failure. German Study Group for Growth Hormone Treatment in Chronic Renal Failure. *N Engl J Med* 2000; **343**:923–30.
141. Feldt-Rasmussen B, Lange M, Sulowicz W, Gafter U, Lai KN, Wiedemann J, Christiansen JS, El NM. Growth hormone treatment during hemodialysis in a randomized trial improves nutrition, quality of life, and cardiovascular risk. *J Am Soc Nephrol* 2007;**18**:2161–71.
142. Niemczyk S, Sikorska H, Wiecek A, Zukowska-Szczechowska E, Zalecka K, Gorczynska J, Kubik M, Czerwienska B, Gosek K, Veldhuis JD, Wagner DA, Gaudreau P, Hakonen T, Kay SW, Jouhikainen T, Schaefer F. A super-agonist of growth hormone-releasing hormone causes rapid improvement of nutritional status in patients with chronic kidney disease. *Kidney Int* 2010; **77**:450–8.
143. Kosmadakis GC, John SG, Clapp EL, Viana JL, Smith AC, Bishop NC, Bevington A, Owen PJ, McIntyre CW, Feehally J. Benefits of regular walking exercise in advanced pre-dialysis chronic kidney disease. *Nephrol Dial Transplant* 2012;**27**:997–1004.
144. Balakrishnan VS, Rao M, Menon V, Gordon PL, Pilichowska M, Castaneda F, Castaneda-Sceppa C. Resistance training increases muscle mitochondrial biogenesis in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2010;**5**:996–1002.
145. Castaneda C, Gordon PL, Parker RC, Uhlin KL, Roubenoff R, Levey AS. Resistance training to reduce the malnutrition-inflammation complex syndrome of chronic kidney disease. *Am J Kidney Dis* 2004;**43**:607–16.
146. Biolo G, Ciocchi B, Bosutti A, Situlin R, Toigo G, Guarnieri G. Pentoxifylline acutely reduces protein catabolism in chronically uremic patients. *Am J Kidney Dis* 2002;**40**:1162–72.
147. Szeto CC, Wong TY, Chow KM, Leung CB, Li PK. Oral sodium bicarbonate for the treatment of metabolic acidosis in peritoneal dialysis patients: a randomized placebo-control trial. *J Am Soc Nephrol* 2003;**14**:2119–26.
148. Stein A, Moorhouse J, Iles-Smith H, Baker F, Johnstone J, James G, Troughton J, Bircher G, Walls J. Role of an improvement in acid-base status and nutrition in CAPD patients. *Kidney Int* 1997;**52**: 1089–95.
149. Bossola M, Giungi S, Tazza L, Luciani G. Long-term oral sodium bicarbonate supplementation does not improve serum albumin levels in hemodialysis patients. *Nephron Clin Pract* 2007;**106**: c51–6.
150. Brady JP, Hasbargen JA. Correction of metabolic acidosis and its effect on albumin in chronic hemodialysis patients. *Am J Kidney Dis* 1998;**31**:35–40.
151. Williams AJ, Dittmer ID, McArley A, Clarke J. High bicarbonate dialysate in haemodialysis patients: effects on acidosis and nutritional status. *Nephrol Dial Transplant* 1997;**12**:2633–7.
152. Papadoyannakis NJ, Stefanidis CJ, McGeown M. The effect of the correction of metabolic acidosis on nitrogen and potassium balance of patients with chronic renal failure. *Am J Clin Nutr* 1984;**40**:623–7.
153. Reaich D, Channon SM, Scrimgeour CM, Daley SE, Wilkinson R, Goodship TH. Correction of acidosis in humans with CRF decreases protein degradation and amino acid oxidation. *Am J Physiol* 1993;**265**:E230–5.
154. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol* 2009;**20**:2075–84.

155. Dubey AK, Sahoo J, Vairappan B, Haridasan S, Parameswaran S, Priyamvada PS. Correction of metabolic acidosis improves muscle mass and renal function in chronic kidney disease stages 3 and 4: a randomized controlled trial. *Nephrol Dial Transplant* 2018:gfy214.
156. Di IB, Aucella F, Conte G, Cupisti A, Santoro D. A prospective, multicenter, randomized, controlled study: the correction of metabolic acidosis with use of bicarbonate in Chronic Renal Insufficiency (UBI) Study. *J Nephrol* 2012;**25**:437–40.
157. Gaggl M, Cejka D, Plischke M, Heinze G, Fraunschiel M, Schmidt A, Horl WH, Sunder-Plassmann G. Effect of oral sodium bicarbonate supplementation on progression of chronic kidney disease in patients with chronic metabolic acidosis: study protocol for a randomized controlled trial (SoBic-Study). *Trials* 2013; **14**:196.
158. Bellasi A, Di ML, Santoro D, Marzocco S, De SE, Cozzolino M, Di LL, Guastaferro P, Di IB. Correction of metabolic acidosis improves insulin resistance in chronic kidney disease. *BMC Nephrol* 2016;**17**:158.
159. Kalantar-Zadeh K, Cano NJ, Budde K, Chazot C, Kovesdy CP, Mak RH, Mehrotra R, Raj DS, Sehgal AR, Stenvinkel P, Ikizler TA. Diets and enteral supplements for improving outcomes in chronic kidney disease. *Nat Rev Nephrol* 2011;**7**:369–84.
160. Heaf JG, Honore K, Valeur D, Randlov A. The effect of oral protein supplements on the nutritional status of malnourished CAPD patients. *Perit Dial Int* 1999;**19**:78–81.
161. Moretti HD, Johnson AM, Keeling-Hathaway TJ. Effects of protein supplementation in chronic hemodialysis and peritoneal dialysis patients. *J Ren Nutr* 2009;**19**:298–303.
162. Laorpatanaskul S, Pochanugool C, Sitprija V. The use of oral essential amino acids in hemodialysis patients. *J Med Assoc Thail* 1991;**74**:66–70.
163. Gonzalez-Espinoza L, Gutierrez-Chavez J, del Campo FM, Martinez-Ramirez HR, Cortes-Sanabria L, Rojas-Campos E, Cueto-Manzano AM. Randomized, open label, controlled clinical trial of oral administration of an egg albumin-based protein supplement to patients on continuous ambulatory peritoneal dialysis. *Perit Dial Int* 2005;**25**:173–80.
164. Pupim LB, Flakoll PJ, Brouillette JR, Levenhagen DK, Hakim RM, Ikizler TA. Intradialytic parenteral nutrition improves protein and energy homeostasis in chronic hemodialysis patients. *J Clin Investig* 2002;**110**:483–92.
165. Eustace JA, Coresh J, Kutchey C, Te PL, Gimenez LF, Scheel PJ, Walser M. Randomized double-blind trial of oral essential amino acids for dialysis-associated hypoalbuminemia. *Kidney Int* 2000; **57**:2527–38.
166. Teixido-Planas J, Ortiz A, Coronel F, Montenegro J, Lopez-Menchero R, Ortiz R, Gomez C, Donate T. Oral protein-energy supplements in peritoneal dialysis: a multicenter study. *Perit Dial Int* 2005;**25**:163–72.
167. Pupim LB, Majchrzak KM, Flakoll PJ, Ikizler TA. Intradialytic oral nutrition improves protein homeostasis in chronic hemodialysis patients with deranged nutritional status. *J Am Soc Nephrol* 2006; **17**:3149–57.
168. Cano NJ, Fouque D, Roth H, Aparicio M, Azar R, Canaud B, Chauveau P, Combe C, Laville M, Leverve XM. Intradialytic parenteral nutrition does not improve survival in malnourished hemodialysis patients: a 2-year multicenter, prospective, randomized study. *J Am Soc Nephrol* 2007;**18**:2583–91.
169. Guida B, Parolisi S, Coco M, Ruoppo T, Veccia R, di MM, Trio R, Memoli A, Cataldi M. The impact of a nutritional intervention based on egg white for phosphorus control in hemodialyis patients. *Nutr Metabol Cardiovasc Dis* 2019;**29**:45–50.
170. Montes-Delgado R, Guerrero Riscos MA, Garcia-Luna PP, Martin HC, Pereira Cunill JL, Garrido VM, Lopez M,I, Suarez Garcia MJ, Martin-Espejo JL, Soler Junco ML, Barbosa MF. Treatment with low-protein diet and caloric supplements in patients with chronic kidney failure in predialysis. Comparative study. *Rev Clin Esp* 1998;**198**:580–6.
171. Kasiske BL, Lakatua JD, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am J Kidney Dis* 1998;**31**:954–61.
172. Levey AS, Greene T, Sarnak MJ, Wang X, Beck GJ, Kusek JW, Collins AJ, Kopple JD. Effect of dietary protein restriction on the progression of kidney disease: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. *Am J Kidney Dis* 2006;**48**:879–88.
173. Mitch WE, Walser M, Steinman TI, Hill S, Zeger S, Tungsanga K. The effect of a keto acid-amino acid supplement to a restricted diet on the progression of chronic renal failure. *N Engl J Med* 1984;**311**:623–9.
174. Prakash S, Pande DP, Sharma S, Sharma D, Bal CS, Kulkarni H. Randomized, double-blind, placebo-controlled trial to evaluate efficacy of ketodiet in predialytic chronic renal failure. *J Ren Nutr* 2004;**14**:89–96.
175. Levey AS, Adler S, Caggiula AW, England BK, Greene T, Hunsicker LG, Kusek JW, Rogers NL, Teschan PE. Effects of dietary protein restriction on the progression of advanced renal disease in the Modification of Diet in Renal Disease Study. *Am J Kidney Dis* 1996;**27**:652–63.
176. Aparicio M, Bellizzi V, Chauveau P, Cupisti A, Ecder T, Fouque D, Garneata L, Lin S, Mitch WE, Teplan V, Zakar G, Yu X. Protein-restricted diets plus keto/amino acids–a valid therapeutic approach for chronic kidney disease patients. *J Ren Nutr* 2012; **22**:S1–21.
177. National Kidney Foundation. *Dietary guidelines for adults starting on hemodialysis*. National Kidney Fundation; 2015. 1-29-2019. Ref Type: Online Source.
178. Scialla JJ, Appel LJ, Wolf M, Yang W, Zhang X, Sozio SM, Miller III ER, Bazzano LA, Cuevas M, Glenn MJ, Lustigova E, Kallem RR, Porter AC, Townsend RR, Weir MR, Anderson CA. Plant protein intake is associated with fibroblast growth factor 23 and serum bicarbonate levels in patients with chronic kidney disease: the Chronic Renal Insufficiency Cohort study. *J Ren Nutr* 2012;**22**:379–88.
179. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, Britt EB, Fu X, Wu Y, Li L, Smith JD, DiDonato JA, Chen J, Li H, Wu GD, Lewis JD, Warrier M, Brown JM, Krauss RM, Tang WH, Bushman FD, Lusis AJ, Hazen SL. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med* 2013;**19**:576–85.
180. Garneata L, Stancu A, Dragomir D, Stefan G, Mircescu G. Ketoanalogue-supplemented vegetarian very low-protein diet and CKD progression. *J Am Soc Nephrol* 2016;**27**:2164–76.
181. Ikizler TA, Cano NJ, Franch H, Fouque D, Himmelfarb J, Kalantar-Zadeh K, Kuhlmann MK, Stenvinkel P, TerWee P, Teta D, Wang AY, Wanner C. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. *Kidney Int* 2013;**84**:1096–107.
182. Kopple JD, Monteon FJ, Shaib JK. Effect of energy intake on nitrogen metabolism in nondialyzed patients with chronic renal failure. *Kidney Int* 1986;**29**:734–42.
183. Aguilera A, Bajo MA, Espinoza M, Olveira A, Paiva AM, Codoceo R, Garca P, Sanchez S, Celadilla O, Castro MJ, Selgas R. Gastrointestinal and pancreatic function in peritoneal dialysis patients: their relationship with malnutrition and peritoneal membrane abnormalities. *Am J Kidney Dis* 2003;**42**: 787–96.

QUESTIONS AND ANSWERS

Question 1

A 35-year-old woman with type 1 diabetes mellitus since childhood (age 12) was admitted to the hospital because of recurrent nausea, vomiting, anorexia, and weight loss. Individuals like her with PEW in CKD have nutrient insufficiency due to which of the following reasons?

A. Anorexia, increased energy expenditure, changes in gastric motility, changes in taste
B. Anorexia, gastric hypermotility changes, increased energy expenditure, disruption of appetite sensing molecules, changes in taste, depression, and inflammation
C. Increased energy expenditure, disruption of appetite sensing molecules, depression
D. Anorexia, gastric hypomotility changes, disruption of appetite sensing molecules, changes in taste, depression, and inflammation
E. Anorexia, gastric hypomotility changes, increased energy expenditure, disruption of appetite sensing molecules, depression, and inflammation

Answer: D

CKD patients have (1) spontaneous decrease in energy and protein intake, (2) changes in gastric motility that prevent nutrient uptake, (3) disruption of appetite sensing molecules, such as ghrelin and leptin, (4) changes in taste, (5) changes in mental status, such as depression, and (6) increased inflammatory cytokines. Patients with CKD do not have increased energy expenditure, but patients with ESRD do show increased energy expenditure. However, adjustment for LBM in ESRD patients changes energy expenditure levels comparable to individuals with normal kidney function. This patient has gastric hypomotility issues which contribute to her nutrient insufficiency.

Question 2

Insulin resistance contributes to PEW by which of the following reasons?

A. Increasing glucocorticoid levels, increasing expression of FOXO, activation of atrogin-1 and MuRF1, increasing muscle proteolysis through the ubiquitin signaling pathway
B. Metabolic acidosis, increasing glucocorticoid levels, increased FOXO activity, activation of atrogin-1 and MuRF1, increasing muscle proteolysis through the ubiquitin signaling pathway
C. Increasing glucocorticoid levels, increased FOXO activity, activation of atrogin-1 and MuRF1, increasing muscle proteolysis through the ubiquitin signaling pathway
D. Increasing glucocorticoid levels, increasing expression of FOXO, activation of atrogin-1 and MuRF1, increasing muscle proteolysis through the ubiquitin signaling pathway, low vitamin D levels
E. Increased FOXO activity, activation of atrogin-1 and MuRF1, increasing muscle proteolysis through the ubiquitin signaling pathway

Answer: C

CKD patients have insulin resistance, which contributes to PEW in the following ways: (1) increased glucocorticoid levels, (2) increased FOXO activity, (3) activation of E3 ubiquitin conjugating enzymes atrogin-1 and MuRF1, (4) increasing muscle proteolysis through the ubiquitin signaling pathway. Metabolic acidosis and low vitamin D exacerbates insulin resistance but do not directly contribute to PEW through insulin resistance.

Question 3

A 62-year-old man with long-standing history of hypertension for 20 years and stage 4 CKD was admitted to the hospital due to fever, cough, and weight loss of one-month duration. A chest X-ray revealed a right-sided lobar pneumonia. Which of the following causes of PEW is most likely behind his symptoms?

A. Inflammation
B. Insulin resistance
C. Anorexia and nutrient insufficiency
D. Muscle biology dysfunction
E. Oxidative stress

Answer: A

This man is suffering from pneumonia, increasing his inflammation. Inflammation causes PEW by contributing to insulin resistance, GH resistance. It also activates the ubiquitin signaling pathway and induces expression of glucocorticoids.

Question 4

A 45-year-old female with recently diagnosed nephrotic syndrome was admitted to the hospital because of anorexia and increased leg swelling with 3+ leg edema. Urinalysis on admission showed 4+ proteinuria. Which of the following are necessary for a diagnosis of PEW?

A. Biochemical indicators such as albumin, serum prealbumin, or serum cholesterol
B. Weight loss
C. Loss of muscle mass
D. Unintentional low protein or energy intake
E. At least three of the four answers above

Answer: E

At least three of the four criteria above must be met: (1) biochemical indicators such as albumin, serum prealbumin, or serum cholesterol, (2) weight loss, (3) loss of muscle mass, (4) unintentional low protein or energy intake. In addition, measurement of these criteria should be seen at least three times at intervals of two to four weeks.

Question 5

Which of the following treatments has decreased inflammation as one if its benefits?

A. MC4-R antagonists
B. Resistance training
C. Insulin-sensitizing agents such as rosiglitazone or thiazolidinedione
D. A and B
E. All of the above

Answer: D

Both MC4-R antagonists and resistance training have demonstrated decreased inflammation as measured by inflammatory cytokines. Resistance training lowered levels of IL-6 and CRP, while MC4-R antagonism returned levels of IL-6 and TNF-α to normal.

CHAPTER

17

Aging and the Kidney: Clinical and Pathophysiologic Issues

Lynn E. Schlanger, James L. Bailey, Jeff M. Sands

Renal Division, Emory University, Atlanta, GA, United States

Abstract

The aging kidney undergoes structural and functional phenotypic changes with time. There is a decline in glomerular filtration rate, renal plasma flow, and tubular function, characterized histologically by glomerulosclerosis, tubulointerstitial fibrosis, and atrophy. These changes appear to be influenced by the environment, genetic factors, and gender and result in a profibrotic, proinflammatory, apoptotic state. These adaptations may increase the elderly's susceptibility to acute and chronic kidney disease (CKD), allograft failure, and be responsible for the higher mortality rates frequently seen in the elderly. Modification of the cellular and molecular mechanisms underlying age-associated renal changes, with various medications, transcription factor inhibitors, or caloric restriction may modify or attenuate these changes and prevent progression to CKD.

INTRODUCTION

At the turn of the last century, a person's life expectancy was around 50 years of age, and it was rare for most individuals to live into their 70s. With advances in medical technology, the average life span has increased. It is now 76.1 years for men and 81.1 years for women in the US.[1] In parallel with this longevity, the population of the elderly (aged 65–80 years) and the very elderly (aged greater than 80 years) in the US has grown from 3.1 million at the turn of the 20th century to 40.3 million in 2010.[2] This number is expected to double by 2050.[2]

With this growth, there has been a rise in the prevalence of chronic kidney disease (CKD) in the elderly.[3–5] The National Health and Examination Nutrition Survey (NHANES) observed an increase in the prevalence of CKD from 10.3% in 1988 to 13.1% in 2004.[5] Over 48% of those with CKD stages 3–5 were 70 years of age or older. This rise in CKD was attributed to diabetes mellitus, obesity, and hypertension, which are factors commonly associated with aging. With aging, there is a decline in adaptive capacity to hemodynamic changes, an increase in apoptosis, and changes in gene expression that result in fibrosis and inflammation.[6–10]

The kidney undergoes structural changes beginning in the third to fourth decade of life that are associated with morphologic changes, such as an increase in glomerulosclerosis, tubulointerstitial fibrosis, vascular hyalinosis, and arterial intimal fibrosis.[9,11,12] Glomerular filtration rate (GFR), renal plasma flow (RPF), and renal tubular function decline, while renal vascular resistance (RVR) increases as patients[12] and experimental animals age.[13] These findings were underscored by the Baltimore Longitudinal Study of Aging, which observed middle- and upper-class male volunteers ranging from 22 to 97 years of age over a 23-year span.[14,15] During the study, five or more serial 24-hour urine collections for creatinine clearance determinations were obtained from each volunteer. After age 40, mean decline in the creatinine clearance was 0.75 mL/min/year in those with no underlying disease, renal disease, or hypertension.[15] There was a greater rate of decline with increasing age, -1.49 ± 0.29 mL/min/year in the 70 to 79.9 age group, compared with -0.35 mL/min/year in the 40–49.9 age group.[14] This decline correlated independently with an elevated mean arterial blood pressure greater than 107 mm Hg. Interestingly, this was not a universal finding. A third of the volunteers showed no decline of renal function with aging, and a very small percentage actually showed a statistically significant increase in renal function.[15]

Age-related kidney changes are associated with a mild loss of function in the presence of no underlying illness. What is considered normal kidney function in

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00017-6

the elderly and very elderly, and what are the consequences? The decline in GFR, RPF, and tubular function is usually well tolerated, with no adverse outcomes unless the kidney is exposed to exogenous or endogenous stresses. With aging, there is a decreased ability of the kidney to adapt to stress. This may account for the higher age-related incidence in acute kidney injury (AKI) leading to CKD,[16,17] an increase in electrolyte abnormalities,[18] and an increased risk of cardiovascular disease (CVD).[19,20] Understanding the changes in the cellular and molecular pathways in the aging kidney may provide insight into prevention and treatment and decrease the high prevalence of CKD with its associated morbidity and mortality.

PATHOPHYSIOLOGY

Structural and Morphologic Changes

The aged human kidney grossly appears granular and pitted because of underlying arterial disease and loss of lobulations. Although renal mass increases from 50 g at birth to greater than 400 g during the third and fourth decades of life, it generally declines to less than 300 g by the ninth decade of life.[9,21] Gourtsoyiannis and colleagues [22] studied renal parenchymal volume in 360 individuals, ranging from 20 to 80 years of age, with no underlying renal disease or radiologic abnormalities by computerized tomography (CT) scans. There was a 10% decline per decade in the renal parenchymal volume, irrespective of gender, beginning around the third to fourth decade. The most rapid decline occurred in the group 60–70 years of age. In another study, predonation CT scan images of 1520 living kidney donors showed an increase in cysts and smaller cortical volume:medullary volume ratio, that was associated with nephrosclerosis with aging and accounted for the decline in volume with aging.[23]

In humans, the histological and morphological changes seen in "aging-related nephropathy" were mainly gathered from postmortem exams[24,25] and living "healthy" kidney donors (LKD).[11,23,26,27] In rats, similar studies were done, but the changes varied among species and gender.[6,13,28–32] Certain strains developed severe changes accompanied by proteinuria, while others had only very mild changes. Therefore, conclusions and comparisons from animal studies to the human condition need to be made with caution.

The dominant "aging" morphologic findings include expansion of the mesangium in the cortical sclerotic glomeruli with sparing of the medulla, cell proliferation resulting in obliteration of the glomerular loop, capillary tuft collapse, podocyte enlargement and detachment, reduplication of glomerular basement membranes and Bowman's capsule with areas of focal thickening, synechiae of glomeruli within Bowman's capsule, tubulointerstitial fibrosis, and tubular atrophy (Figure 17.1 and Table 17.1).[9,11,12,24–27] Although these changes were noted in the mid-1900s, the expected number of sclerotic glomeruli with aging was not well established until 1975. At that time, Kaplan and colleagues[24] determined the incidence of glomerulosclerosis in 122 autopsied kidneys ranging from 1 to 89 years of age, from patients with no underlying renal disease. They

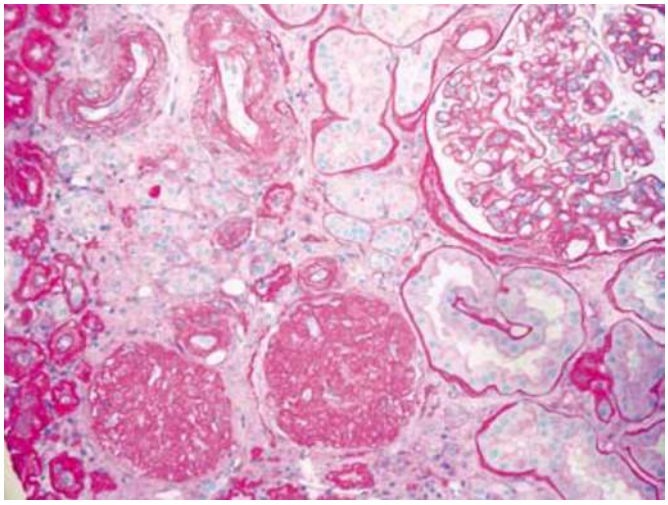


FIGURE 17.1 The aging kidney. Two glomeruli show solidified global glomerulosclerosis (GSG). The nonsclerotic glomerulus displays ischemic changes. There are also moderate tubular atrophy and interstitial fibrosis. The arterioles reveal significant hyalinosis (periodic acid–Schiff stain; ×200). Permission granted. Reference 9.

TABLE 17.1 Morphologic Changes in the Aging Kidney

	Changes
Glomeruli	Global sclerosis
	Wrinkling glomerulus
	Synechiae within Bowman's capsule
	Replication of glomerular basement membrane
	Hypertrophy
	Atrophy and absorption
Interstitium	Tubular atrophy
	Loss of peritubular capillaries
	Interstitial fibrosis
	Inflammatory cells
Vessels	Hyalinosis of arterioles
	Arterial intimal fibrosis
	Aglomerular afferent–efferent arterioles

observed less than 10% sclerotic glomeruli in those younger than 40 years of age, and greater than 10% sclerotic glomeruli in those older than 40 years of age. Forty years later, Kremers et al.[26] used quantile regression to estimate the 95th percentile of GSG as an upper reference limit for age in 2052 LKD kidney biopsies. In the 18- to 29-year-old group, there was 1 GSG compared with 5.5 GSG in those 70 years old, in biopsy samples with 17−32 glomeruli.[26] Those with hypertension had an increased risk of GSG compared with those without underlying comorbidities, suggesting that the upper limit of GSG in healthy LKD may help differentiate between aging and an underlying disease processes and prognosis.

In a cross-sectional study of LKD biopsies, there was a 48% lower number of nonsclerotic glomeruli (NSG) in the youngest group, compared with the oldest group of donors, from 990,661 to 520,410 NSG.[27] This was accompanied by a 15% increase in GSG on biopsy in the oldest group, as well as a 16% loss of cortical volume as determined from the predonation CT scan. This greater decline in NSG and a decrease in cortical volume was the result of both atrophy and reabsorption of the sclerotic glomeruli.[27]

As in other renal diseases, there are changes in the interstitium with aging that may correlate with prognosis and progression. Tubulointerstitial damage consists of tubular atrophy, intratubular casts, tubular dilation, thickening and splitting of the basement membranes, and widening of the interstitium from fibrosis.[9,30,31] Thomas and colleagues[30] evaluated the changes in the tubulointerstitial area by immunohistochemistry in Sprague-Dawley rats at 3 ($n = 9$) and 24 months of age ($n = 8$). The 24-month-old rats had an increase in interstitial fibrosis and tubular injury associated with areas of focal tubular cell proliferation, apoptosis, myofibroblast activation, and inflammation with macrophage/lymphocyte infiltration. This correlated with immunostaining for proliferating cell nuclear antigen, terminal deoxynucleotidyl transferase dUTP nick end labeling, α smooth muscle actin, and 1ED-1/OX-1, respectively. Type IV collagen was also increased. The loss of the cortical peritubular capillaries was associated with scarring and atrophy, with attenuation of endothelial nitric oxide synthetase (NOS) and a decline in the numbers of endothelial cells (RECA-1).

Abrass and colleagues[32] observed changes in the degree and composition of extracellular matrix (ECM) in aging Fischer 344 rats, with interstitial fibrosis being one of the earliest findings. The change in composition of the ECM consisted of a greater accumulation of fibronectin (FN) and thrombospondin, as well as accumulation of collagen III and extra domain A (ED-A)-FN, in areas adjacent to atrophic tubules. Other findings included thickening of both the glomerular basement membrane and Bowman's capsule with greater laminin isoforms than collagen IV and FN. In animal studies, these areas were associated with an increase in expression of transforming growth factor (TGF)-β RNA and protein, suggesting there is gene upregulation resulting in inflammation and fibrosis in aging.[6,7] The ECM accumulates as a consequence of an imbalance between production and degradation of the matrix.

Satoh and colleagues[33] observed loss of angiogenesis in the hypoxic areas in the cortex, characterized by decreased expression of vascular endothelial growth factor and decline in RECA-1 antibody staining in 24-month-old Wistar rats. This coincided with mitochondrial dysfunction, suggesting a decrease in O_2 sensing as a cause for the disturbance in angiogenesis.

Arteriosclerosis is found in the renal vessels with aging.[34,35] Takazakura et al.[34] noted an increase in two types of arteriole-glomerular units in 63 autopsied kidneys, ranging from 9 months to 92 years of age with aging. The cortex showed various stages of degeneration with aging and culminated in atrophic arteriole-glomerular units. In the medulla, continuity of afferent and efferent arterioles was maintained with an intervening degenerated glomerulus. This was termed the "continuous type," resulting in the diversion of blood to the medulla. In the smaller renal arteries, there was progressive reduplication of the elastic lamina and associated intimal thickening with medial hypertrophy, intimal proliferation, and hyalinization that was most pronounced in vessels less than 100 micrometers in diameter. In human studies, a greater correlation was observed between the degree of arterial intimal fibrodysplasia in the arcuate and interlobular arteries and glomerulosclerosis than from hyaline afferent arteriolosclerosis and glomerulosclerosis.[36,37]

Clinical and Functional Changes

With age, there is a decline in kidney function that is marked by a decrease in GFR and RPF,[12,38] inability to concentrate or dilute urine,[39] an alteration in sodium homeostasis,[40] decreased responsiveness to vasodilators,[41,42] decreased ability to excrete acid and potassium,[18,43] and decreased levels of serum renin and aldosterone.[44] (Table 17.2). Davies et al.[38] observed a decline in the GFR and effective renal plasma flow (eRPF) with advancing age in 72 males free of cardiac and renal disease, ranging from 24 to 89 years of age. There were declines in inulin clearance by 46% (from 122.6 to 65.3 mL/min/1.73 m^2), in eRPF by 53% (from 613 to 289 mL plasma/min/1.73 m^2), and tubular excretory capacity by 43.5%. The filtration fraction increased significantly with age.

TABLE 17.2 Functional Changes in the Aging Kidney

Decrease of renal blood flow by 10% per year after age 40
Glomerular filtration rate decreases after age 40
Increase in renal vascular resistance
Decreased diluting capacity
Decreased concentrating capacity
Slow response to salt deprivation or salt load
Decreased excretion of potassium and acid
Abnormal renal reserve

Hoang and colleagues[12] studied two groups to determine the mechanism for hypofiltration noted in aging. In group 1, with 152 healthy individuals ranging from 18 to 88 years of age, there was a negative correlation of advancing age and GFR and RPF, which was similar to previous findings. In group 2 with 33 LKD, with donor ages ranging from 23 to 69 years, morphometric analysis was performed to determine the glomerular hydraulic permeability and filtration surface area. Mathematical models were used to calculate the glomerular ultrafiltration coefficient (Kf) for 2-kidneys from the GFR determinants and a single nephron (SN) Kf from morphometric analysis. They observed a decline in the 2-kidney K_f from 53% to 21% ($p < 0.005$). SNKf declined by 30% ($p = 0.09$). Hoang and colleagues concluded that the decline in GFR with aging was from structural changes that lower the Kf, partly related to a decline in the number of functioning glomeruli.[12]

In a large study in 1388 LKD, the SNGFR was maintained until 70 years of age, with a decline in total GFR. The decline in total GFR in aging was from the decline in the number of functioning glomeruli.[45]

Glomerulopenia is likely one of the causes for the decline in GFR, but what influence does nephrosclerosis have? In a 10-year cross-sectional study, the prevalence of nephrosclerosis and its relationship to GFR in 1203 LKD was studied.[11] Nephrosclerosis was defined by the presence of two or more of the following: glomerulosclerosis, tubular atrophy, interstitial fibrosis >5%, and arteriosclerosis. Nephrosclerosis was noted to increase with age from less than 5% in people from 18 to 29 years old to 73% in people 70–77 years old. They found no correlation between the degree of nephrosclerosis and the decline in GFR with age, suggesting there were additional mechanisms responsible for the decline in kidney function rather than the degree of sclerosis.

Fuiano et al.[41] evaluated the maximal functional renal reserve in "healthy" kidney donors by infusing a combination of amino acids and renal dose dopamine in younger and older participants. The younger group had a greater increase in the GFR and RPF following the amino acid infusion than the older group (43% vs. 20%, $p < 0.05$ and 43% vs. 25%, $p < 0.005$, respectively). RVR was higher in the older group before and after infusion. There was also a blunted response to both the amino acid and dopamine infusion. This decline in RPF and increase in the RVR may be associated with functional or structural changes in the renal vasculature.

In both animal and human studies, there is an attenuated response to vasodilators including nitric oxide (NO), endothelial-derived hyperpolarizing factor, and prostacyclin, whereas there is an exaggerated response to angiotensin II in the aging kidney.[42,46–48] Hollenberg and colleagues[46] evaluated renal perfusion and vascular responsiveness in 207 subjects from 17 to 76 years of age undergoing renal arteriogram. The xenon washout technique was used to measure flow per unit tissue mass. Blood flow declined more than renal mass with aging, suggesting that the loss of renal perfusion was secondary to the loss of renal blood flow that began at age 40. The renal vascular response to acetylcholine, a vasodilator, and angiotensin II, a vasoconstrictor, was tested in a subgroup. The effect of acetylcholine on the renal vasculature was attenuated in the older age group, while the angiotensin II response was not different in either age group. In contrast, vasoconstriction increased with infusion of angiotensin II with aging in animal studies.

In the kidney, NO is a vasodilator and an inhibitor of mesangial growth and matrix production.[13,48] NO is synthesized from L-arginine by NOS. It is inhibited by a selective NOS inhibitor, asymmetric dimethylarginine, through competitive blockade.[13,42] Kielstein et al.[47] evaluated the effect of NO and the contribution of plasma ADMA on renal hemodynamics in young adults, healthy normotensive elderly, and mild hypertensive elderly participants. There was a decrease in GFR and RPF in the elderly groups compared with the younger subjects. Renovascular resistance and plasma levels of ADMA were increased significantly in the elderly groups compared with the younger subjects. In adjusted logistic regression analysis, only ADMA levels were an independent determinant of RVR ($r^2 = 0.67$) and RPF ($r^2 = 0.80$).

Loss of the vasodilator response may predispose the elderly to AKI[17] because of their inability to tolerate hypotension from sepsis, volume depletion, or certain medications. AKI in the elderly is associated with a poor prognosis. Although there may be recovery from the acute insult, renal function often worsens with time, culminating in a higher incidence of ESRD and increased mortality. A study of a cohort of hospitalized elderly Medicare patients examined the risk of ESRD in those who develop AKI.[16] After adjustment for age, gender, race, diabetes, and hypertension, the hazard ratio for developing ESRD was 41.2 for those with AKI and CKD, 25.2 for those with AKI only, and 8.4 for those

with underlying CKD without AKI. The likelihood of progressing to ESRD at 2 years was 7.0% for AKI only, 14.3% for AKI and CKD, and only 2.5% for CKD only. The risk was just 0.5% in those patients without AKI or CKD.

With aging, both animal and human subjects demonstrate a decreased ability to concentrate and dilute the urine. In large part, this accounts for the increased prevalence of hyponatremia (23.6%) and hypernatremia (1.3%) in the elderly population.[49] Hyponatremia is most likely to be iatrogenic, and commonly related to the many medications prescribed to the elderly, such as thiazide diuretics, selective serotonin reuptake inhibitors, and antiseizure medications.[50–53] Another common cause of hyponatremia is the syndrome of inappropriate antidiuretic hormone release. The hospital mortality associated with hyponatremia approaches 47% and is associated with both short- and long-term mortality.[52] Even mild hyponatremia has been associated with an increased risk for fractures, decreased reaction time and unstable gait, and an increase in short- and long-term mortality.[50,53]

Hypernatremia is common in the infirm, particularly in those with an inability to get to a water source.[54] The majority of elderly patients presenting to the hospital have a higher serum sodium concentration (S[Na]) than younger patients. This degree of hypernatremia does not correlate with an increase in mortality, but recurrence during the hospital stay is associated with an elevated mortality rate. The overall high mortality of 48.7% appears to be associated with the underlying disease process.[54]

Why are elderly persons more prone to water disorders? With aging, there is a decreased sensation of thirst, coupled with a decrease in intake of both water and solutes. There is also an inability to dilute and concentrate the urine, and total body water is decreased.[39,55,56] Although secretion of vasopressin is not decreased, older patients respond to dehydration with an increased release of vasopressin. The response may even be greater than seen in younger adults. Even so, elderly patients are unable to concentrate their urine to the level younger adults achieve. This suggests that renal responses may be involved in the development of both hyponatremia and hypernatremia in the elderly.

Animal studies show changes in the transporters in the distal nephron, which may play a role in the handling of water and solutes in the aging.[56–59] In rat studies, there is a decreased expression with aging of many of the transporters and channels responsible for maintaining the countercurrent system in the medulla, which is responsible in large part for dilution or concentration of the urine.[56,57] In older female WAG/Rij rats, there is downregulation of aquaporin (AQP) 2 and 3 in the inner medulla, by 80 and 50%, respectively, but only a modest decrease in AQP2 in the outer medulla compared with 3-month-old rats.[56] No changes in AQP1 or AQP4 expression were found.[56] Under normal conditions, older female WAG/Rij rats show a decline in the abundance of AQP2 vesicles and phosphorylated AQP2 located in subapical vesicles in the inner medullary collecting tubules.[57] With water deprivation, older rats showed an increase in abundance of AQP2 and P-AQP2 in the apical membrane location in the inner medulla. This was accompanied by an increase in urine osmolality, elevated vasopressin levels, and a decrease in urine volume, but the urine was never as concentrated as that attained in young adult rats.[57]

Urea transporters (UT) in the inner medulla also have a major role in concentrating the urine.[39,58] Downregulation of UT-A1, UT-A3, and UT-B1 expression in the tip of the inner medulla was observed in aging rats.[39,58] Other cotransporters and channels that have a role in diluting and concentrating ability are downregulated as well.[39,59] These include the sodium-potassium-chloride cotransporter (NKCC2), the epithelial sodium channel (ENaC) β- and γ-subunits, the sodium-chloride cotransporter ,and the sodium hydrogen exchanger.[39,59] The reason for the decrease in expression of these transporters is not known but may be secondary to an increased oxidative state found with aging. This is supported by a study examining the effect of N-acetylcysteine, a reactive oxygen species (ROS) scavenger and vasodilator in Wistar rats.[60] Compared with controls, the treated rats showed an increase in protein expression of AQP2, UT-A1, NKCC2, and klotho and a decrease in expression of p53 and inflammatory cells.

In older subjects, there is a decreased ability to excrete a potassium load.[43] This becomes apparent when medications that interfere with potassium excretion are prescribed. In both animal and human studies, there is a decrease in serum and urine renin and aldosterone levels that may contribute to a decline in potassium excretion.[44,61] There is also a decrease in excretion of an acid load and a decreased ability to conserve sodium or excrete a salt load with aging.[18]

PATHOGENESIS

The cellular and molecular mechanisms responsible for the phenotypic changes of aging are being identified. Cellular senescence, genetics, oxidative stress, and mitochondrial dysfunction are linked to cellular and molecular changes in aging (Figure 17.2).[62,63,66–73] Cellular senescence is characterized by cell cycle arrest in the G1 phase, either from loss of a critical telomere length known as “replicative senescence” or from stress related to aberrant signaling-induced senescence.[8,63] In humans, replicative senescence was observed *in vitro*

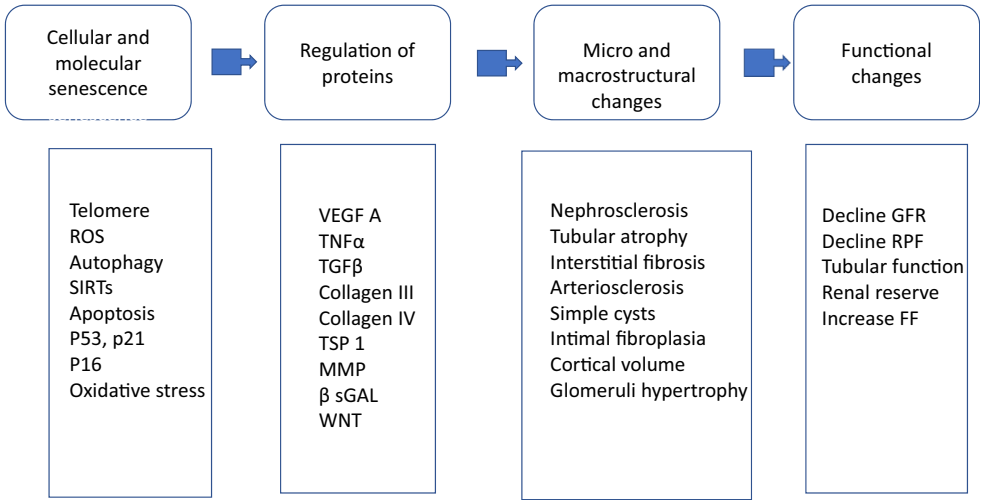


FIGURE 17.2 A schematic of senescence beginning at the cellular level with cellular arrest from loss of the telomere and increase in stress. There is a decline in cell replication and change in the expression of proteins disrupting the adaptability with an increase in fibrosis/atrophy and a decline in the regeneration of vessels and in the breakdown of extracellular matrix. This results in the loss of kidney function. References 20,25,32,40,41,43,62–65.

by Haylick, who noted cessation of replication after a critical number of cell divisions. With each cell division, there is a loss of the telomere DNA sequence, TTAGGG. TTAGGG is a nucleoprotein cap on the end of the double-stranded DNA that protects the DNA against chromosomal fusion.[8,63] When the telomere reaches a critical length, the cell cycle arrests, no further division through the $p53/p21^{WAF1/CIP1}$ pathway occurs, and apoptosis results. There is an increase in senescence markers, such as senescence-associated β-galactosidase (SA β-gal) and lipofuscin granules.[8,63] Interestingly, rodents contain telomerase that allows the telomere to repair and lengthen, but even so Melk et al.[63] showed cell cycle arrest in rats. Besides replicative senescence, cell cycle arrest can occur through stress with an increase in expression of $P16^{INK4a}$.[68] $P16^{INK4a}$ is a cyclin-dependent kinase (CDK) inhibitor of CDK 4 and 6. $P16^{INK4a}$ results in hypophosphorylation of a retinoblastoma protein as well, through the $p53/p21^{CIF1/WAF1}$ pathway.[67] The expression of $P16^{INK4a}$ has been found in the cortex and medulla in aging human kidneys and is seen in areas of inflammation, fibrosis, and apoptosis. These cells are metabolically active but are reprogrammed for expression of proinflammatory and profibrotic cytokines such as TGF-β, tumor necrosis factor-α, and vascular cell adhesion molecule (VCAM)-1.[6,67]

Wiggins and colleagues[71] performed an elegant study evaluating the linear alteration in glomerular gene expression in Fischer 344 rats from 2 to 24 months of age on an ad libitum vs. a caloric restricted (CR) diet. Using genetic techniques, they identified a pattern of gene expression in aging glomeruli that resembled atherosclerosis, involving proinflammatory and profibrotic processes. Nuclear factor-kappa B (NF-κB) was further identified as a transcription factor candidate for these alterations in gene expression, suggesting a common pathway for diseases and aging in organs.

Mitochondria have been proposed to play a key role in aging.[66,68,70] Mitochondrial (mt) DNA is altered more with aging and is partially responsible for the increase in ROS that results in disruption of the redox state and an increase in oxidative stress and damage commonly seen with aging.[69–71] Protein oxidation and lipid peroxidation cause cellular and protein damage that culminates in apoptosis and the decline in autophagy and replication.[70,74]

SIRT1[64,65,72,74–76] and klotho[73,77–83] are considered antiaging modulators. Sirtuins are members of the Sir2 (silent information regulator 2) family, and seven mammalian Sirtuins have been identified.[64,75] The most widely studied in the kidney is SIRT1. They are class III deacetylases. Of the seven Sirtuins, Sirt1 has been the most extensively studied, for its role in life span longevity in the setting of CR. SIRT1, a NAD^+-dependent protein deacetylase, functions as an intracellular energy sensor *via* NAD^+. It regulates and attenuates intracellular hypoxia-induced fibrosis, inflammation, and apoptosis. Sirt1 deacetylates many intranuclear transcription factors and proteins.[65,74,76] SIRT1 declines with aging, possibly from increased oxidative stress. Various roles of Sirt1 that occur through deacetylation have been identified. These include inhibiting the activity of NF-κB,[64] apoptosis by p53 deacetylation, increasing autophagy through forkhead box 03 (FOXO 3),[76] and suppressing TGF-β-related apoptosis

through Smad7 deacetylation.[65] More recently, it was shown that SIRT1 has a role in maintaining podocyte function. SIRT1 declines with age, resulting in damage and loss of podocytes.[72]

The *klotho* (kl) gene is known as the antiaging gene. Klotho-deficient mice display a premature aging phenotype, commonly found in humans, characterized by osteoporosis, arteriosclerosis, atrophic skin, emphysema, and shortened life span.[77] Klotho regulates calcium and phosphorus metabolism and is critical in the development of mineral bone disease.[78] The *klotho* gene encodes a single pass transmembrane protein that is expressed predominantly in the distal convoluted tubules, the parathyroid gland, and the choroid plexus.[79] There is a decline in the renal expression of both klotho mRNA and protein in CKD patients.[80] When its transmembrane protein binds with a coreceptor specific for fibroblast growth factor-23, phosphate reabsorption and production of $1,25(OH)_2D_3$ are suppressed. Besides the membrane-bound protein, there is a soluble klotho protein.[81] This soluble klotho protein is released from the extracellular membrane into the serum and urine, but declines with age, and has an inverse relationship with decline in estimated GFR (eGFR) in the elderly.[81]

Soluble klotho affects local transporters, including ROMK-1, transient receptor potential vallinoid (TRPV) 5 and 6, the calcium channel, and the NaPi-2a transporter.[82] In mutant kl^{-}/kl^{-} deficient mice, treatment with an intraperitoneal infusion of soluble klotho ameliorated the age-related phenotype. There was a decrease in renal fibrosis through the downregulation of TGF-β and $p21^{cip1}$ expression and a decrease in renal and aortic calcification compared with vehicle treated kl^{-}/kl^{-} mice.[83]

Autophagy plays a role in aging and the degradation pathway in the cell. Autophagy is responsible for the removal of damaged organelles and aberrant macromolecules, thereby preventing further injury and cellular dysfunction. Cellular homeostasis is maintained.[62]

DIAGNOSIS

There are no clinical laboratory tests to diagnose changes in the aging kidney in healthy elderly individuals with a GFR greater than 60 mL/min/1.73 m^2. The normal GFR for those who are elderly and very elderly has been an area of debate. Should those with eGFR slightly lower than 60 mL/min/1.73 m^2 with no other clinical findings to suggest CKD such as proteinuria, active urine sediment or radiologic findings be considered to have normal function consistent with aging, or do they have CKD? This can and will affect referrals, medical expenses, and concerns for patients.

The loss of muscle mass with aging makes S[Cr] a poor surrogate marker for changes in renal function.[84,85] On the other hand, cystatin C, a cysteine protease inhibitor, is not affected by changes in muscle mass or urinary secretion and is a more reliable marker for determining changes in renal function. Fliser and colleagues[78] compared serum cystatin C and S[Cr] as GFR markers to measured inulin clearance in 16 healthy normotensive young adults, 22 healthy normotensive older adults, and 19 hypertensive older adults. They observed cystatin C to be a superior marker for the decline in GFR compared with S[Cr] in the elderly. Unfortunately, cystatin C is not readily available for clinical use. Instead the Modification of Diet in Renal Disease (MDRD) GFR, which was formulated in 1999, is used to determine one's GFR clinically and has replaced the Cockcroft–Gault formula. The MDRD equation has been reformulated to improve its bias, accuracy, and precision in those with a GFR greater than 60 mL/min/1.73 m^2, because the S[Cr]-based GFR underestimates the measured (m) GFR in the general population. Many of the S[Cr]-based GFRs were validated in a younger population, but not in the elderly. In the healthy older population, the eGFR may fall within CKD stages 2 to 3a and be considered normal.

A newer formula, the CKD-EPI (CKD Epidemiology Collaboration), used a more diverse pool of patients and is more accurate and less biased than previous MDRD-derived formulas.[86] Unfortunately, these studies did not include a large older population. Using cross-sectional analyses, Inker and colleagues[87] developed CKD-EPI based on cystatin C alone or S[Cr]-cystatin C (cr-cyst) formulas and compared the two. A total of 5352 participants were included. There was good representation of the elderly (13% and 21% in each group, respectively). Improved accuracy and precision were found in the cr-cyst-based formulation, with 16.9% of the cr-cyst group reclassified into a higher CKD classification.

In a prospective cohort study, 394 participants greater than 74 years of age of European ancestry were recruited to validate four GFR formulas: $CKD\text{-}EPI_{cr}$, $MDRD_{cr}$, $CKD\text{-}EPI_{cyst}$, and $CKD\text{-}EPI_{cr\text{-}cyst}$, compared with mGFR. For GFR less than 60 mL/min/1.73 m^2, the $MDRD_{cr}$, $CKD\text{-}EPI_{cr}$, and $CKD\text{-}EPI_{cr\text{-}cyst}$ overestimated and $CKD\text{-}EPI_{cyst}$ underestimated the GFR.[88] All equations overestimated the GFR when it exceeded 60 mL/min/1.732 m^2, but the three CKD-EPI formulas were more accurate. Although using iothalamate to determine the GFR is ideal, it is not clinically feasible, so various eGFR formulas must be used. Overall, the creatinine-cystatin C formulated GFR was satisfactory in both older patients and in younger age groups. The overestimate of eGFR and use of S[Cr]-based formulas

in the elderly may underestimate the true number of elderly people diagnosed with CKD.

Albuminuria is a well-established clinical marker for underlying renal disease and endothelial dysfunction. In rodents, there is an increase in proteinuria that coincides with the decline in renal function and histological changes that typically occur with aging. This is not true for healthy elderly individuals. A Spanish population-based study evaluated the prevalence of albuminuria in men and women with aging.[89] There was a greater prevalence of albuminuria in the elderly than in the younger cohort, 10.9 vs. 3.4% ($p < 0.001$). Albuminuria was commonly associated with hypertension, and to a lesser degree with diabetes mellitus. Similarly, NHANES studies evaluated the prevalence of microalbuminuria in the US population, sampling 22,244 participants 6 years of age or older.[90] The presence of microalbuminuria increased after 40 years of age. There was a greater prevalence in those with underlying diabetes, hypertension, and female gender. The prevalence of microalbuminuria in those older than 60 years of age with no adverse conditions was only 4.9% in men and 5.4% in women.

TREATMENT

Understanding how the kidney ages may lead to interventions that prevent or retard the progression of CKD. Today, CR is the only established intervention shown to combat aging. CR has been shown to increase longevity in some animal species, decrease oxidative stress, improve metabolic parameters, and ameliorate phenotypic aging.[6,58,59,91–96] Two longitudinal studies in nonhuman primates involving rhesus monkeys, *Macaca mulatta*, showed mixed results.[91,92] The Wisconsin National Primate Research Center (WNPRC) study showed a benefit of CR, whereas the National Institute of Aging (NIA) study showed no increase in longevity.[92] The WNPRC found an increase in longevity with CR with a 37% incidence of death in the control group vs. 13% in the CR group.[92] NIA found no increase in life span with CR, but there was improvement in many of the health issues which accompany aging, including glucoregulatory function, oxidative stress, and a decreased incidence of malignancies.[91] The decrease in longevity was associated with hyperinsulinemia. Because of this discrepancy, a direct comparison of the longitudinal data from both studies was performed and included survival, body weight, food intake, fasting glucose level, and age-related morbidity.[93] Differences in diet, age of onset on CR diet, and origin of the rhesus monkey may have affected the differences; however, the authors concluded that both CR studies showed a benefit.[93]

In a randomized controlled study of healthy overweight sedentary individuals, Heilbrom and colleagues[94] evaluated biomarkers of longevity, metabolic adaptation, and oxidative stress when they were randomly placed on four different diets: (a) weight maintenance, (b) 25% CR diet, (c) 12.5% CR diet and 12.5% exercise energy expenditure, and (d) severe CR diet followed by a maintenance diet for 6 months. Over the short time period, those on the CR diet displayed a significant decline in body energy expenditure, insulin levels, core temperature, and a decrease in DNA damage. Sirtuins appear to play a role in the CR diet by decreasing oxidative stress, increasing autophagy, and decreasing apoptosis.[62,74] Wood and colleagues[95] observed increased longevity in metazoans placed on the sirtuin activator agent (STAC), resveratrol, which was similar to that seen with CR alone. In the presence of Sir-2.1 (mammalian homolog null mutants), the addition of STAC had no effect on longevity.

Besides increasing longevity, CR decreases oxidative stress and apoptosis while improving autophagy and cell survival in various animal studies.[74,96] Adult C57BL/6 mice on long-term CR showed attenuation of mitochondrial DNA oxidative damage, with improved histology and function, and an increase in autophagy in the proximal convoluting tubule (PCT) compared with *ad libitum* fed mice.[74] CR increased expression of the Sirt1/Foxo3/Bnip and p27Kip1 pathways and resulted in hypoxia-induced autophagy, cellular arrest, and decline in apoptosis in the PCT. Short-term CR can also attenuate oxidative stress. Jung and colleagues[96] evaluated a 10-day CR in Fischer 344 male rats aged 6 and 24 months. They observed suppression in oxidative stress and inhibition of the oxidative-induced proinflammatory transcription factor, NF-κB, and decline in expression of proinflammatory enzymes and adhesion molecules linked to aging (such as inducible NOS, cyclooxygenase-2, VCAM-1, and intracellular adhesion molecule-1).

CR may be difficult for elderly persons to sustain. Moreover, there is the danger that such a diet may result in malnutrition. An alternative might be prescribing an "antiaging medication." This may seem preposterous. However, certain medications prescribed for the elderly population for diabetes mellitus, hypertension, and atherosclerosis have been touted for their antiaging effects. These medications include N-acetylcysteine,[60] metformin,[97] thiazolidinedione,[98,99] resveratrol,[95] HMG-CoA reductase inhibitors,[100] and angiotensin receptor blockers.[30]

Recently, promising results using pioglitazone, a thiazolidinedione, which is a well-known peroxisome proliferation-activated receptor γ agonist, show that it may reverse or attenuate the aging process.[99] In a

murine model using atherosclerotic prone mice (apolipoprotein E-deficient ($ApoE^{-/-}$) mice), the effect of pioglitazone on aging phenotype and morphologic changes was studied. The long term and low dose of pioglitazone significantly reduced aortic atherosclerosis, age-related nephrosclerosis, hepatic steatosis, and improved skin turgor compared with control. The treated mice showed a decline in inflammation with a decline in myeloperoxidase, reduction of ROS, an increase in Sirt1 mRNA and klotho mRNA, and a decrease in p53.[99] Therefore, pioglitazone may be an agent against aging and age-related disorders. Further research is necessary to determine whether such treatments may have an effect on general aspects of aging, kidney function, and meaningful outcomes.

SUMMARY

The aging kidney undergoes structural and functional phenotypic changes with time. There is a decline in GFR, RPF, and tubular function, characterized histologically by glomerulosclerosis, tubulointerstitial fibrosis, and atrophy. These changes appear to be influenced by the environment, genetic factors, and gender and result in a profibrotic, proinflammatory, apoptotic state. These adaptations may increase the elderly's susceptibility to acute and CKD, allograft failure, and be responsible for the higher mortality rates frequently seen in the elderly. Modification of selected cellular and molecular mechanisms with various medications, transcription factor inhibitors, or CR may modify or attenuate these changes and prevent progression to CKD. As nephrologists, we need to be cognizant of changes in the aging kidney, shortcomings of the estimation of GFR in elderly, and the effect of medications frequently prescribed such as NSAIDS, diuretics, and RAAS-blocking agents in our patients.

References

1. Kochanek KD, Murphy SL, Xu J. *Mortality in the United States, 2016. NCHS Data Brief. No. 293*. Hyattville, MD: National Center for Health Statistics; 2016.
2. *65+ in United States: 2010-census*. http://www.census.gov/prod/2014pubs/p23-212.pdf.
3. Hallan SI, Coresh J, Astor BC, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol* 2006;**17**(8):2275–84.
4. *2016 USRDS annual data report: epidemiology of kidney disease in the United States, volume 1: CKD in the United States*. https://www.usrds.org/2016/download/v1.CKD_16.pdf.
5. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *J Am Med Assoc* 2007;**298**(17):2038–47.
6. Lim JH, Kim EN, Kim MY, et al. Age-associated molecular changes in the kidney in aged mice. *Oxid Med Cell Longev* 2012;**2012**:1–10.
7. Sataranatarajan K, Feliers D, Mariappan MM, et al. Molecular events in matrix protein metabolism in aging kidney. *Aging Cell* 2012;**11**(6):1065–73.
8. Yang H, Fogo AB. Cell senescence in the aging kidney. *J Am Soc Nephrol* 2010;**21**(9):1436–9.
9. Zhou XJ, Rakheja D, Yu X, Saxena R, Vaziri ND, Silva GF. The aging kidney. *Kidney Int* 2008;**74**(6):710–20.
10. Joosten SA, van Ham V, Nolan CE, et al. Telomere shortening and cellular senescence in model of chronic renal allograft rejection. *Am J Pathol* 2003;**162**(4):1305–12.
11. Rule AD, Amer H, Cornell LD, et al. The association between age and nephrosclerosis on renal biopsy among healthy adults. *Ann Intern Med* 2010;**152**(9):561–7.
12. Hoang K, Tan JC, Derby G, et al. Determinants of glomerular hypofiltration in aging humans. *Kidney Int* 2003;**64**(4):1417–24.
13. Baylis C. Change in renal hemodynamics and structure in the aging kidney; sexual dimorphism and the nitric oxide system. *Exp Gerontol* 2005;**40**(4):271–8.
14. Lindeman RD, Tobin JD, Shock NW. Association between blood pressure and the rate of decline in the renal function with age. *Kidney Int* 1984;**26**(6):861–8.
15. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc* 1985;**33**(4):278–85.
16. Ishani A, Xue JL, Himmelfarb PW, et al. Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol* 2009;**20**(1):223–8.
17. Abeulo JG. Normotensive ischemic acute kidney failure. *N Engl J Med* 2007;**357**(8):797–805.
18. Luckey AE, Parsa CJ. Fluid and electrolytes in the aged. *Arch Surg* 2003;**138**(10):1055–60.
19. Fried LF, Shlipak MG, Crump C, Bleyer AJ, Gottdiener JS, Kronmal RA. Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. *J Am Coll Cardiol* 2003;**41**(3):1364–72.
20. O'Hare AM, Bertenthal D, Covinsky KE, et al. Mortality risk stratification in chronic kidney disease: one size for all ages? *J Am Soc Nephrol* 2006;**17**(3):846–53.
21. Luyckx VA, Brenner BM. The clinical importance of nephron mass. *J Am Soc Nephrol* 2010;**21**(6):898–910.
22. Gourtsoyiannis N, Prassopoulos P, Cavouras D, Pantelidis N. The thickness of the renal parenchyma decreases with age: a CT study of 360 patients. *Am J Roentgenol* 1990;**155**(3):541–4.
23. Denic A, Alexander MP, Kaushik V, et al. Detection and Clinical patterns of Nephron hypertrophy and nephrosclerosis among apparently healthy adults. *Am J Kidney Dis* 2016;**68**(1):58–67.
24. Kaplan C, Pasternack B, Shah H, Gallo G. Age-related incidence of sclerotic glomeruli in human kidneys. G *Am J Pathol* 1975;**80**(2):227–34.
25. Hoy WE, Douglas-Denton RN, Hughson MD, Cass A, Johnson K, Betram JF. A stereological study of the glomerular number and volume: preliminary findings in a multiracial study of kidneys at autopsy. *Kidney Int Suppl* 2003;**63**(Suppl. 83):S31–7.
26. Kremers WK, Denic A, Lieske JC, et al. Distinguishing age-related from disease-related glomerulosclerosis on kidney biopsy: the Aging Kidney Anatomy study. *Nephrol Dial Transplant* 2015;**30**(12):2034–9.
27. Denic A, Lieske JC, Chakkera HA, et al. The substantial loss of nephrons in healthy human kidneys with aging. *J Am Soc Nephrol* 2017;**28**(1):313–20.

28. Ma L-J, Nakamura S, Whitsitt JS, Marcantoni C, Davidson JM, Fogo AB. Regression of sclerosis and angiotensin inhibition-induced in PA1-1. *Kidney Int* 2000;**58**(6):2425–36.
29. Ortman J, Amann K, Brandes RP, et al. Role of podocytes for reversal of glomerulosclerosis and proteinuria in the aging kidney after endothelin inhibitors. *Hypertension (Dallas)* 2004;**44**(6): 974–81.
30. Thomas SE, Anderson S, Gordon KL, Oyama TT, Shankland SJ, Johnson RJ. Tubulointerstitial disease in aging: evidence for underlying pericapillary damage, a potential role for renal ischemia. *J Am Soc Nephrol* 1998;**9**(2):231–42.
31. Maric C, Sandberg K, Hinojosa-Laborde C. Glomerulosclerosis and tubulointerstitial fibrosis are attenuated with 17beta-estradiol in the aging Dahl salt sensitive rat. *J Am Soc Nephrol* 2004;**15**(6):1546–56.
32. Abrass CK, Adcox MJ, Rauji GJ. Aging-associated changes in renal extracellular matrix. *Am J Pathol* 1955;**146**(3):742–52.
33. Satoh M, Fujimoto S, Horike H, et al. Mitochondrial damage-induced impairment of angiogenesis in the aging rat kidney. *Lab Invest* 2011;**91**(4):190–202.
34. Takazakura E, Sawabu N, Handa A, Takada A, Shinoda A, Takeuchi J. Intrarenal vascular changes with age and disease. *Kidney Int* 1972;**2**(4):224–30.
35. Darmady EM, Offer J, Woodhouse MA. The parameters of the ageing kidney. *J Pathol* 1973;**109**(3):195–207.
36. Tracey RE. Age trends of renal arteriolar hyalinization explored with the aid of sections. *Nephron Clin Pract* 2007;**105**(4):c171–7.
37. Tracey RE, Ishii T. What is nephrosclerosis? A lesson from the USA, Japan and Mexico. *Nephrol Dial Transplant* 2000;**15**(19): 1357–66.
38. Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J Clin Investig* 1950;**29**(5):496–507.
39. Sands J. Urine concentrating and diluting ability in aging. *J Gerontol* 2012;**67**(12):1352–7.
40. Liamis G, Rodenburg EM, Hofman A, Zietse R, Stricker BH, Hoorn EJ. Electrolyte disorders in community subjects: prevalence and risk factors. *Am J Med* 2013;**126**(3):256–63.
41. Fuiano G, Sund S, Mazza G, et al. Renal hemodynamic response to maximal vasodilating stimulus in healthy older subjects. *Kidney Int* 2001;**59**(3):1052–8.
42. Long DA, Mu W, Price KL, Johnson RJ. Blood vessels and the aging kidney. *Nephron Exp Nephrol* 2005;**101**(3):e95–9.
43. Musso CG, Miguel RD, Algranati L, Farias Edos R. Renal potassium excretion: comparison between chronic renal disease patients and old people. *Int Urol Nephrol* 2005;**37**(1):167–70.
44. Ferder LF, Inserra F, Basso N. Effects of renin-angiotensin system blockade in the aging kidney. *Exp Gerontol* 2003;**38**(3):237–44.
45. Denic A, Matthew J, Lerman LO, et al. Single- nephron glomerular filtration rate in healthy adults. *N Engl J Med* 2017;**376**: 2349–57.
46. Hollenberg NK, Adams DF, Solomon HJ, Rashid A, Abrams HL, Merrill JP. Senescence in the renal vasculature in normal man. *Circ Res* 1974;**34**(3):309–16.
47. Kielstein JT, Bode-Böger SM, Frölich JS, Ritz E, Haller H, Fliser D. Asymmetric dimethyl, blood pressure, and renal perfusion in the elderly subjects. *Circulation* 2003;**107**(14):1891–985.
48. Erdely A, Greenfeld Z, Wagner L, Baylis C. Sexual dimorphism in the aging kidney: effects on injury and nitric oxide system. *Kidney Int* 2003;**63**(3):1021–6.
49. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta* 2003;**337**(1–2):169–72.
50. Kengne GF, Andres C, Sattar L, Melot C, Decaux G. Mild hyponatremia and risk of fracture in the ambulatory elderly. *QJM* 2008; **101**(7):535–88.
51. Chow KM, Szeto CC, Wong TY, Leung C, Li PK. Risk factors for thiazide-induced hyponatremia. *QJM* 2003;**96**(12):911–7.
52. Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. *Am J Med* 2009; **122**(9):857–65.
53. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med* 2006;**119**(1):71 e1–8.
54. Borro SL, Beredo R, Kleinfeld M. Hypernatremia in the aging: causes, manifestations, and outcome. *J Natl Med Assoc* 1995; **87**(3):220–4.
55. Davies I, O'Neill PA, McLean KA, Catania J, Bennett D. Age-associated alterations in thirst and arginine vasopressin in response to water or sodium load. *Age Aging* 1995;**24**(2):151–9.
56. Preisser L, Teillet L, Aliotti S, et al. Downregulation of aquaporins-2 and -3 in aging kidney is independent of V(2) vasopressin receptor. *Am J Physiol Renal Physiol* 2000;**279**(1):F144–52.
57. Combet S, Gouraud S, Gobin R, et al. Aquaporin-2 downregulation in kidney medulla of aging rats is posttranscriptional and is abolished by water deprivation. *Am J Physiol Renal Physiol* 2008;**294**(6):F1408–14.
58. Trinh-Trang-Tan MM, Geelen G, Teillet L, Corman B. Urea transporter expression in aging kidney and brain during dehydration. *Am J Physiol Regul Integr Comp Physiol* 2003;**285**(6):R1355–65.
59. Tian Y, Riaz S, Khan O, et al. Renal ENaC subunit, Na–K–2Cl and Na–Cl cotransporter abundances in aged, water-restricted F344×Brown Norway rats. *Kidney Int* 2006;**69**(2):304–12.
60. Shimizu MH, Volpini RA, de Bragança AC, et al. N-acteylcysteine attenuates renal alteration induced by senescence in rat. *Exp Gerontol* 2013;**48**(2):298–303.
61. Corman B, Barrault MB, Klingler C, et al. Renin gene expression in aging kidney: effect of sodium restriction. *Mech Ageing Dev* 1995; **84**(1):1–13.
62. Takabatake Y, Kimura T, Takahashi A, Isaka Y. Autophagy and kidney: health and disease. *Nephrol Dial Transplant* 2014;**29**(4): 1639–47.
63. Melk A, Kittikowit W, Sandhu I, et al. Cell senescence in rat kidney in vivo increases with growth and despite lack of telomere shortening. *Kidney Int* 2003;**63**(6):2134–43.
64. Katida M, Kume S, Takeda-Watanabe A, Kanasaki K, Koya D. Sirtuins and renal diseases: relationship with aging and diabetic nephropathy. *Clin Sci* 2013;**124**(3):153–64.
65. Kume S, Haneda M, Kanasaki K, et al. SIRT 1 inhibits transforming growth factor β-induced apoptosis in glomerular mesangial cells via Smad7 deacetylation. *J Biol Chem* 2007;**282**(1):151–8.
66. Schmitt R, Melk A. New insight of molecular mechanisms on renal aging. *Am J Transplant* 2012;**12**(11):2892–900.
67. Melk A, Schmidt BM, Takeuchi O, Sawitzki B, Rayner DC, Halloran PF. Expression of pk16INK4a and other cell cycle regulator and senescence associated genes in aging human kidney. *Kidney Int* 2004;**6**(2):510–20.
68. Shimizu H, Bolati D, Adijiang A, et al. NF-KB plays a role in indoxyl sulfate-induced cellular senescence, fibrotic gene expression, and inhibition of proliferation of proximal tubular cells. *Am J Physiol Cell Physiol* 2011;**301**(5):C1201–12.

69. Lim HA, Lee EK, Kim JP, et al. PPARγ activation by baicalin suppresses NF-kB-mediated inflammation in aged rat kidney. *Biogerontology* 2012;**13**(2):133–45.
70. Qiao X, Chen X, Wu D, et al. Mitochondrial pathway is responsible for aging-related increase tubular cell apoptosis in renal ischemia/reperfusion injury. *J Gerontol Biol Sci Med Sci* 2005; **60A**(7):830–9.
71. Wiggins JE, Patel SR, Shedden KA, et al. NFkappaB promotes inflammation, coagulation, and fibrosis in the aging kidney. *J Am Soc Nephrol* 2010;**21**(4):587–97.
72. Chuang PY, Cai W, Li X, et al. Reduction in Podocytes SIRT1 accelerating kidney injury in aging mine. *Am J Physiol Renal Physiol* 2017;**313**(3):F621–628.
73. Zou Z, Lei H, Wang X, Wang Y, Sonntag W, Su Z. Aging-related kidney damage is associated with a decrease in klotho expression and increased superoxide production. *Age* 2011;**33**(3):261–74.
74. Kume S, Uzi T, Horiike K, et al. Calorie restriction enhances cell adaptation to hypoxia through Sirt1-dependent mitochondrial autophagy in mouse aged kidney. *J Clin Investig* 2010;**120**(4): 1042–55.
75. Hoa C-H, Hasse VH. Sirtuins and their relevance to the kidney. *J Am Soc Nephrol* 2010;**21**(10):1620–7.
76. Kume S, Haneda M, Kanasaki K, et al. Silent information regulator 2(SIRT1) attenuated oxidative stress induced mesangial cell apoptosis. *Free Radic Biol Med* 2006;**40**(12):2175–82.
77. Kuro-o M, Matsumura Y, Aizawa H, et al. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature* 1997; **390**(6):45–51.
78. John GB, Cheng C-Y, Kuoro-o M. Role of Klotho in aging, phosphate metabolism and CKD. *Am J Kidney Dis* 2011;**58**(1):127–34.
79. Hu MC, Shi M, Zhang J, et al. Klotho: a novel phosphaturic substance acting as an autocrine enzyme in renal proximal tubules. *FASEB J* 2010;**24**(9):3438–50.
80. Koh N, Fujimori T, Nishiguchi S, et al. Severely reduced production of klotho in human chronic renal failure kidney. *Biochem Biophys Res Commun* 2001;**280**(4):1015–20.
81. Drew DA, Katz R, Kritchevsky S, et al. Association between soluble klotho and change in kidney function: The Health Aging and Body Composition Study. *J Am Soc Nephrol* 2017;**28**(6):1859–66.
82. Lu P, Boros S, Chang Q, Bindels RJ, Hoenderop JC. The β-glucuronidase klotho exclusively activates the epithelial Ca2+ channels TRPV5 and TRPV6. *Nephrol Dial Transplant* 2008;**23**(11):3397–402.
83. Chen T-H, Kuro-O M, Chen CH, et al. The secreted Klotho protein restores phosphate and suppresses accelerated aging in Klotho mutant mice. *Eur J Pharmcol* 2013;**698**(1–2):67–73.
84. Filler G, Bökenkamp A, Hofmann W, Le-Bricon T, Martínez-Bću C, Grubb A. Cystatin C as a marker of GFR-history, indications, and future research. *Clin Biochem* 2005;**38**(1):1–8.
85. Fliser D, Ritz E. Serum cystatin C concentration as a marker of renal dysfunction in the elderly. *Am J Kidney Dis* 2001;**37**(1):79–83.
86. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**(9): 604–12.
87. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012;**367**(1):20–9.
88. Kildbride HS, Stevens PE, Eaglestone G, et al. Accuracy of the MDRD (Modification of Diet in Renal Disease) study and CKD-EPI (CKD Epidemiology Collaboration) equations for estimation of GFR in elderly. *Am J Kidney Dis* 2012;**61**(1):57–66.
89. Robles NR, Felix FJ, Fernandez-Berges D, et al. Prevalence of abnormal urinary albumin excretion in elderly people: a Spanish survey. *Int Urol Nephrol* 2013;**45**(2):553–60.
90. Jones CA, Francis ME, Eberhardt MS, et al. Microalbuminuria in US population: Third National Health and Nutritional Examination Survey. *Am J Kidney Dis* 2002;**39**(3):445–59.
91. Mattison JA, Roth GS, Beasley TM, et al. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. *Nature* 2012;**489**(7145):316–21.
92. Bodkin NL, Alexander TM, Ortmeyer HK, Johnson E, Hansen BS. Mortality and morbidity in laboratory-maintained rhesus monkeys and effect of long term dietary restriction. *J Gerontol Biol Sci Med Sci* 2003;**58**(3):B212–9.
93. Mattison JA, Colman RJ, Beasley TM, et al. Caloric restriction improves health and survival of rhesus monkeys. *Nat Commun* 2017; **8**:14063. https://doi.org/10.1038/ncomms14063. 1-13.i, www.nature.com/naturecommunicatins.
94. Heilbrom LK, de Jonge L, Frisard MI, et al. Effect of 6 month calorie restriction of biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals. *J Am Med Assoc* 2006;**295**(13):1539–48.
95. Wood JC, Rogina B, Lavu S, et al. Sirtuin activators mimic caloric restriction delay aging in metazoans. *Nature* 2004;**430**(7000): 686–9.
96. Jung KJ, Lee EK, Kim JY, et al. Effect of short term calorie restriction on pro-inflammatory NF-kB and AP-1 aged kidney. *Inflamm Res* 2009;**58**(3):143–8.
97. Smith Jr DL, Elam Jr CF, Mattison JA, et al. Ingram DK. Metformin supplementation and life span in Fischer 344 rats. *J Gerontol* 2010; **65A**(5):468–74.
98. Sung B, Park S, Yu BP, Chung HY. Amelioration of age-related inflammation and oxidative stress by PPARγ activator: suppression of NF-κB by 2,4-thiazolidinedione. *J Gerontol* 2006;**41**(6): 590–9.
99. Shen D, Li H, Lui M-J, Yu H, Wu DF. Pioglitazone attenuates aging-related disorders in aged apolipoprotein E deficient mince. *Exp Gerontol* 2018;**102**:101–8.
100. Boccardia V, Barbieri M, Rizzo MR, et al. A new pleiotropic effect of statins in elderly: modulation of telomerase. *FASEB J* 2013;**27**(6): 1–7.

QUESTIONS AND ANSWERS

Question 1

An 80-year-old woman was brought to her physician by her daughter for evaluation of confusion. The daughter, who was visiting from Las Vegas, noted that her mother thought that the year was 2000 and that the day was Sunday. The patient confirmed this. Her physician inquired if she was taking any new medications at the time the confusion started. The daughter related that her mother was placed on chlorthalidone and taken off amlodipine 2 weeks ago because of leg and ankle edema. Her blood pressure, which had been around 180/80 mm Hg, was now 150/79 mm Hg. Physical examination revealed resolution of the leg and ankle edema. S[Na] 125 mEq/L, S[Cl] 95 mEq/L, S[K] 3.0 mEq/L, and S[HCO_3] 27 mEq/L. Serum osmolality was 262 mOsm/L. Urinalysis was bland with specific gravity 1.015. What is the cause of her hyponatremia?

A. Poor intake
B. Excessive thirst
C. Chlorthalidone
D. Increased total body water
E. Lower basal vasopressin level

Answer: C

Thiazides are a common cause of hyponatremia in the elderly and account for over 30% of the cases. Multivariate analysis has shown that low total body water, female sex, and hypokalemia are associated with diuretic-induced hyponatremia. Although "beer potomania," which is associated with low solute intake and low urinary osmolality, is a possibility, it is unlikely given that her urine osmolality is not <100 mOsm/kg. The elderly have decreased thirst sensation as a consequence of a decrease in afferent sensory output from the oropharynx, stomach, and esophagus. Total body water decreases with age secondary to sarcopenia and results in a higher incidence of dysnatremias. Studies have shown elevated basal vasopressin levels and a greater response to tonicity in the elderly.

Question 2

An 86-year-old man is referred to a local nephrologist for evaluation of low GFR, 70 mL/min/1.73 m^2 found on laboratory examination done 3 weeks ago. He is independent and lives alone. He exercises three to four times a week, eats three meals daily, and is able to manage his expenses. Physical examination reveals a well-nourished man with a completely normal examination. Laboratory results including a urinalysis are normal. No microalbuminuria is detected (16 mg albumin:g creatinine). An ultrasound of the kidneys is normal. The right kidney measures 10 cm and the left kidney measures 10.5 cm in length.

The man is concerned about being diagnosed with CKD. What should you suggest to him?

A. The MDRD GFR and Cockcroft–Gault formulas underestimate the true GFR in those over 65 years of age
B. The MDRD GFR has not been validated in the elderly
C. Elderly patients diagnosed with CKD Stage IIIa (eGFR 45–60 mL/mm/1.73 m^2) are more likely to progress to ESRD than die from CVD
D. He has no evidence of CKD but a decline in renal function commonly occurs with aging
E. Refer the man to a dietitian to discuss restricting his dietary protein intake because this slows the rate of progression of kidney disease

Answer: D

After age 40, individuals can expect to lose renal function on the order of 10 mL/min/decade. However, this man has no microalbuminuria or any other urinary findings to suggest that he has any kidney disease. Recently, the MDRD-modified formula was validated, and it can be used to estimate GFR in the elderly. However, this estimate hinges on normal body habitus. If this man were cachectic, a 24-hour urine collection measuring creatinine clearance would be a far better estimate of his true GFR. The Cockcroft–Gault equation consistently underestimates the true GFR, whereas the MDRD GFR overestimates it. Moreover, this man is not likely to progress to ESRD but is more likely to develop CVD. At this point, he does not require dietary protein restriction as this maneuver has not been shown to slow the rate of progression of kidney disease at this level of GFR. Protein malnutrition, a consequence of low dietary protein intake, has been associated with an increased risk of mortality.

Question 3

A healthy 70-year-old woman, with no history of hypertension or diabetes mellitus, undergoes a right nephrectomy for renal cell carcinoma. Her postoperative recovery is uneventful, and her S[Cr] increases by 0.2 mg/dL and remains stable. Her physician inquires if she wants a copy of the pathology report which includes a biopsy report of the normal renal parenchyma. The patient is taken aback when she reads that scarring is seen and wants to know what this means. The light microscopy reports that 2 of 10 glomeruli are sclerosed. There is associated mild tubular atrophy, arteriolar hyalinosis, and fibrosis. The remainder of the glomeruli and interstitium appear normal. Except for the slight increase in S[Cr], the patient's laboratory examination is

normal. The patient makes an appointment to see you. How should you respond?

A. Aging is usually not associated with any morphologic changes within the kidney
B. The number of sclerotic glomeruli varies but usually approaches more than 50% by age 40
C. The amount of scarring seen on the biopsy suggests that the patient will experience a severe decline in renal function, and she should not have had the nephrectomy
D. These are normal findings seen in aging and should have no significant impact on her kidney function
E. She needs to follow-up with a nephrologist because she is at increased risk of developing CK

Answer: D

With aging there is an increase in sclerosis in the kidney, associated with a decline in GFR and RPF. This amount of scarring is commonly seen in her age group. Interestingly, a decline in GFR does not correlate with the degree of sclerosis, but the degree of sclerosis does correlate with the amount of glomerulopenia. The number of sclerosed glomeruli increases after 40 years of age but is usually not more than 5%. She is not at increased risk for development of CKD. To be effective, a CR diet is necessary.

Question 4

A 70-year-old man was reading the magazine *Aging — What Can You Do?* and came across an advertisement for resveratrol. After reading all the antiaging claims, he went online to read more about it. Which of the following information he found in the advertisement was true?

A. Resveratrol is an activator of Sirt1
B. The level of Sirt1 in the kidney is higher in older animals
C. Resveratrol has been shown to increase life span in humans
D. Sirt1 increases oxidative stress and cellular senescence
E. For resveratrol to be effective, a CR diet is necessary

Answer: A

Resveratrol increases the levels of Sirt1. In animal studies, the expression of Sirt1 decreases with aging. The addition of a CR diet and resveratrol showed no increased benefit with longevity in metazoans, and there has not been any documentation that resveratrol increases life span in humans. Increases in Sirt1 decrease oxidative stress, improve autophagy, and decrease apoptosis. Resveratrol does not have to be linked to a CR diet to be effective.

Question 5

A 75-year-old man with a history of peripheral vascular disease and tobacco use was started on the ACEI, lisinopril, 10 mg daily. A baseline S[Cr] was 1.0 mg/dL. Blood pressure was $\geq$140/90 mm Hg on three separate clinic visits. He returns in 1 week for laboratory evaluation and blood pressure check. He reports feeling a little lightheaded, but he had not taken his blood pressure because his machine had malfunctioned. His blood pressure in the office was 100/61 mm Hg. Laboratory work revealed that the S[Cr] had increased to 2.4 mg/dL. All of the following contribute to worsening renal function in the elderly except?

A. Renal blood flow decreases with aging
B. There is a decreased ability of the kidney to undergo autoregulation
C. There is an increased response to acetylcholine in the renal arteries that occurs with aging
D. NOS declines with aging
E. Maintenance of renal perfusion generally requires a higher mean arterial pressure

Answer: C

Responses to vasoactive substances change with aging. There is a decline in renal blood flow and an increase in renovascular resistance. Older people are less responsive to vasodilators such as acetylcholine and experience greater sensitivity to vasoconstrictors. This results in the decreased ability of the kidney to undergo autoregulation. Caution needs to be taken with excessive blood pressure control in the elderly.

Question 6

Look back at the information in Question 5. The patient stops lisinopril, expecting his renal function will improve. He returns to your clinic in another week to check his S[Cr]. It has now gone from 2.4 mg/dL to 6 mg/dL. As a nephrologist, you inquire if he was taking anything else with lisinopril. He states he was taking naproxen for shoulder pain. A microscopic urinalysis shows 3—4 coarse pigmented granular casts per high power field. The patient is instructed to discontinue naproxen and is admitted to the hospital. S[Cr] returns to baseline in 3 weeks, and he does not require renal replacement therapy. Should the patient have any concerns about his renal function in the future?

A. No, he has no underlying kidney disease so he should not be worried
B. No, he should not be concerned because he did not require renal replacement therapy

C. Because he experienced an episode of AKI, he is at higher risk for morbidity and mortality than if he had CKD alone

D. He is at a higher risk for morbidity and mortality if he just had CKD than if he had AKI alone

E. He needs to schedule an appointment for vein mapping because he will need dialysis soon because his renal function will rapidly deteriorate

Answer: C

Elderly individuals have an increased incidence of diabetes and hypertension. Although the incidence of diabetes declines after age 65, the incidence of hypertension continues to increase as people age. Both these conditions are associated with CKD and progression to ESRD. Besides developing CKD, the elderly are more likely to develop AKI. There is a higher mortality and higher likelihood for the development of ESRD in those who develop AKI while hospitalized than those with CKD without AKI. Ishani and colleagues[16] observed that the hazard ratio for ESRD was 24 vs. 8 for those who develop AKI vs. those with CKD alone.

CHAPTER

18

Pathophysiology of Chronic Kidney Disease Progression: Organ and Cellular Considerations

Anupam Agarwal[a], *Karl A. Nath*[b]

[a]Division of Nephrology, University of Alabama at Birmingham, Birmingham Veterans Administration Medical Center, Birmingham, AL, United States; [b]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, United States

Abstract

Progression of chronic kidney disease (CKD) involves the recruitment and engagement of *cellular processes* originating in specific compartments of the kidney on the one hand and *biochemical pathways* of cell injury that contribute to these processes on the other hand. Many of these processes possess the capacity to ramify broadly beyond the compartment where they initially arose. It is this essential consideration that contributes so fundamentally to the increasing loss of functional nephrons and the progression of CKD. A number of different biochemical pathways contribute to CKD progression: angiotensin II induces TGF-β1 and the consequent elaboration of extracellular matrix; angiotensin II also induces oxidative stress which itself can upregulate TGF-β1 in vicinal cells and thus the propagation of a fibrosing response. This lack of containment of compartmental processes, and this versatility of injurious biochemical pathways, not only underlies the pathogenesis of CKD but also holds substantial therapeutic significance. Namely, the best hope for retarding or preventing the progression of CKD resides in a combined, multipronged therapeutic approach that interrupts these processes and pathways at separate and several steps.

INTRODUCTION

Along with a steady decline in glomerular filtration rate (GFR), the progression of chronic kidney disease (CKD) is attended by characteristic renal histologic changes.[1–3] These structural alterations usually involve all compartments of the kidney. Glomeruli exhibit varying degrees of extracapillary adhesion formation, sclerosis, and obliteration of the capillary tuft. Tubules become atrophic. The interstitium is expanded by a mononuclear cellular infiltrate and extracellular matrix, and the renal vasculature displays sclerosis and dropout of capillaries in the cortical interstitium. Nephrons are heterogeneously and asynchronously affected. Interspersed among variably atrophic tubules, sclerotic glomeruli, and amidst an expanded interstitium are hypertrophied and presumably hyperfunctioning nephrons. Progressive decline in renal function in CKD thus reflects the cumulative functional loss resulting from injury to and obsolescence of increasing numbers of nephrons, with hyperfunctioning by certain subsets of surviving nephrons offering a mitigating, but insufficient, response.

A concept common to all mechanisms proposed to date regarding the progression of CKD is that processes centered in a particular compartment of the kidney—glomerular, tubular, interstitial, vascular—can recruit injurious processes in others. It is this increasing elicitation and interaction of diverse pathobiologic processes, involving multiple renal compartments, that drive the progression of CKD.[1–5]

These compartmental processes and how they interact in the progression of CKD are reviewed in this chapter, in conjunction with the role of specific mediators and inhibitors of chronic renal injury. Mechanisms that are specific for diabetic nephropathy and polycystic kidney disease are discussed elsewhere.

COMPARTMENTAL PROCESSES

Glomerular Processes

Glomerular Extracapillary Processes

Glomerular diseases involve endocapillary, extracapillary, or both sets of processes. Processes confined to the endocapillary compartment are generally not considered critical in progressive CKD.[2] In contrast, alterations in the extracapillary compartment—in particular, alterations

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00018-8

involving podocytes—set the stage for progressive glomerulosclerosis, tubulointerstitial inflammation and fibrosis, and tubular atrophy.[2,6–8] Extracapillary processes may occur *de novo* or may reflect the extension of pathobiologic processes that initially resided in the endocapillary compartment.[9]

In health, podocytes and, in particular, their foot processes, determine glomerular permselectivity. Thus, injury to podocytes that disrupt their foot processes and their attachment to the glomerular basement membrane (GBM) leads to glomerular proteinuria and the consequent tubular trafficking of reabsorbed proteins.[2,6–8] Injured podocytes also exhibit a variety of ultrastructural changes including cellular extensions across Bowman's space. These extensions to parietal epithelial cells (PECs) lead to the formation of cellular bridges. Bridge formation is attended by increased extracellular matrix production and adhesions (synechia) with Bowman's capsule. Therefore, a sclerosing process can ensue that closes off the adherent capillary tuft.[2,6,8] Adhesions to Bowman's capsule can also occur at areas of the GBM denuded of podocytes. Adhesions impair the integrity of the parietal epithelium and the parietal basement membrane (PBM) such that glomerular filtrate insudates into the interstitium. This misdirected glomerular filtrate triggers an inflammatory interstitial response and the vicinal congregation of immune cells and fibroblasts. Glomerular filtrate may also aberrantly track inside the PBM around the glomerulus and extend around the glomerulotubular junction, thereby collecting in the space between the proximal tubular epithelium and the tubular basement membrane (TBM). Such fluid collection compromises tubular patency and transport activity, and thus promotes the development of tubular atrophy.[2,8]

Proliferation of PECs is often a consequence of podocyte injury.[2,10] Proliferating PECs may migrate across cellular bridges/adhesions and cover denuded areas of the GBM. Proliferating PECs, however, may also migrate circumferentially around Bowman's capsule to the glomerulotubular junction, narrowing this junction and impeding the flow of glomerular filtrate into tubules. Eventually, this migrating front of proliferating PECs severs off the tubule from the glomeruli, thereby producing atubular glomeruli and aglomerular tubules.

Podocyte Pathobiology and CKD

Major glomerular-based mechanisms in progressive CKD invariably involve pathobiologic processes/responses in podocytes, and the following are relevant considerations.[2,6–8,10–14] First, podocytes are terminally differentiated cells that cannot reproduce equivalently differentiated offspring. However, dedifferentiated podocytes can proliferate, migrate, assume a proinflammatory and profibrotic phenotype, and thereby promote the formation of bridges and adhesions. Notably, the concept of "mitotic catastrophe" in podocytes has been articulated wherein injured podocytes initiate DNA synthesis but ultimately fail to undergo mitosis. Podocytes exhibiting mitotic arrest are unstable and eventually undergo apoptosis or detachment from the GBM.[13] Second, the severity of the initial loss of podocytes determines the risk for and severity of glomerulosclerosis and progressive CKD.[15–17] This reflects not only the entrainment of injurious extracapillary processes in the early phase after podocytic injury and loss but also, in the later phases, the steady propagation of injury to previously uninjured surviving podocytes.[18,19] These responses include, in part, hypertrophy of surviving podocytes in an attempt to cover the bare areas of the GBM. However, such hypertrophic responses do not achieve the requisite coverage of the exposed GBM. Furthermore, hypertrophy of surviving podocytes may lead to less stable anchorage of the foot processes of these enlarged cells to GBM, such that, in time, these cells lose their footing to the GBM and are sloughed into the urinary space. In effect, a self-perpetuating cycle of injury to and loss of podocytes ensues. Third, podocyte injury and loss lead to the trafficking of plasma proteins across the filtration barrier. Endocytosis of these proteins by podocytes, however, can itself lead to podocyte injury, thereby providing another self-perpetuating pathway for progressive disease.[20] Fourth, podocytes are directly vulnerable to the damaging effects of many of the candidates involved in CKD, namely, the renin–angiotensin system, TLR4-dependent cytokines, monocyte chemoattractant protein (MCP)-1, TGF-β1, and endothelin-1. Other intracellular signaling systems that are instigated by these and other ligands, which can activate and injure podocytes, include Wnt, Notch, ERKs, Smads, and NK-kB.[21–24] Fifth, podocytes are a major source of vascular endothelial growth factor (VEGF), which preserves endothelial integrity. Podocyte injury and loss may lead to less availability of this trophic factor for endothelial cells, thereby jeopardizing the integrity of the endothelium and glomerular tuft.

Maladaptive Glomerular Responses in Surviving Nephrons

An accepted tenet in progressive CKD is that maladaptive processes in surviving nephrons damage these previously uninjured nephrons, thereby providing a self-perpetuating pathway of injury.[3,4,25,26] Nephrons that survive after a renal insult or subtotal reduction in renal mass exhibit hyperfunction and hypertrophy in glomerular and tubular compartments.[25,26] Glomerular filtration rates in surviving glomeruli are increased, in part, by the increased glomerular transcapillary hydraulic pressure gradient, the latter imposing hemodynamic stress on the capillary tuft.[25–27] Podocytes sense

and respond to mechanical stress, but if such responses are aberrant or insufficient, attendant podocyte injury can occur.[6,27] Additionally, as glomeruli enlarge in surviving nephrons, podocytes undergo hypertrophy, which, however, may be insufficient to cover the GBM. Areas of the GBM are thus exposed and vulnerable to adhesion formation.[2,6] Hemodynamic and structural alterations in surviving glomeruli may thus damage podocytes, and thereby recruit extracapillary processes contributing to CKD.

TUBULAR PROCESSES

Tubular Trafficking of Reabsorbed Proteins

Albumin and other proteins leaked into the urinary space are avidly taken up by the proximal tubule *via* megalin and cubilin receptors which are present on the apical surface of the epithelium. In health, small amounts of plasma proteins filtered at the glomerulus are reclaimed *via* these receptors and are metabolized by the endosomal-lysosomal system. However, in proteinuric states, this salvaging mechanism leads to enhanced trafficking of proteins and their metabolism by the proximal tubule. Such protein overload and protein metabolism generate assorted chemotactic species, proinflammatory and profibrogenic cytokines, other inflammatory mediators, and cytotoxic species—including IL-6, IL-8, MCP-1, endothelin-1, RANTES, TGF-β1, and complement C3—which induce interstitial inflammation, tubular apoptosis, and tubular atrophy.[3,4,28,29] Proximate events in triggering this proinflammatory response involve signaling pathways (protein kinase C, ERK, and JAK/STAT), oxidant generation, and the activation of the transcription factor NF-kB.

The following lines of experimental and clinical observations illustrate the applicability of this pathway to a specific chemokine, MCP-1 (CCL2), a potent, NF-kB-dependent chemotactic stimulus for monocytes and T cells. First, exposure of tubular epithelial cells to albumin *in vitro* or injection of albumin to rodents markedly induces MCP-1.[29] Second, in human CKD, expression of MCP-1 is increased in the renal tubular epithelium and correlates with interstitial leukocyte infiltration, whereas increased urinary excretion of MCP-1 in CKD correlates with interstitial leukocytic infiltration and renal dysfunction.[30–32] Third, strategies that interrupt receptor (CCR2)-mediated actions of MCP-1 (CCL2) reduce interstitial leukocytic infiltration and tubulointerstitial injury in murine models of protein overload nephropathy and renal fibrosis.[33–35]

Trafficking of protein as a pathway for progressive disease has been assessed in at least two studies of glomerular disease in which glomerular injury is imposed in mice with reduced expression of megalin, one of the apical receptors that enables tubular incorporation of filtered protein.[36,37] These studies came to divergent conclusions regarding the instigation of tubular injury when megalin is deficient in states of glomerular proteinuria.[36–38] Such lack of congruence between studies may possibly reflect the following considerations: the relative duration of these studies, the variability and extent to which megalin is deleted in these models, and that pathways other than megalin-dependent ones may also contribute to tubular uptake of protein in the diseased kidney.

Tubular Injury as the Basis for CKD

For many glomerulopathies, acute tubular injury is a prominent finding, and acute kidney injury (AKI) is now recognized as a risk factor for human CKD. A triphasic response has been described when the kidney is exposed to repetitive episodes of AKI, which sequentially includes sensitivity to AKI, resistance to acute injury, and, ultimately, chronic inflammation and CKD.[39] These studies undertaken 20 years ago were the first to specifically articulate the concept that AKI is a risk factor for CKD.[39] More recent studies have examined the long-term outcome from toxic insults specifically directed to the proximal tubule.[40] With low doses of such a toxic insult, AKI is restricted to the S1 and S2 segments and attended by a localized inflammatory response. Subsequently, these inflammatory responses entirely resolve and tubular integrity fully restored. However, when insults are administered at weekly intervals, chronic tubulointerstitial fibrosis ensues in conjunction with glomerulosclerosis.[40] These findings thus demonstrate that failure to recover from a localized insult to the proximal tubule, because of repetitive insults to the same site, can entrain cellular events that damage the glomerular compartment.[40,41] Mechanisms underlying this relay of injury include the following adverse effects emanating from injured proximal tubular epithelial cells: the attraction and activation of proinflammatory leukocytes, the secretion of cytokines such as TGF-β1 that can lead to cell cycle arrest and a profibrogenic response, and the dislodging of pericytes from peritubular capillaries, attendant capillary dropout, and ensuing interstitial fibrosis (*vide infra*).

Maladaptive Tubular Responses in Surviving Nephrons

Remnant nephrons in the diseased kidney or following reduction of renal mass exhibit not only glomerular enlargement and hyperfiltration but also tubular hypertrophy, hyperplasia, and hyperfunction.

These tubular processes are also implicated in CKD.[3,25,42,43] Increased single nephron glomerular filtration rates in surviving nephrons necessitate increased sodium reabsorption to achieve glomerulotubular balance. Sodium reabsorption by the kidney is the principal determinant of renal oxygen consumption. Indeed oxygen consumption/nephron in the remnant kidney model[44] and oxygen consumption/GFR in human CKD[45] are both increased. However, oxygen consumption factored for sodium transport in the remnant kidney, compared with the intact kidney, is higher, thereby indicating augmented metabolic costs entailed by the hyperfunctioning and hypertrophied nephrons.[44,45] Such metabolic alteration is implicated in CKD in at least two ways. First, such increased oxygen consumption may engender oxidative stress and attendant injury.[44] Second, increased oxygen consumption by surviving nephrons may contribute to cortical hypoxia, a recognized pathway for CKD.[46–48] Moreover, there may be a positive feedback between these pathways. Cortical hypoxia induced by increased oxygen consumption can itself promote mitochondrial oxidant generation, and oxidant stress can augment mitochondrial consumption.[47]

Another metabolic adaptation in surviving nephrons is enhanced ammoniagenesis, the latter needed to maintain net acid excretion in CKD.[49] Such increased ammonia production leads to increased cortical partial pressure of ammonia with accompanying activation of the alternative complement pathway.[49] Bicarbonate supplementation reduces renal ammonia production and tubulointerstitial injury. Other mechanisms underlying the beneficial effects of bicarbonate supplementation involve reduced generation of reactive oxygen species[50] and decreased production of endothelin-1.[51] A number of studies in humans demonstrate the beneficial effects of base supplementation in retarding the progression of CKD.[51]

Hematuria-Induced Tubular Injury

Hematuria occurs in a substantial portion of glomerular disease, and there is clinical evidence that hematuria is risk factor for progressive CKD.[52] Erythrocytes present in the urine are engulfed by tubular epithelial cells.[53] Such incorporation and destruction of erythrocytes in tubular epithelial cells, as previously suggested,[3] are harmful to the tubular epithelium because of increased intracellular content of hemoglobin, a heme-containing protein. Heme is prooxidant, proinflammatory, and profibrogenic, inducing, for example, NF-kB-dependent pathways such as MCP-1 production.[54,55] Heme also inhibits proliferation and can cause apoptosis.[56] Thus, hematuria may contribute to progressive CKD by activating heme-dependent pathways of CKD.

INTERSTITIAL PROCESSES

Interstitial Inflammation

One of the best histologic predictors of renal functional decline is the severity of interstitial cellular infiltration and fibrosis, a finding that emphasizes the importance of these processes in progressive CKD.[1] Interstitial inflammation involves infiltrating T lymphocytes and monocytes which are recruited by chemotactic cues originating from injured tubules, capillaries, and glomeruli and are activated to produce a host of inflammatory cytokines and other mediators.[4,5,57] Interstitial infiltration can congregate in areas surrounding injured glomeruli, especially in response to misdirected glomerular filtration. Such interstitial inflammation can synergize with extracapillary glomerular processes in the progression of CKD. Interstitial infiltration and accompanying fibrosis, if especially vigorous in the regions surrounding the S1 proximal tubular segment and the glomerulotubular junction, may encroach on the latter, eventually interrupting tubular patency and disconnecting the tubular and glomerular compartments.

Dendritic cells in the kidney are increasingly recognized for their capacity to drive interstitial inflammation and their contribution to progressive CKD following glomerular inflammation.[58] For example, dendritic cells can activate T cells by presenting antigens leaked from injured glomeruli.[59,60] Dendritic cells can also generate antigens from processing of filtered protein which leads to the activation of T lymphocytes.[61] However, there are subsets of dendritic cells that inhibit inflammatory responses as there are for T lymphocytes (Tregs) and macrophages (M2 macrophages).

If interstitial inflammation continues unchecked, increased extracellular matrix production and interstitial fibrosis inevitably ensue. The predominant cellular source of such matrix synthesis is the interstitial fibroblast and, in particular, the activated myofibroblast.

Interstitial Fibrosis

Interstitial myofibroblasts vigorously synthesize interstitial collagens I, III, and IV and other extracellular matrix proteins (such as fibronectin), express alpha-smooth muscle actin (αSMA), and are motile.[4,5,57,62,63] αSMA is a critical component of stress fibers in myofibroblasts. *Via* these stress fibers, myofibroblasts are linked with the interstitial extracellular matrix. Myofibroblasts possess properties of both fibroblasts and myocytes, the former underlying their capacity to elaborate extracellular matrix proteins, the latter enabling their contractility and motility. To the extent that αSMA largely reflects myofibroblastic activity, the significance of myofibroblasts in CKD is highlighted

by the fact that expression of αSMA correlates with renal fibrosis and functional decline.[62] There is considerable debate regarding the origin of the myofibroblast, the latter variably ascribed to epithelial-mesenchymal transition (EMT), endothelial-mesenchymal transition, renal interstitial resident stromal cells (such as pericytes, perivascular fibroblasts), and bone marrow-derived cells (fibrocytes and macrophages).[4,5,57,62–70] From such analyses, it appears that the role of EMT is controversial; the involvement of the renal interstitial resident stromal cells such as pericytesis is increasingly accepted; and the contribution of the bone marrow-derived cells and endothelial-mesenchymal transition is currently unclear.

EMT describes the transformation of epithelial cells into mesenchymal cells and is a recognized phenomenon during normal development and carcinogenesis.[5,57,63,66] Applied to CKD, EMT reflects the transitioning of polarized renal tubular epithelial cells into nonpolar mesenchymal cells and eventually into myofibroblasts. EMT requires not only cell transition but also cell migration across the TBM into the interstitium. The evidence for such transition is especially strong in studies *in vitro* which expose renal tubular epithelial cells to TGFβ1-containing media, recapitulating the fibrogenic milieu presumably present in the diseased kidney. Under such conditions, cellular transitioning is readily observed, as cells lose epithelial-specific markers (for example, β-catenin and E-cadherin) and acquire mesenchymal features and markers (for example, fibroblast-specific protein-1 and αSMA).[5,57,63,66] The evidence against EMT as a principal pathway for interstitial fibrosis *in vivo* has been reviewed and is summarized along at least three main lines.[66] First, while there is one study based on the mapping of cell fate for the existence of this phenomenon *in vivo*, an increasing number of recent, rigorous studies have failed to demonstrate that interstitial myofibroblasts arise from EMT. Second, there is little or no evidence *in vivo* that tubular epithelial cells putatively undergoing EMT do produce collagen I (a critical component of interstitial matrix).[66] Third, convincing histologic confirmation is not yet available that sequentially demonstrates, *in vivo*, the structural conversion of the epithelial cell into a myofibroblast or has captured these transitioning cells in the act of migration across the TBM and into the interstitium.[66] Thus, there is an emerging view that while many of the salient features of EMT are clearly demonstrable *in vitro*, there is circumspection regarding whether this phenomenon, as originally articulated, occurs *in vivo* in CKD and serves as a significant source for interstitial activated myofibroblasts. "Partial EMT" is a term used by some experts to reflect the fact that the early steps in the transition, but not the complete transition, may be relevant to the progression of CKD.[68–70]

In contrast, the pericyte is increasingly recognized as the precursor of the myofibroblast in CKD.[64–66] In health, pericytes are implanted in the capillary basement membrane surrounding peritubular capillaries, precapillary arterioles, and postcapillary venules. Through cytoplasmic extensions, pericytes connect with endothelial cells of the peritubular capillary they surround as well endothelial cells in vicinal capillaries. Pericytes maintain the structural and functional integrity of capillaries with which they are in contact.[64,65] Studies based on cell fate and lineage-mapping in models of CKD demonstrate that an early event is the dislodgement of pericytes from the peritubular capillary basement membrane, their migration into the interstitium, and their transformation into myofibroblasts. Furthermore, the loss of the pericyte around the capillary perturbs the integrity and viability of endothelial cells and the capillary, thereby leading to endothelial cell loss, capillary dropout, and capillary rarefaction. This sets the stage for cortical ischemia and hypoxia and attendant tubular atrophy.[64,65]

In health, there is a clear symbiosis between the capillary endothelium and the pericyte, and injury to one of these cells may beget injury to the other.[67–70] The molecular basis for cellular events that perturb and dislodge the pericyte in CKD may involve, in part, perturbed growth factor-dependent signaling between the endothelial cell and the pericyte.[71] Endothelial cells express the VEGF receptor and produce platelet-derived growth factor (PDGF), whereas pericytes express PDGF receptors and produce VEGF. Aberrant or inordinate production and signaling of these or other growth factors may injure either the endothelial cell or the pericyte, with attendant damage to the other. Interestingly, a pairing of molecules that maintains the mutual health of the capillary endothelium and the pericyte involves ephrinB2 and its receptor EphB4, both of which are expressed on these cells. Disrupting the dialogue between these molecules may also contribute to capillary rarefaction and interstitial fibrosis.[72]

Myofibroblast production of collagen I and III and fibronectin, and other key matrix components that constitute interstitial fibrosis, is transcriptionally regulated and is driven by TGF-β1, PDGF, connective tissue growth factor (CTGF), fibroblast growth factor, and angiotensin II.[5,57,62,67–70] Intracellular signaling processes instigated by these fibrogenic stimuli are collated, at least in part, by integrins, which are transmembrane proteins that interface between these intracellular processes and the extracellular buildup of matrix proteins.[5] Seminal studies by Humphreys and colleagues have shown that, in models of tubulointerstitial disease, kidney perivascular cells that express the zinc finger transcription factor glioma-associated oncogene homolog 1 (Gli1) account for the majority of activated renal

myofibroblasts and much of the attendant interstitial fibrosis that ensues.[69] The mechanisms whereby such Gli1 expression account for this effect on activated myofibroblasts and the specific origin and significance of Gli1-negative myofibroblasts are both uncertain at the present time.[69]

Capillary Rarefaction

The destabilization and dropout of peritubular capillaries because of pericyte disengagement lead to tubular ischemia and cortical hypoxia, the latter exacerbated as remaining capillaries are increasingly separated from tubules by progressive interstitial fibrosis.[64,65,71] Cortical hypoxia exerts diverse inflammatory and fibrogenic effects.[46–48] Hypoxia promotes the differentiation of dendritic cells and their attendant ability to stimulate T-cell proliferation.[73] Hypoxia fosters hypoxia-induced factor (HIF)1α-dependent, TGF-β1-dependent, and other pathways for fibrosis.[5,46,47,57] Capillary rarefaction also adversely affects the glomerular compartment because attenuation in the peritubular capillary network increases post glomerular resistance, thereby predisposing to increased glomerular hydrostatic pressure and hemodynamic glomerular injury.[1]

Crosstalk in the Tubulointerstitium and the Progression of Chronic Kidney Disease

Disease-provoking interactions occur between relevant cells in the tubulointerstitium and include crosstalk among the following[67–70]: different tubular epithelial cells, tubular epithelial cells and interstitial pericytes, tubular epithelial and inflammatory cells, inflammatory cells and myofibroblasts, and endothelial and other tubulointerstitial cells. It is such aberrant interactions between and among these cell populations, culminating in the activation of myofibroblasts and elaboration of interstitial matrix, that largely drive the progression of CKD.[67–70]

A salient series of interactions begins with injury to tubular epithelial cells (for example, by proteinuria or cytokines leaked into the urinary space from diseased glomeruli).[67–70] Such tubular epithelial cell injury promotes dedifferentiation of tubular epithelial cells through TGF-β1 and other mediators. Injured tubular epithelial cells cause pericytes to transform into activated myofibroblasts *via* such mediators as TGF-β1, PDGF, hedgehog, and Wnt, among others, thereby engendering the production of large amounts of extracellular matrix. The destabilization of the pericyte *pari passu* impairs the integrity of the capillary endothelium. This along with excessive matrix production promotes capillary rarefaction and cortical hypoxia. The latter instigates proinflammatory and fibrogenic effects, thereby perpetrating continued harm to the interstitial milieu. Moreover, the injured tubular epithelium and injured capillary endothelium activate innate immunity, thereby recruiting inflammatory cells and immune processes as additional effectors of tubulointerstitial injury.

Recent insights have identified two key drivers of disease-provoking cellular crosstalk in the tubulointerstitium. The first is the senescence-associated secretory phenotype (SASP) of the dedifferentiated tubular epithelial cell. The second is the secretome of the injured capillary endothelium.[74,75] When tubular epithelial cells are injured and dedifferentiate, they acquire a senescence phenotype characterized by cell cycle arrest, resistance to apoptosis, and the production of SASP factors. SASP factors represent a plethora of cytokines, growth factors, and proapoptotic, profibrotic, and vasoactive molecules, among others, that engender aberrant communication among tubulointerstitial cells. Similarly, injury to the capillary endothelium instigates an abnormal and copious endothelial secretome, the constituents of which not only display pleotrophic cellular effects resembling those of SASP factors but may also activate the myofibroblast.[75]

INTEGRATION OF GLOMERULAR, TUBULAR, INTERSTIAL, AND VASCULAR PROCESSES IN PROGRESSIVE CKD

Table 18.1 summarizes the salient processes in each compartment and their interaction in progressive CKD.

SPECIFIC MEDIATORS AND INHIBITORS OF CHRONIC KIDNEY DISEASE

Transforming Growth Factor-β

TGF-β has a central role in initiating and modulating tissue repair. Its aberrant expression is directly involved in the pathogenesis of progressive CKD, regardless of the underlying etiology.[76] TGF-β is a member of a large family of proteins that include the inhibin/activin family, the bone morphogenetic protein (BMP) family, and the TGF-β family.[77] TGF-β signals through binding to a serine-threonine kinase receptor, the type II TGF-β receptor (TβRII), which then results in the activation of the type I receptor (TβRI). The intracellular signaling of TGF-β is mediated by a group of proteins called Smads.[78] The receptor-regulated Smads (Smad 1, 2, 3, 5, and 8) are then phosphorylated by interaction with the receptors.[78,79] This allows the receptor-regulated Smads to form oligomeric complexes with the common

TABLE 18.1 Summary of Major Compartmental Processes Contributing to Progressive Chronic Kidney Disease

GLOMERULAR PROCESSES
• Injury to and/or loss of podocytes and adhesion formation
• Proliferative PECs migrate around the glomerulus and eventually disrupt the glomerulotubular junction, leading to atubular glomeruli and aglomerular tubules
• Misdirected glomerular filtration tracks into the interstitium and incites inflammation
• Misdirected glomerular filtration tracks around the glomerulus, insudating between the TECs and TBM and leading to tubular atrophy
• Tubular trafficking of filtered protein
• Delivery of antigens from injured glomeruli to the tubulointerstitium
• Seepage of cytokines from inflammed glomeruli into the tubulointerstitium
• Alterations in glomerular hemodynamics as a pathway for injury in surviving nephrons
TUBULAR EPITHELIAL CELL PROCESSES
• Tubular trafficking and metabolism of filtered proteinuria with attendant interstitial inflammation and fibrosis
• Tubular injury leading to interstitial inflammation and fibrosis
• Tubular injury induced by hematuria
• Metabolic tubular adaptations in surviving nephrons
• Dedifferentiation and senescence of TECs and the production of senescence-associated secretory phenotype (SASP) factors
• Partial epithelial-mesenchymal transition (EMT)
INTERSTITIAL PROCESSES
• T lymphocyte-monocyte/macrophage–dendritic cell interaction and proliferation
• Congregation of interstitial inflammation in periglomerular areas and the synergizing of such inflammation with extracapillary glomerular processes
• Interstitial inflammation congregating around the glomerulotubular junction may disrupt this junction and may predispose to the formation of aglomerular tubules
• Recruitment of pericytes, the major myofibroblast precursor, from peritubular capillaries
• Proliferation and increased synthetic activity of interstitial myofibroblasts
• Recruitment of fibrocytes
• Increased extracellular matrix production and fibrosis
VASCULAR PROCESSES
• Loss of pericapillary pericytes destabilizes interstitial capillaries leading to dropout
• Interstitial capillary rarefraction
• Tubular ischemia and cortical hypoxia leading to tubular atrophy
• Cortical hypoxia as a stimulus for further interstitial inflammation and fibrosis
• Loss of peritubular capillaries increases postglomerular vascular resistance, thereby increasing glomerular hydrostatic pressure and predisposing to glomerular hemodynamic injury
• Endothelial-mesenchymal transition
• Adverse effects of the secretome of the injured endothelial cell

For details please see text. *EMT*, epithelial mesenchymal transition; *PECs*, parietal epithelial cells; *TBM*, tubular basement membrane; *TECs*, tubular epithelial cells.

Smad protein (Smad 4), subsequently to translocate to the nucleus and activate transcription of target genes.[78,79] Another class of Smad proteins, Smad 6 and 7, is responsible for inhibiting the activity of the receptor-regulated Smads.[78,79] TGF-β is also involved in activation of target genes through Smad-independent pathways (e.g. mitogen-activated protein kinase, Rho family, and phosphoinositol-3 kinase).[80]

Three of five distinct members of the TGF-β family (TGF-β 1, 2, 3) are expressed in mammals and have been extensively studied.[81] TGF-β and BMP-7 share similar signaling pathways through the Smad proteins but are counterregulatory to each other to maintain a balance. In CKD, TGF-β is increased *via* Smad2/3, whereas BMP-7 is downregulated through Smad1/5/8. Increased levels of TGF-β blocks BMP-7 signaling and increased BMP-7, reverses TGF-β signaling. BMP-7 is expressed in multiple cell types and serves to promote repair mechanisms in the kidney. Studies using an orally administered BMP7 agonist (THR-123) showed promising results in animal models of kidney disease including diabetic nephropathy, where it attenuated renal fibrosis.[82]

TGF-β1 is implicated in a number of pathological conditions such as IgA nephropathy, cyclosporin-induced nephrotoxicity, focal segmental glomerulosclerosis, crescentic glomerulonephritis, lupus nephritis, diabetic nephropathy, obstructive nephropathy, light chain deposition disease, and chronic transplant rejection.[76,83–85] In experimental and human disease, TGF-β1 has been implicated in the pathogenesis of renal fibrosis, not only by inducing apoptosis and promoting ECM accumulation but also by decreasing the synthesis of proteases and increasing the levels of protease inhibitors such as tissue inhibitor of metalloproteinases and integrins.[86,87] TGF-β1 overexpressing mice exhibit nephrotic syndrome and progressive glomerulosclerosis and uremia and die by 15 weeks of age.[88] TGF-β1 expression

is associated with apoptotic tubular cells that are thought to underlie the mechanism of tubular atrophy seen in CKD.[89] TGF-β has also been implicated in the pathogenesis of proteinuria by inducing podocyte apoptosis and depletion.[90] Similarly, TGF-β induces apoptosis in endothelial cells that may explain the loss of peritubular capillaries associated with tubulointerstitial fibrosis and tubular atrophy.[91] TGF-β also regulates the expression of several microRNAs (miRNAs) that are pathogenic in the progression of renal fibrosis in CKD.

In diabetes, advanced glycation end products induce TGF-β overexpression in proximal tubular cells, leading to tubulointerstitial fibrosis.[92] High glucose is a potent stimulus for increased TGF-β expression in various renal cell types.[93,94] Additionally, both experimental animals and humans with diabetes display marked increase in the renal levels of TGF-β.[95,96] Overexpression of TGF-β in the glomerulus causes proteinuria and fibrosis,[97] and the early manifestations of diabetic renal disease in mice are attenuated by administration of anti-TGF-β antibody.[98] Transient hyperglycemia in healthy individuals is associated with increased urinary levels of TGF-β1 along with F2-isoprostanes, a marker for oxidative stress.[99]

Although chronic elevation of TGF-β1 plays an important pathogenic role in the progression of renal diseases, TGF-β1 also stabilizes and attenuates tissue injury and displays a "good" side. One mechanism by which the beneficial effects of TGF-β may be mediated and its harmful effects counteracted is through induction of cytoprotective proteins such as heme oxygenase-1 (HO-1) (discussed below).[100–103] Studies have demonstrated the importance of the TGF-β receptor in renal epithelial cells in progressive CKD. Deletion of the TGF-β type 2 receptor in proximal tubular epithelial cells in mice results in tubular damage and tubulointerstitial fibrosis.[104] In this study, the kidneys showed dysregulated Wnt/catenin signaling. Restoring β-catenin activity was able to reverse the phenotype observed.

The central role of TGF-β in renal fibrosis and CKD is widely accepted. The TGF-β/Smad signaling pathway is now a viable candidate for antifibrotic therapeutic strategies. Encouraging results in preclinical models have led to clinical trials with a monoclonal TGF-β antibody (fresolimumab) in patients with steroid-resistant focal and segmental glomerulosclerosis, as well as in diabetic kidney disease, although the results have not been promising.[105,106] Another therapeutic target for the TGF-β pathway involves thrombospondin-1 (TSP-1), a multifunctional protein that regulates the activation of latent TGF-β. Peptide antagonists of TSP1 block only TGF-β activity stimulated by mediators such as high glucose or angiotensin II, and may represent a better approach to block TGF-β signaling.

The Renin–Angiotensin–Aldosterone System

The renin–angiotensin–aldosterone system (RAAS) is a highly regulated hormonal system that plays an important role in the control of blood pressure, cardiovascular and renal function, particularly for fluid and electrolyte balance.[14] The juxtaglomerular cells in the macula densa of the nephron secrete renin into the circulation on sensing decreased renal perfusion. Renin converts angiotensinogen (from the liver) into angiotensin I, the latter subsequently converted into angiotensin II by angiotensin-converting enzyme (released from the lungs). Angiotensin II acts on target tissues *via* type 1 (AT_1) and type 2 (AT_2) receptors (both G protein-coupled receptors). Two other receptor subtypes for angiotensin II and its metabolites have also been described (AT_3 and AT_4). The AT_1 receptor is abundant in the kidney, heart, vasculature, adrenal cortex, lung, and the brain and mediates the vasoconstrictor effects of angiotensin II. The AT_1 receptor also mediates aldosterone release and vascular smooth muscle cell proliferation. The AT_2 receptor is involved in apoptosis, regulation of extracellular matrix production and cell differentiation.

The mechanisms by which activation of the RAAS perpetuates progression of CKD include systemic and local hemodynamic effects, and key nonhemodynamic effects which promote oxidative stress, inflammation, and fibrosis.[14] These actions are mediated through direct and indirect effects on the intrarenal vasculature, particularly the afferent and efferent arterioles and intraglomerular capillary network, mesangial cells, podocytes, and the tubulointerstitial compartment.[68] While the hemodynamic effects of the RAAS are well known and extensively studied, the prooxidant, proinflammatory, and profibrotic effects have important implications in progression of CKD.[69] Angiotensin II promotes superoxide generation through activation of NADH and NADPH oxidase enzyme systems in vascular smooth muscle cells. Angiotensin II activates the proinflammatory transcription factor, NF-kB, and also regulates a number of cytokines, growth factors, chemokines, and adhesion molecules. Angiotensin II also interacts with growth factors (e.g. TGF-β and CTGF) and extracellular matrix proteins (e.g. collagen, fibronectin) to promote renal fibrosis. Angiotensin II also mediates renal hemodynamic effects by interacting with the nitric oxide pathway and activation of the heme oxygenase-1 enzyme system. Angiotensin II also stimulates aldosterone release from the adrenal glands.

Experimental animal models suggest an important role for aldosterone, a steroid hormone with mineralocorticoid activity, in the progression of CKD.[70] Aldosterone mediates its effects through genomic and nongenomic pathways, predominantly *via* the mineralocorticoid

receptor (MR), although other aldosterone receptors such as GPR30 have also been identified. In addition to the well-recognized actions of aldosterone in the kidney in regulating fluid and electrolyte balance, direct effects on the vasculature and the kidney and other organ systems through increased oxidative stress, inflammation, and fibrosis also contribute to the potential harmful effects of aldosterone in progressive CKD.[68]

Oxidative Stress

Oxidative stress is defined as tissue damage resulting from an imbalance between an excessive generation of prooxidants and insufficient antioxidant mechanisms. The predominant source of oxidants comes from the univalent reduction of molecular oxygen by membrane-bound NAPDH oxidases, as well as in the mitochondrial electron transport chain, resulting in the liberation of superoxide anion, which is rapidly converted by superoxide dismutases into hydrogen peroxide, the latter detoxified by glutathione peroxidase (a high affinity, low capacity enzyme) and catalase (a low affinity, high capacity enzyme). Superoxide can interact with nitric oxide to produce peroxynitrite. Hydrogen peroxide can undergo the Fenton reaction, to generate the hydroxyl radical. Myeloperoxidase can catalyze the interaction between hydrogen peroxide with chloride to form hypochlorous acid. The kidney generates hydrogen peroxide during the course of normal metabolism, the latter driven by the relatively high rates of oxygen consumption largely needed for sodium transport. Oxidants can be produced all along the nephron, from resident and infiltrating interstitial cells and from the intrarenal vasculature. Because red blood cells contain high levels of glutathione and antioxidant enzymes, the presence of anemia of CKD also fosters a prooxidant state.

The markers used to measure oxidative stress are usually measures of modification of lipids, proteins, DNA, or carbohydrates, representing "footprints" of oxidative stress. Direct measurement of oxidants is challenging, due to the highly reactive nature of these molecules, most with very short half-lives of a few seconds. Commonly used markers that are increased in CKD include thiobarbituric acid reactive substances (TBARS), malondialdehyde, oxidized lipids, F2 isoprostanes, protein carbonyls, nitrotyrosine, asymmetric dimethylarginine and even nucleic acids, and 8-hydroxy-2-deoxyguanosine. On the other hand, several in built antioxidant mechanisms are decreased in CKD. For example, levels of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase are decreased. Antioxidant vitamins E and C as well as metal-binding proteins such as transferrin and selenoproteins are reduced.

The evidence for oxidative stress in CKD is supported by the findings of (a) increased generation of oxidants in animal models and humans with primary and secondary glomerular diseases, (b) antioxidant strategies are beneficial in animal models, and (c) oxidants can induce changes in normal kidneys that resemble CKD.[72] Several factors implicated in progressive renal disease mediate their effects *via* oxidant generation or are activated *via* oxidant species. These include albumin from proteinuria, angiotensin II, oxidized lipids, uric acid, nitric oxide, growth factors, shear stress, aldosterone, and others. As a consequence of loss of glomerular permselectivity, proteins gain access to the urinary space. Proteins such as albumin are endocytosed by receptor-mediated mechanisms involving megalin and cubilin and can result in the activation of a number of signaling cascades, transcription factors such as NF-kB, and its target genes including MCP-1, endothelin-1, cytokines, and chemokines, which are released at the basolateral surface of the proximal tubule and can have effects in the tubulointerstitial compartment. Proteins can also activate complement and induce apoptosis. Several of these effects are preceded by increased generation of reactive oxygen species, are mimicked by oxidants, and are blocked by antioxidants.

Proteinuric renal diseases are often associated with lipid abnormalities. Renal tubular cells are exposed to an array of macromolecules including lipoproteins. Filtered lipoproteins can undergo oxidation in the glomerular microcirculatory bed, in the prooxidant urinary space by metals such as iron from transferrin or by heme released from red blood cells, or by tubular cells following intracellular uptake. Analogous to the pathogenic role of lipids in atherosclerosis, modified lipids can also instigate tubulointerstitial injury by increasing reactive oxygen species, activating NF-kB and proinflammatory genes, expansion of extracellular matrix, inducing tubular cell apoptosis, and promoting vascular injury.

Oxidants have diverse cellular actions, and disruption of the balance between prooxidants and antioxidants leads to increased oxidative stress, thus representing an appealing target for therapies to prevent progression of renal disease.[72] While results from animal models are encouraging, human studies have not proven their effectiveness. A phase 3 clinical trial, BEACON, testing the efficacy of an antioxidant and antiinflammatory agent, bardoxolone methyl, in CKD from diabetic kidney disease was prematurely terminated due to adverse cardiovascular side effects.[74] This agent is a potent activator of the redox-sensitive transcription factor, Nrf2 (NF-E2 related factor-2). In initial phase 2 studies, bardoxolone methyl showed promising results in slowing progression of diabetic kidney disease.[75] *Post hoc* analyses of the BEACON study have reported

that bardoxolone resulted in significant weight loss[107] and preserved kidney function, delaying the development of ESRD in type 2 diabetics with Stage 4 CKD.[108]

Endothelin

Endothelins are a family of peptides with highly potent vasoconstrictor actions, including ET-1, ET-2, and ET-3 isoforms. ET-1 is the major isoform expressed in endothelial cells and in the kidney, wherein the protein localizes to the glomerulus (endothelial, podocytes, and mesangial cells), renal tubular epithelial cells, the collecting duct, and interstitial cells (resident and infiltrating).[104] The protein is produced as a 212 amino acid prepro-ET-1, which is cleaved to big ET-1 with 38 amino acids, and then by the action of ET-converting enzyme, active ET-1 is generated. Several stimuli that are involved in the pathogenesis of CKD result in the generation of ET-1, including angiotensin II, vasopressin, reactive oxygen species, growth factors (TGF-β and PDGF), and acidosis. On the other hand, stimuli such as nitric oxide, prostacyclin, and natriuretic peptides inhibit ET-1 expression. ET-1 mediates its effects *via* binding to two receptors, ET_A and ET_B. Activation of the ET_A receptor, present abundantly in vascular smooth muscle cells, causes vasoconstriction, whereas activation of ET_B receptors, found predominantly in the vascular endothelium, mediates vasodilatory responses *via* nitric oxide and prostacyclin. ET_B receptors are also abundant in the collecting system.

Endothelin plays an important role not only in maintaining normal physiologic functions but also is a major factor in several pathophysiologic processes in the kidney and other organ systems.[109] In the kidney, ET-1 regulates renal blood flow and glomerular filtration, natriuresis, volume, and acid-base balance.[106] In pathophysiologic states, ET-1 contributes to the development of hypertension, endothelial dysfunction, increased vascular tone, and arterial stiffness and can increase proteinuria through effects on glomerular hemodynamics. ET-1 serves as a chemoattractant for monocytes, binds to interstitial fibroblasts, and promotes their proliferation and extracellular matrix production by these cells, contributing thereby to tubulointerstitial inflammation and fibrosis. Although characterized as the most potent vasoconstrictor, ET-1 has a number of effects that are independent of changes in blood pressure.[104] Systemic overexpression of ET-1 in mice results in inflammation and fibrosis of the kidney, heart, and lungs.[107] Endothelial-specific ET-1 overexpression leads to vascular inflammation in the absence of hypertension.[108] The pathophysiologic roles of ET-1 in the progression of CKD have led to ongoing clinical studies to evaluate the efficacy of ET-1 receptor antagonists to ameliorate changes in blood pressure, proteinuria, inflammation, and fibrosis in diabetic and nondiabetic kidney diseases.[104]

Micro RNAs

miRNAs are noncoding small RNAs, 22 nucleotides in length, which bind to the 3′-UTR of target genes and, thereby, repress translation and/or induce degradation of target mRNAs of a variety of genes. miRNAs regulate numerous molecular and cellular processes. Aberrant expression of miRNAs is associated with initiation and progression of pathologic processes, including progression of CKD, most notably with renal fibrosis.[110] Primary miRNA transcripts are initially generated that are processed to precursor miRNAs in the nucleus by an enzyme, Drosha, and a double strand RNA-binding protein, DGCR8. The ~70-nucleotide hairpin precursor miRNAs are exported out of the nucleus by exportin 5, and then cleaved by Dicer to RNA duplexes. The miRNA duplexes are unwound and the mature single strand, miRNA, containing the complementary mRNA target sequences, is loaded into the RNA-induced silencing complex (RISC)—the latter containing Argonaute 2, Dicer, and transactivating response RNA-binding proteins. The miRNAs in this complex are then guided to the 3-UTR of target genes.[39] In addition to inhibiting posttranscriptional mechanisms involving initiation and elongation, miRNAs can also target promoter regions and repress gene expression.

Several miRNAs are expressed in the kidney, and their levels are increased or decreased in diseased states.[110,111] For example, miRNA-192, an miRNA highly expressed in the kidney, is increased in glomeruli in animal models of diabetic kidney disease. High glucose and TGF-β increase the expression of miRNA-200 and miRNA-192 family in mesangial cells and promote expression of extracellular matrix genes such as collagen. In contrast, in cancer cell lines, TGF-β downregulates miRNA-200 and miRNA-192 expression, suggesting that the effects mediated by miRNAs are cell-type specific. Another miRNA, miRNA-377, has also been shown to be pathogenic in mouse models of diabetic kidney disease, wherein it downregulates p21-activated kinase and manganese superoxide dismutase and increases fibronectin levels. In animal models of renal inflammation and fibrosis, miRNA-21, one of the first mammalian miRNAs to be identified, is markedly upregulated and blocking miRNA-21 or miRNA-21 knockout mice display reduced renal fibrosis.[49,54] These effects are mediated through attenuation of TGF-β, extracellular matrix production, inflammation, and epithelial metabolic pathways, particularly the PPAR-α-regulated lipid metabolic signaling pathway. Studies using cell-specific deletion of Dicer in podocytes have

revealed important roles of miRNAs in glomerular biology causing significant phenotypical changes characterized by proteinuria, foot process effacement, GBM abnormalities, and rapid progression of kidney disease.[112,113]

Specific targeting of miRNAs using antagomirs is being explored in preclinical models of CKD as potential therapeutic strategies. It is important to note that a single miRNA can regulate different genes, and several miRNAs may be involved in the regulation of the same gene. Hence, it is important to consider the specificity of the gene−miRNA interaction in determining the functional effects. There is also considerable redundancy within miRNA families, and understanding miRNA−miRNA interactions would be critical before embarking on specific therapeutic targeting strategies.[39]

Wnt Signaling

The Wnt pathway is a highly complex and conserved cell-to-cell communication pathway that regulates many critical aspects of cellular functions, including cell fate decisions, branching morphogenesis, cell proliferation, polarization, and migration.[114] The term Wnt was derived from a combination of Int (the Integration 1 gene) and Wg (the Wingless gene) and stands for Wingless-related integration site. Three Wnt pathways have been described, including the canonical Wnt pathway (or Wnt/β-catenin pathway), the noncanonical planar cell polarity pathway, and the noncanonical Wnt/calcium pathway. The Wnt/β-catenin pathway causes an accumulation of β-catenin in the cytoplasm, and its eventual translocation into the nucleus, where it activates transcription factors (T-cell factor and/or lymphoid enhancer factor) and regulates expression of several downstream target genes involved in matrix production and fibrosis (e.g. plasminogen activator inhibitor-1 (PAI-1), fibronectin, fibroblast-specific protein 1, and matrix metalloproteinase-7). The noncanonical planar cell polarity pathway regulates cytoskeleton functions and dictates cellular shape. The noncanonical Wnt/calcium pathway regulates intracellular calcium levels. Wnt signaling also interacts with other pathways, such as the GSK3 signal pathway.

The critical role of the Wnt signaling pathway in the developing kidney is well established. The importance of reactivation and dysregulated Wnt signaling in kidney diseases including diabetic nephropathy, chronic allograft nephropathy and polycystic kidney disease, particularly in the pathogenesis of renal fibrosis, is recognized.[114] Monocytes from patients with Stage 4 and 5 CKD display high levels of activation of the Wnt/β-catenin signaling pathway, compared with healthy controls.[115] Studies have also identified the anti-aging protein, Klotho, as an endogenous antagonist of the Wnt/β-catenin pathway.[116] Klotho blocks Wnt-triggered activation and nuclear translocation of β-catenin and its target genes.[116] Orally active Wnt modulators are in development and could provide important tools for further investigating the role of Wnt/beta-catenin signaling in renal fibrosis.[109]

Heme Oxygenase

Heme oxygenases catalyze the rate-limiting step in the degradation of heme into equimolar amounts of iron, carbon monoxide (CO), and biliverdin.[117−119] Biliverdin is subsequently converted into bilirubin *via* biliverdin reductase, while iron is sequestered by ferritin. Two isoforms of heme oxygenase (HO-1, HO-2) have been identified.[117−119] HO-1 is induced by heme products, as well as a wide variety of nonheme stimuli, several of which are pathogenic in the progression of CKD, including angiotensin II, hypoxia, and growth factors (e.g. PDGF and TGF-β1).[117−119] In contrast, HO-2 is a constitutive enzyme and functions as a physiologic regulator of cellular function. The cytoprotective effects of HO-1 induction are due to the degradation of the heme moiety (a prooxidant molecule) and the generation of beneficial products such as biliverdin/bilirubin and CO. Bilirubin has antioxidant properties *via* scavenging peroxy radicals and inhibiting lipid peroxidation.[120] Ferritin, an intracellular iron repository, is coinduced with HO-1, allowing safe sequestration of unbound iron liberated from heme degradation.[121] CO has vasodilatory effects mediated *via* cGMP and potassium channels,[122] as well as antiapoptotic and immunomodulatory functions.[123] The protective effects of HO-1 overexpression have also been attributed to the upregulation of the cell-cycle regulatory protein, p21.[124]

The antifibrogenic properties of HO-1 and its products, particularly CO, in different pathological conditions and tissues have been extensively studied. Fujita et al. demonstrated that inhaled CO increased survival of HO-$1^{-/-}$ mice with lethal ischemic lung injury by inhibiting a key profibrotic agent, plasminogen activator inhibitor-1.[125] In a rat hypoxia model, chemical inhibition of HO-1 increased type I and III collagen and TGF-β expression, an effect attributed to a decrease in CO levels.[126] Exogenous CO administration has also been shown to decrease proliferation of human fibroblasts.[127]

Numerous studies have demonstrated the protective effects of HO-1 in both *in vitro* and *in vivo* models of injury and disease.[117−119] Repeated exposure of HO-$1^{-/-}$ mice to heme proteins leads to intense interstitial cellular inflammation, with significant increase in MCP-1 expression and activation of nuclear factor-κB.[55] In addition to protecting against acute cytotoxicity, HO-1 downregulates the inflammatory response in both

renal and nonrenal tissues.[128] The phenotype of the HO-$1^{-/-}$ mouse (at ages beyond 20–24 weeks) is characterized by chronic renal and hepatic inflammation, tissue iron deposition, anemia, splenomegaly, and increased susceptibility to cardiovascular diseases, which highlights the functional and biological significance of HO-1.[129]

These *in vitro* and animal model findings are also corroborated in human case reports. Two patients with HO-1 deficiency have been described who presented with several phenotypic similarities with the HO-$1^{-/-}$ mouse and had extensive atherosclerosis and marked renal tubulointerstitial injury associated with tubular dilation and atrophy, inflammatory cell infiltration and interstitial fibrosis.[130,131] The level of HO-1 expression can be variable within the human population, because the promoter of human HO-1 gene is highly polymorphic and contains a (GT) repeat region. Evidence suggests that patients with lower (GT)n repeats have higher HO-1 expression, thereby associated with better patient outcomes in a number of clinical conditions such as renal graft survival,[132] vascular stenosis,[133] arteriovenous fistula patency in hemodialysis patients,[134] polycystic kidney disease, and IgA nephropathy.[135] Furthermore, there are now ongoing clinical trials examining the beneficial effects of HO-1 by-products including CO in kidney transplantation (clinicaltrials.gov, NCT 00531856) and bilirubin in endotoxemia (clinicaltrials.gov, NCT 00916448).

Acid-Base Status

Acid-base disturbances, specifically metabolic acidosis, are a frequent complication during the later stages of CKD, emphasizing the key role of the kidney in the maintenance of normal acid-base homeostasis. A major source of acid load to the kidney is from the diet. Metabolic acidosis is linked to progression of CKD and also contributes to muscle wasting seen in patients with end-stage renal disease.[136] The mechanisms underlying the progression of CKD by acidosis have been studied in animal models.[49] A reduction in renal mass results in increased renal ammoniagenesis from the remnant nephrons. Ammonia instigates local tubular toxicity and inflammatory pathways *via* the alternative complement pathway by the reaction of ammonia with the C3 thiolester, leading to complement-mediated tissue injury.[49] These changes are reversed by sodium bicarbonate supplementation in the remnant kidney model. Acid loading also increases expression of angiotensin II, aldosterone, and endothelin-1, which promote hydrogen ion excretion and are also pathogenic in the progression of CKD and renal fibrosis.[137]

Metabolic acidosis fosters a catabolic state in skeletal muscle by inhibiting albumin production through activation of the ubiquitin-proteasome pathway. Chronic metabolic acidosis increases urinary calcium excretion due to effects on osteoclastic bone resorption, leading to bone and muscle loss and growth retardation in children. Metabolic acidosis also results in abnormalities in growth hormone and thyroid secretion, insulin sensitivity, and β2-microglobulin deposition. A proposed mechanism by which metabolic acidosis in CKD is pathogenic in the progression of the disease is summarized in Figure 18.1. A single-center randomized clinical trial has shown that exogenous bicarbonate supplementation slows progression of CKD in patients.[138] More recently, a sodium-free, nonabsorbable hydrochloric acid binder, TRC101, was shown to increase sodium bicarbonate levels in patients with CKD,[110] although its effects on slowing progression of CKD have not as yet been studied. Further large multicenter clinical studies will be needed to provide clear evidence for the use of alkali supplementation in slowing progression of CKD.

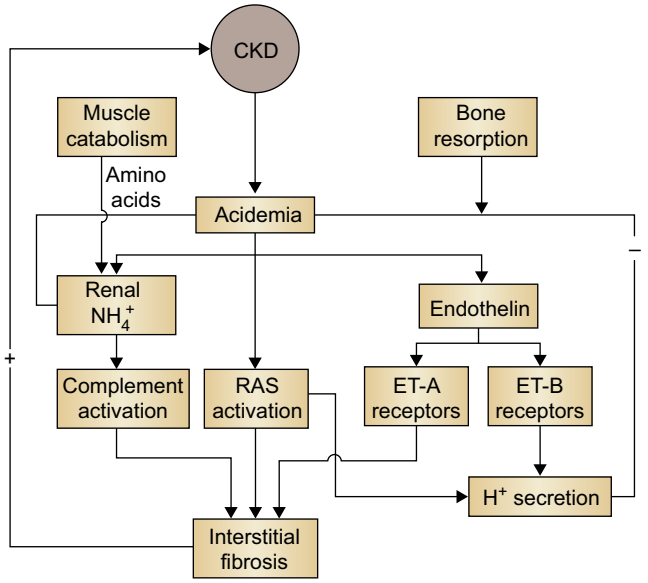


FIGURE 18.1 **Proposed mechanisms by which metabolic acidosis worsens progression of chronic kidney disease**. To maintain isohydria, nephrons show an increase in ammoniagenesis, which activates the alternative complement pathway and synthesis of inflammatory mediators. Another nephrotoxic agent is endothelin-1 (ET-1), which induces vasoconstriction, inflammation, and fibrosis, as well as renal acidification. This activity is associated with angiotensin II and free-radical reactions. Increased ET-1 synthesis is caused by acid retention concomitant with decreased glomerular filtration rate, which also causes increased serum aldosterone concentration. Further consequences of acidosis include disturbances of muscle and bone metabolism, leading to renal osteodystrophy. *CKD*, chronic kidney disease; *RAS*, renin–angiotensin system. *Reproduced with permission from Loniewski, Wesson.* Kidney Int *2014.*[137]

CONCLUSIONS

This perspective regards the progression of CKD as involving the recruitment and engagement of *cellular processes* originating in specific compartments of the kidney on the one hand and *biochemical pathways* of cell injury that contribute to these processes on the other hand. Many of these processes possess the capacity to ramify broadly beyond the compartment where they initially arose, and it is this essential consideration that contributes so fundamentally to the increasing loss of functional nephrons and the progression of CKD. For example, processes begun in the extracapillary glomerular compartment elicit processes in renal tubules and the interstitium that drive pericyte recruitment and interstitial fibrosis, the latter, eventually, feeding back to adversely affect glomerular behavior. This capacity to propagate injury is also true for the described biochemical pathways. Angiotensin II induces TGF-β1 and the consequent elaboration of extracellular matrix. Angiotensin II also induces oxidative stress, which itself can upregulate TGF-β1 in vicinal cells and thus the propagation of a fibrosing response. This lack of containment of compartmental processes, and this versatility of injurious biochemical pathways, not only underlies the pathogenesis of CKD but also holds substantial therapeutic significance. The best hope for retarding or preventing the progression of CKD resides in a combined, multipronged therapeutic approach, which will interrupt these processes and pathways at separate and several steps.

Acknowledgments

The authors acknowledge support from NIH grants R01 DK059600 and O'Brien Center P30 DK079337 (to AA) and R01 DK070124 and R37 DK047060 (to KAN). AA serves as a consultant for DynaMed and is on the advisory board of Goldilocks Therapeutics. Both roles have no conflict of interest with this work.

References

1. Bohle A, von Gise H, Mackensen-Haen S, Stark-Jakob B. The obliteration of the postglomerular capillaries and its influence upon the function of both glomeruli and tubuli. Functional interpretation of morphologic findings. *Klin Wochenschr* 1981;**59**(18):1043–51.
2. Kriz W, LeHir M. Pathways to nephron loss starting from glomerular diseases-insights from animal models. *Kidney Int* 2005;**67**(2): 404–19.
3. Nath KA. Tubulointerstitial changes as a major determinant in the progression of renal damage. *Am J Kidney Dis* 1992;**20**(1):1–17.
4. Harris RC, Neilson EG. Toward a unified theory of renal progression. *Annu Rev Med* 2006;**57**:365–80.
5. Liu Y. Cellular and molecular mechanisms of renal fibrosis. *Nat Rev Nephrol* 2011;**7**(12):684–96.
6. Kriz W, Shirato I, Nagata M, LeHir M, Lemley KV. The podocyte's response to stress: the enigma of foot process effacement. *Am J Physiol Renal Physiol* 2013;**304**(4):F333–47.
7. Reiser J, Sever S. Podocyte biology and pathogenesis of kidney disease. *Annu Rev Med* 2013;**64**:357–66.
8. Theilig F. Spread of glomerular to tubulointerstitial disease with a focus on proteinuria. *Ann Anat* 2010;**192**(3):125–32.
9. Schlondorff D, Banas B. The mesangial cell revisited: no cell is an island. *J Am Soc Nephrol* 2009;**20**(6):1179–87.
10. Smeets B, Moeller MJ. Parietal epithelial cells and podocytes in glomerular diseases. *Semin Nephrol* 2012;**32**(4):357–67.
11. D'Agati VD. Pathobiology of focal segmental glomerulosclerosis: new developments. *Curr Opin Nephrol Hypertens* 2012;**21**(3): 243–50.
12. Jefferson JA, Alpers CE, Shankland SJ. Podocyte biology for the bedside. *Am J Kidney Dis* 2011;**58**(5):835–45.
13. Lasagni L, Lazzeri E, Shankland SJ, Anders HJ, Romagnani P. Podocyte mitosis – a catastrophe. *Curr Mol Med* 2013;**13**(1):13–23.
14. Assady S, Wanner N, Skorecki KL, Huber TB. New insights into podocyte biology in glomerular health and disease. *J Am Soc Nephrol* 2017;**28**(6):1707–15.
15. Asano T, Niimura F, Pastan I, Fogo AB, Ichikawa I, Matsusaka T. Permanent genetic tagging of podocytes: fate of injured podocytes in a mouse model of glomerular sclerosis. *J Am Soc Nephrol* 2005; **16**(8):2257–62.
16. Matsusaka T, Xin J, Niwa S, et al. Genetic engineering of glomerular sclerosis in the mouse via control of onset and severity of podocyte-specific injury. *J Am Soc Nephrol* 2005; **16**(4):1013–23.
17. Wharram BL, Goyal M, Wiggins JE, et al. Podocyte depletion causes glomerulosclerosis: diphtheria toxin-induced podocyte depletion in rats expressing human diphtheria toxin receptor transgene. *J Am Soc Nephrol* 2005;**16**(10):2941–52.
18. Matsusaka T, Sandgren E, Shintani A, et al. Podocyte injury damages other podocytes. *J Am Soc Nephrol* 2011;**22**(7):1275–85.
19. Sato Y, Wharram BL, Lee SK, et al. Urine podocyte mRNAs mark progression of renal disease. *J Am Soc Nephrol* 2009;**20**(5): 1041–52.
20. Okamura K, Dummer P, Kopp J, et al. Endocytosis of albumin by podocytes elicits an inflammatory response and induces apoptotic cell death. *PLoS One* 2013;**8**(1):e54817.
21. Fligny C, Barton M, Tharaux PL. Endothelin and podocyte injury in chronic kidney disease. *Contrib Nephrol* 2011;**172**:120–38.
22. Herman-Edelstein M, Weinstein T, Gafter U. TGFbeta1-dependent podocyte dysfunction. *Curr Opin Nephrol Hypertens* 2013;**22**(1): 93–9.
23. Kato H, Susztak K. Repair problems in podocytes: Wnt, Notch, and glomerulosclerosis. *Semin Nephrol* 2012;**32**(4):350–6.
24. Wennmann DO, Hsu HH, Pavenstadt H. The renin-angiotensin-aldosterone system in podocytes. *Semin Nephrol* 2012;**32**(4): 377–84.
25. Hostetter TH. Hyperfiltration and glomerulosclerosis. *Semin Nephrol* 2003;**23**(2):194–9.
26. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol* 1981;**241**(1): F85–93.
27. Endlich N, Endlich K. The challenge and response of podocytes to glomerular hypertension. *Semin Nephrol* 2012;**32**(4):327–41.
28. Morigi M, Macconi D, Zoja C, et al. Protein overload-induced NF-kappaB activation in proximal tubular cells requires H(2)O(2) through a PKC-dependent pathway. *J Am Soc Nephrol* 2002;**13**(5): 1179–89.
29. Zoja C, Benigni A, Remuzzi G. Cellular responses to protein overload: key event in renal disease progression. *Curr Opin Nephrol Hypertens* 2004;**13**(1):31–7.
30. Eardley KS, Zehnder D, Quinkler M, et al. The relationship between albuminuria, MCP-1/CCL2, and interstitial macrophages in chronic kidney disease. *Kidney Int* 2006;**69**(7):1189–97.

31. Grandaliano G, Gesualdo L, Ranieri E, et al. Monocyte chemotactic peptide-1 expression in acute and chronic human nephritides: a pathogenetic role in interstitial monocytes recruitment. *J Am Soc Nephrol* 1996;**7**(6):906–13.
32. Prodjosudjadi W, Gerritsma JS, van Es LA, Daha MR, Bruijn JA. Monocyte chemoattractant protein-1 in normal and diseased human kidneys: an immunohistochemical analysis. *Clin Nephrol* 1995;**44**(3):148–55.
33. Kitagawa K, Wada T, Furuichi K, et al. Blockade of CCR2 ameliorates progressive fibrosis in kidney. *Am J Pathol* 2004;**165**(1): 237–46.
34. Shimizu H, Maruyama S, Yuzawa Y, et al. Anti-monocyte chemoattractant protein-1 gene therapy attenuates renal injury induced by protein-overload proteinuria. *J Am Soc Nephrol* 2003;**14**(6): 1496–505.
35. Wada T, Furuichi K, Sakai N, et al. Gene therapy via blockade of monocyte chemoattractant protein-1 for renal fibrosis. *J Am Soc Nephrol* 2004;**15**(4):940–8.
36. Motoyoshi Y, Matsusaka T, Saito A, et al. Megalin contributes to the early injury of proximal tubule cells during nonselective proteinuria. *Kidney Int* 2008;**74**(10):1262–9.
37. Theilig F, Kriz W, Jerichow T, et al. Abrogation of protein uptake through megalin-deficient proximal tubules does not safeguard against tubulointerstitial injury. *J Am Soc Nephrol* 2007;**18**(6): 1824–34.
38. Christensen EI, Verroust PJ. Interstitial fibrosis: tubular hypothesis versus glomerular hypothesis. *Kidney Int* 2008;**74**(10): 1233–6.
39. Nath KA, Croatt AJ, Haggard JJ, Grande JP. Renal response to repetitive exposure to heme proteins: chronic injury induced by an acute insult. *Kidney Int* 2000;**57**(6):2423–33.
40. Grgic I, Campanholle G, Bijol V, et al. Targeted proximal tubule injury triggers interstitial fibrosis and glomerulosclerosis. *Kidney Int* 2012;**82**(2):172–83.
41. Lee PT, Chou KJ, Fang HC. Are tubular cells not only victims but also perpetrators in renal fibrosis? *Kidney Int* 2012;**82**(2): 128–30.
42. Schnaper HW. Remnant nephron physiology and the progression of chronic kidney disease. *Pediatr Nephrol* 2014;**29**(2):193–202.
43. Schrier RW, Shapiro JI, Chan L, Harris DC. Increased nephron oxygen consumption: potential role in progression of chronic renal disease. *Am J Kidney Dis* 1994;**23**(2):176–82.
44. Nath KA, Croatt AJ, Hostetter TH. Oxygen consumption and oxidant stress in surviving nephrons. *Am J Physiol* 1990;**258**(5 Pt 2):F1354–62.
45. Kurnik BR, Weisberg LS, Kurnik PB. Renal and systemic oxygen consumption in patients with normal and abnormal renal function. *J Am Soc Nephrol* 1992;**2**(11):1617–26.
46. Mimura I, Nangaku M. The suffocating kidney: tubulointerstitial hypoxia in end-stage renal disease. *Nat Rev Nephrol* 2010;**6**(11): 667–78.
47. Palm F, Nordquist L. Renal tubulointerstitial hypoxia: cause and consequence of kidney dysfunction. *Clin Exp Pharmacol Physiol* 2011;**38**(7):474–80.
48. Fine LG, Orphanides C, Norman JT. Progressive renal disease: the chronic hypoxia hypothesis. *Kidney Int Suppl* 1998;**65**:S74–8.
49. Nath KA, Hostetter MK, Hostetter TH. Pathophysiology of chronic tubulo-interstitial disease in rats. Interactions of dietary acid load, ammonia, and complement component C3. *J Clin Investig* 1985;**76**(2):667–75.
50. Souma T, Abe M, Moriguchi T, et al. Luminal alkalinization attenuates proteinuria-induced oxidative damage in proximal tubular cells. *J Am Soc Nephrol* 2011;**22**(4):635–48.
51. Goraya N, Wesson DE. Does correction of metabolic acidosis slow chronic kidney disease progression? *Curr Opin Nephrol Hypertens* 2013;**22**(2):193–7.
52. Yamagata K, Ishida K, Sairenchi T, et al. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int* 2007;**71**(2):159–66.
53. Hill PA, Davies DJ, Kincaid-Smith P, Ryan GB. Ultrastructural changes in renal tubules associated with glomerular bleeding. *Kidney Int* 1989;**36**(6):992–7.
54. Kanakiriya SK, Croatt AJ, Haggard JJ, et al. Heme: a novel inducer of MCP-1 through HO-dependent and HO-independent mechanisms. *Am J Physiol Renal Physiol* 2003;**284**(3):F546–54.
55. Nath KA, Vercellotti GM, Grande JP, et al. Heme protein-induced chronic renal inflammation: suppressive effect of induced heme oxygenase-1. *Kidney Int* 2001;**59**(1):106–17.
56. Gonzalez-Michaca L, Farrugia G, Croatt AJ, Alam J, Nath KA. Heme: a determinant of life and death in renal tubular epithelial cells. *Am J Physiol Renal Physiol* 2004;**286**(2):F370–7.
57. Zeisberg M, Neilson EG. Mechanisms of tubulointerstitial fibrosis. *J Am Soc Nephrol* 2010;**21**(11):1819–34.
58. Teteris SA, Engel DR, Kurts C. Homeostatic and pathogenic role of renal dendritic cells. *Kidney Int* 2011;**80**(2):139–45.
59. Heymann F, Meyer-Schwesinger C, Hamilton-Williams EE, et al. Kidney dendritic cell activation is required for progression of renal disease in a mouse model of glomerular injury. *J Clin Investig* 2009;**119**(5):1286–97.
60. Hochheiser K, Engel DR, Hammerich L, et al. Kidney dendritic cells become pathogenic during crescentic glomerulonephritis with proteinuria. *J Am Soc Nephrol* 2011;**22**(2):306–16.
61. Macconi D, Chiabrando C, Schiarea S, et al. Proteasomal processing of albumin by renal dendritic cells generates antigenic peptides. *J Am Soc Nephrol* 2009;**20**(1):123–30.
62. Hewitson TD. Renal tubulointerstitial fibrosis: common but never simple. *Am J Physiol Renal Physiol* 2009;**296**(6):F1239–44.
63. Kaissling B, Lehir M, Kriz W. Renal epithelial injury and fibrosis. *Biochim Biophys Acta* 2013;**1832**(7):931–9.
64. Rojas A, Chang FC, Lin SL, Duffield JS. The role played by perivascular cells in kidney interstitial injury. *Clin Nephrol* 2012; **77**(5):400–8.
65. Schrimpf C, Duffield JS. Mechanisms of fibrosis: the role of the pericyte. *Curr Opin Nephrol Hypertens* 2011;**20**(3):297–305.
66. Kriz W, Kaissling B, Le Hir M. Epithelial-mesenchymal transition (EMT) in kidney fibrosis: fact or fantasy? *J Clin Investig* 2011; **121**(2):468–74.
67. Sun YB, Qu X, Caruana G, Li J. The origin of renal fibroblasts/myofibroblasts and the signals that trigger fibrosis. *Differentiation* 2016;**92**(3):102–7.
68. Gewin L, Zent R, Pozzi A. Progression of chronic kidney disease: too much cellular talk causes damage. *Kidney Int* 2017;**91**(3): 552–60.
69. Humphreys BD. Mechanisms of renal fibrosis. *Annu Rev Physiol* 2018;**80**:309–26.
70. Leaf IA, Duffield JS. What can target kidney fibrosis? *Nephrol Dial Transplant* 2017;**32**(Suppl. l_1):i89–97.
71. Lin SL, Chang FC, Schrimpf C, et al. Targeting endothelium-pericyte cross talk by inhibiting VEGF receptor signaling attenuates kidney microvascular rarefaction and fibrosis. *Am J Pathol* 2011;**178**(2):911–23.
72. Kida Y, Ieronimakis N, Schrimpf C, Reyes M, Duffield JS. EphrinB2 reverse signaling protects against capillary rarefaction and fibrosis after kidney injury. *J Am Soc Nephrol* 2013;**24**(4):559–72.
73. Rama I, Bruene B, Torras J, et al. Hypoxia stimulus: an adaptive immune response during dendritic cell maturation. *Kidney Int* 2008;**73**(7):816–25.
74. Schmitt R, Melk A. Molecular mechanisms of renal aging. *Kidney Int* 2017;**92**(3):569–79.
75. Lipphardt M, Song JW, Matsumoto K, et al. The third path of tubulointerstitial fibrosis: aberrant endothelial secretome. *Kidney Int* 2017;**92**(3):558–68.

76. Bottinger EP. TGF-beta in renal injury and disease. *Semin Nephrol* 2007;**27**(3):309–20.
77. Cheng J, Grande JP. Transforming growth factor-beta signal transduction and progressive renal disease. *Exp Biol Med* 2002;**227**(11): 943–56.
78. Moustakas A, Heldin CH. The regulation of TGFbeta signal transduction. *Development* 2009;**136**(22):3699–714.
79. Wrighton KH, Lin X, Feng XH. Phospho-control of TGF-beta superfamily signaling. *Cell Res* 2009;**19**(1):8–20.
80. Derynck R, Zhang YE. Smad-dependent and Smad-independent pathways in TGF-beta family signalling. *Nature* 2003;**425**(6958): 577–84.
81. Pelton RW, Saxena B, Jones M, Moses HL, Gold LI. Immunohistochemical localization of TGF beta 1, TGF beta 2, and TGF beta 3 in the mouse embryo: expression patterns suggest multiple roles during embryonic development. *J Cell Biol* 1991;**115**(4):1091–105.
82. Sugimoto H, LeBleu VS, Bosukonda D, et al. Activin-like kinase 3 is important for kidney regeneration and reversal of fibrosis. *Nat Med* 2012;**18**(3):396–404.
83. Yamamoto T, Noble NA, Cohen AH, et al. Expression of transforming growth factor-beta isoforms in human glomerular diseases. *Kidney Int* 1996;**49**(2):461–9.
84. Liu Y. Renal fibrosis: new insights into the pathogenesis and therapeutics. *Kidney Int* 2006;**69**(2):213–7.
85. Gagliardini E, Benigni A. Therapeutic potential of TGF-beta inhibition in chronic renal failure. *Expert Opin Biol Ther* 2007;**7**(3): 293–304.
86. Hocevar BA, Howe PH. Analysis of TGF-beta-mediated synthesis of extracellular matrix components. *Methods Mol Biol* 2000;**142**: 55–65.
87. Yuan W, Varga J. Transforming growth factor-beta repression of matrix metalloproteinase-1 in dermal fibroblasts involves Smad3. *J Biol Chem* 2001;**276**(42):38502–10.
88. Kopp JB, Factor VM, Mozes M, et al. Transgenic mice with increased plasma levels of TGF-beta 1 develop progressive renal disease. *Lab Invest* 1996;**74**(6):991–1003.
89. Gobe GC, Axelsen RA. Genesis of renal tubular atrophy in experimental hydronephrosis in the rat. Role of apoptosis. *Lab Invest* 1987;**56**(3):273–81.
90. Schiffer M, Bitzer M, Roberts IS, et al. Apoptosis in podocytes induced by TGF-beta and Smad7. *J Clin Investig* 2001;**108**(6): 807–16.
91. Choi ME, Ballermann BJ. Inhibition of capillary morphogenesis and associated apoptosis by dominant negative mutant transforming growth factor-beta receptors. *J Biol Chem* 1995;**270**(36): 21144–50.
92. Yamagishi S, Inagaki Y, Okamoto T, Amano S, Koga K, Takeuchi M. Advanced glycation end products inhibit de novo protein synthesis and induce TGF-beta overexpression in proximal tubular cells. *Kidney Int* 2003;**63**(2):464–73.
93. Rocco MV, Chen Y, Goldfarb S, Ziyadeh FN. Elevated glucose stimulates TGF-beta gene expression and bioactivity in proximal tubule. *Kidney Int* 1992;**41**(1):107–14.
94. Ziyadeh FN, Sharma K, Ericksen M, Wolf G. Stimulation of collagen gene expression and protein synthesis in murine mesangial cells by high glucose is mediated by autocrine activation of transforming growth factor-beta. *J Clin Investig* 1994;**93**(2):536–42.
95. Sharma K, Ziyadeh FN, Alzahabi B, et al. Increased renal production of transforming growth factor-beta1 in patients with type II diabetes. *Diabetes* 1997;**46**(5):854–9.
96. Nakamura T, Fukui M, Ebihara I, et al. mRNA expression of growth factors in glomeruli from diabetic rats. *Diabetes* 1993; **42**(3):450–6.
97. Isaka Y, Fujiwara Y, Ueda N, Kaneda Y, Kamada T, Imai E. Glomerulosclerosis induced by in vivo transfection of transforming growth factor-beta or platelet-derived growth factor gene into the rat kidney. *J Clin Investig* 1993;**92**(6):2597–601.
98. Sharma K, Jin Y, Guo J, Ziyadeh FN. Neutralization of TGF-beta by anti-TGF-beta antibody attenuates kidney hypertrophy and the enhanced extracellular matrix gene expression in STZ-induced diabetic mice. *Diabetes* 1996;**45**(4):522–30.
99. McGowan TA, Dunn SR, Falkner B, Sharma K. Stimulation of urinary TGF-beta and isoprostanes in response to hyperglycemia in humans. *Clin J Am Soc Nephrol* 2006;**1**(2):263–8.
100. Hill-Kapturczak N, Chang SH, Agarwal A. Heme oxygenase and the kidney. *DNA Cell Biol* 2002;**21**(4):307–21.
101. Hill-Kapturczak N, Truong L, Thamilselvan V, Visner GA, Nick HS, Agarwal A. Smad7-dependent regulation of heme oxygenase-1 by transforming growth factor-beta in human renal epithelial cells. *J Biol Chem* 2000;**275**(52):40904–9.
102. Kutty RK, Nagineni CN, Kutty G, Hooks JJ, Chader GJ, Wiggert B. Increased expression of heme oxygenase-1 in human retinal pigment epithelial cells by transforming growth factor-beta. *J Cell Physiol* 1994;**159**(2):371–8.
103. Hill-Kapturczak N, Jarmi T, Agarwal A. Growth factors and heme oxygenase-1: perspectives in physiology and pathophysiology. *Antioxidants Redox Signal* 2007;**9**(12):2197–207.
104. Nlandu-Khodo S, Neelisetty S, Phillips M, et al. Blocking TGF-beta and beta-catenin epithelial crosstalk exacerbates CKD. *J Am Soc Nephrol* 2017;**28**(12):3490–503.
105. Trachtman H, Fervenza FC, Gipson DS, et al. A phase 1, single-dose study of fresolimumab, an anti-TGF-beta antibody, in treatment-resistant primary focal segmental glomerulosclerosis. *Kidney Int* 2011;**79**(11):749–56.
106. Voelker J, Berg PH, Sheetz M, et al. Anti-TGF-beta1 antibody therapy in patients with diabetic nephropathy. *J Am Soc Nephrol* 2017; **28**(3):953–62.
107. Chertow GM, Appel GB, Block GA, et al. Effects of bardoxolone methyl on body weight, waist circumference and glycemic control in obese patients with type 2 diabetes mellitus and stage 4 chronic kidney disease. *J Diabet Complicat* 2018;**32**(12):1113–7.
108. Chin MP, Bakris GL, Block GA, et al. Bardoxolone methyl improves kidney function in patients with chronic kidney disease stage 4 and type 2 diabetes: post-hoc analyses from bardoxolone methyl evaluation in patients with chronic kidney disease and type 2 diabetes study. *Am J Nephrol* 2018;**47**(1):40–7.
109. Zuo Y, Liu Y. New insights into the role and mechanism of Wnt/beta-catenin signalling in kidney fibrosis. *Nephrology* 2018; **23**(Suppl. 4):38–43.
110. Bushinsky DA, Hostetter T, Klaerner G, et al. Randomized, controlled trial of TRC101 to increase serum bicarbonate in patients with CKD. *Clin J Am Soc Nephrol* 2018;**13**(1):26–35.
111. Lorenzen JM, Haller H, Thum T. MicroRNAs as mediators and therapeutic targets in chronic kidney disease. *Nat Rev Nephrol* 2011;**7**(5):286–94.
112. Harvey SJ, Jarad G, Cunningham J, et al. Podocyte-specific deletion of dicer alters cytoskeletal dynamics and causes glomerular disease. *J Am Soc Nephrol* 2008;**19**(11):2150–8.
113. Shi S, Yu L, Chiu C, et al. Podocyte-selective deletion of dicer induces proteinuria and glomerulosclerosis. *J Am Soc Nephrol* 2008; **19**(11):2159–69.
114. Kawakami T, Ren S, Duffield JS. Wnt signalling in kidney diseases: dual roles in renal injury and repair. *J Pathol* 2013;**229**(2): 221–31.
115. Al-Chaqmaqchi HA, Moshfegh A, Dadfar E, et al. Activation of Wnt/beta-catenin pathway in monocytes derived from chronic kidney disease patients. *PLoS One* 2013;**8**(7):e68937.
116. Zhou L, Li Y, Zhou D, Tan RJ, Liu Y. Loss of Klotho contributes to kidney injury by derepression of Wnt/beta-catenin signaling. *J Am Soc Nephrol* 2013;**24**(5):771–85.

117. Tracz MJ, Alam J, Nath KA. Physiology and pathophysiology of heme: implications for kidney disease. *J Am Soc Nephrol* 2007; **18**(2):414–20.
118. Agarwal A, Nick HS. Renal response to tissue injury: lessons from heme oxygenase-1 g ene ablation and expression. *J Am Soc Nephrol* 2000;**11**(5):965–73.
119. Jarmi T, Agarwal A. Heme oxygenase and renal disease. *Curr Hypertens Rep* 2009;**11**(1):56–62.
120. Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN. Bilirubin is an antioxidant of possible physiological importance. *Science* 1987;**235**(4792):1043–6.
121. Balla G, Jacob HS, Balla J, et al. Ferritin: a cytoprotective antioxidant strategem of endothelium. *J Biol Chem* 1992;**267**(25): 18148–53.
122. Wang R. Resurgence of carbon monoxide: an endogenous gaseous vasorelaxing factor. *Can J Physiol Pharmacol* 1998;**76**(1):1–15.
123. Dulak J, Deshane J, Jozkowicz A, Agarwal A. Heme oxygenase-1 and carbon monoxide in vascular pathobiology: focus on angiogenesis. *Circulation* 2008;**117**(2):231–41.
124. Inguaggiato P, Gonzalez-Michaca L, Croatt AJ, Haggard JJ, Alam J, Nath KA. Cellular overexpression of heme oxygenase-1 up-regulates p21 and confers resistance to apoptosis. *Kidney Int* 2001;**60**(6):2181–91.
125. Fujita T, Toda K, Karimova A, et al. Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by derepression of fibrinolysis. *Nat Med* 2001;**7**(5):598–604.
126. Gong LM, Du JB, Shi L, Shi Y, Tang CS. Effects of endogenous carbon monoxide on collagen synthesis in pulmonary artery in rats under hypoxia. *Life Sci* 2004;**74**(10):1225–41.
127. Morse D. The role of heme oxygenase-1 in pulmonary fibrosis. *Am J Respir Cell Mol Biol* 2003;**29**(3 Suppl. l):S82–6.
128. Kapturczak MH, Wasserfall C, Brusko T, et al. Heme oxygenase-1 modulates early inflammatory responses: evidence from the heme oxygenase-1-deficient mouse. *Am J Pathol* 2004;**165**(3): 1045–53.
129. Poss KD, Tonegawa S. Heme oxygenase 1 is required for mammalian iron reutilization. *Proc Natl Acad Sci USA* 1997;**94**(20): 10919–24.
130. Yachie A, Niida Y, Wada T, et al. Oxidative stress causes enhanced endothelial cell injury in human heme oxygenase-1 deficiency. *J Clin Investig* 1999;**103**(1):129–35.
131. Radhakrishnan N, Yadav SP, Sachdeva A, et al. Human heme oxygenase-1 deficiency presenting with hemolysis, nephritis, and asplenia. *J Pediatr Hematol Oncol* 2011;**33**(1):74–8.
132. Ozaki KS, Marques GM, Nogueira E, et al. Improved renal function after kidney transplantation is associated with heme oxygenase-1 polymorphism. *Clin Transplant* 2008;**22**(5):609–16.
133. Exner M, Schillinger M, Minar E, et al. Heme oxygenase-1 gene promoter microsatellite polymorphism is associated with restenosis after percutaneous transluminal angioplasty. *J Endovasc Ther* 2001;**8**(5):433–40.
134. Lin CC, Yang WC, Lin SJ, et al. Length polymorphism in heme oxygenase-1 is associated with arteriovenous fistula patency in hemodialysis patients. *Kidney Int* 2006;**69**(1):165–72.
135. Chin HJ, Cho HJ, Lee TW, et al. The heme oxygenase-1 genotype is a risk factor to renal impairment of IgA nephropathy at diagnosis, which is a strong predictor of mortality. *J Korean Med Sci* 2009;**24**(Suppl. l):S30–7.
136. Scialla JJ, Anderson CA. Dietary acid load: a novel nutritional target in chronic kidney disease? *Adv Chron Kidney Dis* 2013; **20**(2):141–9.
137. Loniewski I, Wesson DE. Bicarbonate therapy for prevention of chronic kidney disease progression. *Kidney Int* 2014;**85**(3):529–35.
138. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol* 2009;**20**(9):2075–84.

CHAPTER

19

Pathophysiology of Diabetic Nephropathy

Charbel C. Khoury[a], *Sheldon Chen*[b], *Fuad N. Ziyadeh*[c]

[a]Washington University in St. Louis, St. Louis, MO, United States; [b]MD Anderson Cancer Center, Houston, TX, United States; [c]Faculty of Medicine, American University of Beirut, Beirut, Lebanon

Abstract

Diabetic nephropathy affects approximately 25–35% of patients with type 1 or type 2 diabetes mellitus. The disease progresses through various clinical stages, from hyperfiltration to microalbuminuria to macroalbuminuria to nephrotic proteinuria to progressive chronic kidney disease, which eventually leads to end-stage renal disease. These stages are generally associated with structural pathological changes affecting all compartments of the kidney: the glomerulus, the tubules, the vasculature, and the interstitium. With increased glycemia, various metabolites and by-products, including advanced glycation end-products and reactive oxygen species, are stimulated. These metabolic insults converge with the main driver of the hemodynamic insult, angiotensin II, to induce diabetic renal pathology at its different levels. Advances in genetics and molecular biology will continue to reveal more about the pathogenesis of diabetic nephropathy, but the multifactorial nature of the disease has defied attempts at a general theory that unifies all the known cellular and biochemical pathways.

INTRODUCTION

As most of the world faces an epidemic of obesity and diabetes (also termed diabesity), the prevalence of diabetic kidney disease (DKD) has been on the rise. DKD is the major cause of end-stage renal disease (ESRD) in the industrialized world and many developing countries and is a significant cause of serious morbidity and increasing mortality. While still considered a microvascular complication of diabetes, nephropathy involves more than just kidney capillaries, extending its damage across the various kidney cells and associated extracellular structures. This chapter will provide a comprehensive review of our current understanding of the pathophysiology of DKD.

PATHOLOGY

DKD is associated with a series of histopathological changes involving all compartments of the kidney, reflecting changes in organ function, and associated with clinical manifestations of the disease (Figure 19.1).

Glomerular basement membrane (GBM) thickening is one of the earliest quantifiable changes in DKD. The thickening results from the build-up of extracellular matrix (ECM) components such as type IV collagen, laminins, and nidogen/entactin in the lamina rara interna of the GBM. Further deposition of matrix components in the other layers of the GBM occurs with progression of the disease, resulting in a near doubling of its normal size.[1] Concurrently, there is a change in the nature of the GBM, with a switch from the classical (ubiquitous) α1(IV) and α2(IV) collagen chains to the restricted α3(IV) and α4(IV) collagen chains.[2] This transition likely affects the compositional quality of the GBM and could explain, at least in part, the correlation of GBM thickness with its functional properties such as macromolecular "leakiness" or the magnitude of proteinuria.[3]

The GBM forms part of the glomerular filtration barrier and is maintained by the glomerular endothelial cells and podocytes, both of which are compromised in the diabetic glomerulus. The podocytes undergo cytoskeletal rearrangement, dedifferentiation, and autophagy manifested by effacement of their foot processes, and decrease in slit diaphragm length with downregulation of its core components, such as nephrin.[4] Importantly, reduction in podocyte density secondary to detachment and dropout of the cells or apoptosis might be a useful predictor of DKD and its progression.[5,6] On the other side of the GBM, the glomerular endothelium is a highly specialized, fenestrated layer

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00019-X

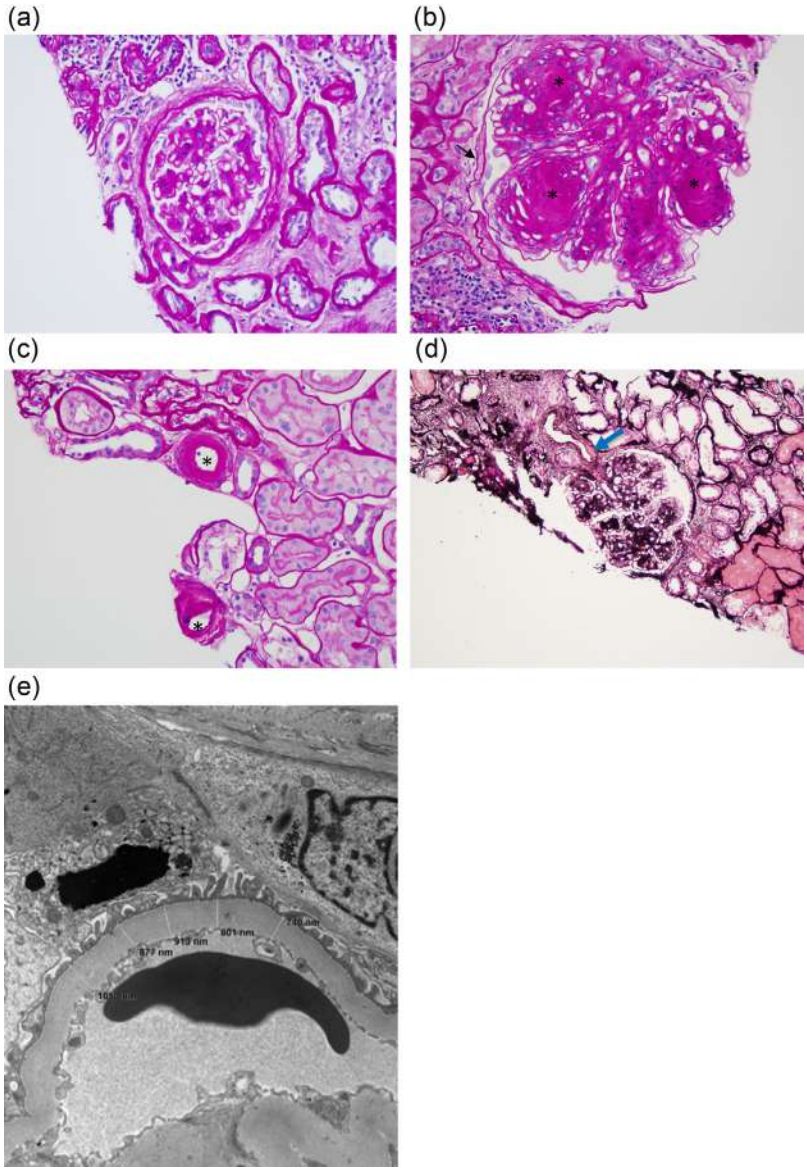


FIGURE 19.1 **Histopathological changes in diabetic nephropathy.** (a) Mesangial expansion and prominent glomerular capillary walls and tubular basement membranes [PAS Stain]; (b) Nodular mesangial expansion, i.e. Kimmelstiel-Wilson nodules with a lamellated appearance likely secondary to repeated injury with mesangiolysis and matrix deposition (asterisk *); there is a capsular drop on Bowman's capsule (arrow) [PAS Stain]; (c) arterioles with PAS-positive hyalinosis (asterisk *) [PAS Stain]; (d) The glomerulus shows mesangial matrix increase and basement membrane thickening; there is arteriolar hyalinization of the afferent or efferent arterioles (arrow), and surrounding interstitial fibrosis and tubular atrophy [Jones Silver stain]; (e) Prominent, uniform thickening of the glomerular basement membranes, with segmental foot process effacement indicative of podocyte injury [electron microscopy]. *Micrographs courtesy of Joseph P. Gaut, MD, PhD Department of Pathology, Washington University School of Medicine, St. Louis.*

that sustains significant damage to its negatively charged glycocalyx.[7]

Another hallmark lesion of DKD is expansion of the mesangium. This is mostly due to increased deposition of extracellular mesangial matrix components, and only minimally to mesangial cell hypertrophy or proliferation. There is indeed only a very modest and self-limited increase in cell number per glomerulus, both early on and as DKD progresses.[8,9] In general, mesangial expansion is diffusely uniform within the glomerulus. As collagen deposition progresses with advanced DKD, diffuse diabetic glomerulosclerosis ensues, and eventually leads to scarring of the glomeruli. However, nodular glomerulosclerosis or the so-called Kimmelstiel–Wilson lesions may also be present. These develop due to continued local expansion of the mesangial matrix, or more likely as a result of mesangiolysis, with separation of the glomerular capillary from the

TABLE 19.1 Glomerular Classification of Diabetic Kidney Disease (DKD)

Class	Description	Inclusion Criteria
I	Mild or nonspecific LM changes and EM-proven glomerular basement membrane (GBM) thickening	Biopsy does not meet any of the criteria mentioned below for class II, III, or IV GBM >395 nm in female and >430 nm in male individuals 9 years of age and older (a)
IIa	Mild mesangial expansion	Biopsy does not meet criteria for class III or IV Mild mesangial expansion in >25% of the observed mesangium
IIb	Severe mesangial expansion	Biopsy does not meet criteria for class III or IV Severe mesangial expansion in >25% of the observed mesangium
III	Nodular sclerosis (Kimmelstiel–Wilson lesion)	Biopsy does not meet criteria for class IV At least one convincing Kimmelstiel–Wilson lesion
IV	Advanced diabetic glomerulosclerosis	Global glomerular sclerosis in >50% of glomeruli Lesions from classes I through III

LM, light microscopy. (a) The basis of direct measurement of GBM width by EM, these individual cutoff levels may be considered indicative when other GBM measurements are used.
From Tervaert et al.[14]

mesangium, and the formation of capillary aneurysms. The new capillary space is subsequently filled with mesangial matrix.[10] Kimmelstiel–Wilson lesions are usually focal, segmental, and only occasionally diffuse. Overall, they can be present in up to 50% of diabetics.

The effect on the renal vasculature is notable for the accumulation of periodic acid–Schiff (PAS)-positive material around both the afferent and efferent arterioles, referred to as arteriolar hyalinosis. Deposition of similar material in the subendothelial space of the glomerular capillaries is referred to as a hyaline cap. These, together with capsular drops (hyaline material underneath the parietal epithelial cells of Bowman's capsule), constitute the exudative lesions of DKD.

Tubular basement membrane thickening develops in parallel with that of the GBM. The width of either of the membranes correlates strongly with the degree of hyperglycemia in type 1 diabetes.[6] A mild degree of interstitial inflammation with some macrophage recruitment can also be seen. Progressive interstitial fibrosis and tubular atrophy reflect advanced DKD and the progression toward ESRD. The degree of tubulointerstitial fibrosis correlates strongly with the progressive decline in glomerular filtration rate (GFR).[11–13]

A classification of the pathology of DKD was introduced by the Renal Pathology Society.[14] This may help with staging the nephropathy, based on the degree of glomerular pathology, with a separate scoring system for tubular and vascular lesions (Table 19.1). However, the classic description of DKD is mostly based on the glomerular pathology of kidneys in type 1 diabetes. While patients with type 2 diabetes and DKD (T2DKD) have been found to have the same pathognomonic glomerular changes,[15] the overall pathological picture within the glomerulus and in the different renal compartments in these patients is more heterogeneous. In T2DKD patients with microalbuminuria, less than a third have the typical glomerular lesions expected in a similar stage of T1DKD.[16,17] This may suggest a different pathogenesis for the kidney disease in patients with T1D compared with T2D. More likely though, it is due to variability in the duration of DKD and the presence of comorbidities such as hypertension, obesity, and aging that have independent effects on the kidney.

CLINICAL COURSE

DKD was classically described by Mogensen and others to progress through distinct clinical stages (Figure 19.2), defined on the basis of the values of the GFR, urinary albumin excretion (UAE), and systemic arterial blood pressure.[18] In T1DKD, these clinical stages correlate, in general, with the severity of renal pathology as described above. However, as with the kidney pathology, DKD in type 2 diabetes is a more heterogeneous disease, with variable degrees of glomerulosclerosis, tubulointerstitial fibrosis, and vasculopathy.[19]

Normoalbuminuria

The initial stage of DKD is a clinically silent period during which the patient remains normoalbuminuric with a normal or high GFR. A relatively large increase in GFR (greater than 150 mL/min/1.73 m^2) occurs in about one-third of T1DM and seems to be positively

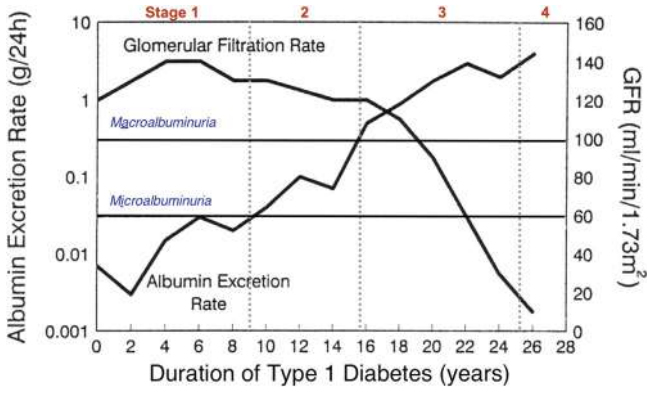


FIGURE 19.2 Progression of albumin:excretion ratio and glomerular filtration rate with time in patients with type 1 diabetes. *Adapted from Molitch ME.* Am J Med ***1997***;*102*:392–8.

associated with glycemic control.[20,21] This hyperfiltration is less common or much more attenuated in T2DM patients.[22]

While still somewhat controversial,[21] hyperfiltration has been shown to predict or be causally linked to the progression of DKD. In a meta-analysis of cohort studies in T1DM, the pooled odds for development of at least microalbuminuria was 2.71 (95% CI 1.20–6.11) in patients with hyperfiltration compared with those with normofiltration.[23] Similar findings were noted by the GFR Study investigators.[24] In their longitudinal study of T2DM patients, the hazard ratio for progression to a minimum of microalbuminuria was 2.16 [95% CI 1.13–4.14]. It was noted that 23.4% (11 of 47) of patients with persistent hyperfiltration progressed to micro- or macroalbuminuria compared with 10.6% (53 of 502) of patients who had hyperfiltration ameliorated at 6 months or who did not develop hyperfiltration since study inclusion.

Microalbuminuria

Microalbuminuria, defined as a UAE of 30–300 mg/day or 20–200 μg/min, can develop beyond the first five years of disease in 20–40% of type 1 diabetic patients. Microalbuminuria can be present at the time of diagnosis in 20–40% of type 2 diabetic patients. Hyperglycemia, hypertension, and elevated body mass index are all independent risk factors for the development of microalbuminuria in type 1 and type 2 diabetic patients.[25] Structurally, the glomerular and tubular basement membranes continue to thicken, and there is some degree of podocyte loss. Mesangial matrix expansion and diffuse glomerulosclerosis may become manifest.

Earlier longitudinal studies suggested that approximately 80% of type 1 diabetic patients progress from microalbuminuria to proteinuria over a period of 6–14 years.[26] More recently, this has been evaluated to be closer to 40%.[27] These findings could be the result of improved control of glycemia and hypertension over the years, and the widespread use of renin–angiotensin system blockers in microalbuminuric patients. They also suggest that microalbuminuria is not a predictor of macroalbuminuria in all diabetic patients.[28] On the other hand, UAE has been repeatedly and strongly validated as a risk factor for cardiovascular disease, peripheral vascular disease, strokes, and mortality from coronary heart disease.[29–32]

This stage is also characterized by the onset of hypertension within 1 or 2 years of microalbuminuria in T1DM. GFR remains normal or is slightly elevated in type 1 diabetic patients with microalbuminuria for at least 5 years if clinical overt nephropathy does not develop.[33] In microalbuminuric type 2 patients, GFR begins to normalize and then decline at rates approximating 3–4 mL/min/yr.[34]

Overt Nephropathy

As the glomeruli start demonstrating diffuse and/or nodular glomerulosclerosis, and as more podocyte loss occurs, overt proteinuria (total urinary protein excretion exceeding 500 mg/day) or macroalbuminuria (UAE exceeding 300 mg/day) becomes established (Figure 19.2). In type 1 patients, this occurs after an average of 15 years of diabetes. Proteinuria by itself is an independent risk factor for further worsening of renal damage.[35] Concurrently, progressive mesangial expansion leads to a reduction in the glomerular surface area available for filtration and has been shown to inversely correlate with declining GFR[36]. Hypertension is almost always present at this stage. The poorer the blood pressure control is, the more rapidly the GFR declines.

Untreated patients may progress to nephrotic-range proteinuria. The GFR drops at a mean rate of 1 mL/min/month (Stage IV) until ESRD ensues, which will require renal replacement therapy (Stage V). Note, however, that this time course is extremely variable among individual patients. The average time from the initial diagnosis of type 1 diabetes to the progression to ESRD is around 20–25 years, with a more rapid course developing in patients with uncontrolled hypertension and/or heavy proteinuria.

Nonetheless, growing evidence suggests that not all patients with diabetes progress through the timeline of stages in a linear manner. Many have been shown to regress from micro- to normoalbuminuria. In a study that followed 386 type 1 diabetic patients for a total of 6 years, Perkins et al. showed that close to 60% of the patients had a significant drop in their UAE.[28] A similar trend was confirmed in type 2 diabetic patients.[37] While the more frequent use of renin–angiotensin–aldosterone system (RAAS) inhibitors may contribute to this trend, some studies have failed to confirm this correlation.[38] Furthermore, it appears that the worsening of GFR may occur during the microalbuminuric stage or even before the development of albuminuria.[39] Data come from cross-sectional studies such as the Developing Education on MicroAlbuminuria for Awareness of renal and cardiovascular risk iN Diabetes study. In this global perspective on DKD, of the 11,315 subjects who were reported to have decreased kidney function, 30.7% had microalbuminuria and a sizable 20.5% were normoalbuminuric.[40] Similar findings have been reported in other prospective studies in type 1 and type 2 diabetes.[41,42] There are several proposed explanations for the disassociation of the grade of albuminuria from the declining GFR. In some patients, RAAS inhibitors may be curbing albuminuria but not halting the loss of GFR. It is possible that there are two parallel but largely independent mechanistic pathways that are responsible for albuminuria progression and GFR loss.

Alternatively, kidney function may preferentially decline secondary to aging or other nondiabetic renal insults not identified in these studies.

METABOLIC DYSREGULATION OF DIABETIC NEPHROPATHY

Hyperglycemia acts as the main driver for the development and progression of DKD. Glycemic control slows the progression of nephropathy and, at times, may reverse the original pathology.[43–47] Under normal conditions, intracellular glucose is metabolized by oxidative phosphorylation. When glucose accumulates to excess, there is increased flux through glycolysis, and possibly through the TCA cycle, with less efficient oxidative phosphorylation.

Indeed, diabetic kidneys upregulate key steps in the control of cellular glycolytic rate. The enhanced expression of glucose transporters GLUT1 and 4 in the glomeruli and the glycolytic enzymes hexokinase and phosphofructokinase are likely sufficient to promote flux into aerobic glycolysis, in a manner reminiscent of the Warburg effect.[48–50] Multiomics approaches to diabetes and diabetic kidney have confirmed the changes in glucose metabolism that are characteristic of the diseased state.[51,52] This altered metabolism has been associated with mitochondrial dysfunction, including increased mitochondrial fission and fragmentation and reduced levels of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) levels in the tubules, abnormalities in electron transport chain complex assembly/activity, and increased expression of uncoupling protein UCP1.[52–54] The mechanisms underlying mitochondrial dysfunction are not fully understood, and it is unclear whether the altered glucose metabolism is the cause or result of diseased mitochondria in diabetic kidneys, or if a bidirectional causality exists.

The alteration in glucose metabolism is associated with increased flux into alternative pathways: the pentose phosphate pathway, sorbitol/polyol pathway, advanced glycation end-products (AGEs) pathway, protein kinase C (PKC) pathway, and hexosamine pathway. In the kidney, these metabolic pathways had long been thought to contribute to glucotoxicity through various mechanisms. Polyol pathway activation was hypothesized to render the kidney susceptible to oxidative stress by consuming NADPH, which is an essential cofactor for production of reduced glutathione.[55] The hexosamine pathway can lead to posttranslational modifications that affect the function of transcription factors and signaling molecules.[56] Activation of the hexosamine pathway in diabetes stimulates the activity of the transcription factor Sp1, that then leads to induction of key prosclerotic factors including transforming growth factor-beta 1 (TGF-β1) and plasminogen activator inhibitor-1.[57]

Alternatively, research from the Joslin Medalist Study suggests that increased glycolytic flux and sorbitol/polyol pathway protected patients with greater than 50 years of T1DM from diabetic nephropathy by reducing the accumulation of glucose toxic metabolites and improving mitochondrial function.[58,59] Further studies will be needed to understand the differences in the regulatory function of glucose metabolism in glomerular and tubular cells and throughout the progression of diabetes.

Evidence is emerging that lipid metabolism may play a role in the progression of DKD. Kimmelstiel and Wilson noted significant intratubular lipid accumulation in their seminal work on diabetic pathology.[60] Defective lipid metabolism likely contributes to lipid accumulation and may be associated with impaired mitochondrial function, and the development of tubulointerstitial fibrosis.[61] Lipotoxicity can also manifest in the podocyte with intracellular accumulation of lipid droplets, abnormal glucose metabolism, inflammation, oxidative stress, endoplasmic reticulum stress, and actin cytoskeleton rearrangements.[62]

Advanced Glycation Reactions

AGEs are proteins, lipids, or nucleic acids that are irreversibly cross-linked with reducing sugars. While AGEs are produced in small amounts with aging, their production is markedly increased in the setting of hyperglycemia both in cellular and extracellular compartments, especially in richly vascularized organs such as the kidney.[63]

The evidence for the role of AGEs in DKD comes from multiple levels. First, various AGEs accumulate in both glomerular and tubular cells in experimental and human DKD.[64,65] Moreover, as renal function declines, higher concentrations of these products are retained in the plasma.[66] Second, the infusion of AGEs into normal rodents leads to increased glomerular volume, accumulation of PAS-positive deposits, basement membrane widening, mesangial matrix expansion, and glomerulosclerosis.[67] Third, the inhibition of AGEs in experimental animal models of diabetes ameliorates albuminuria and glomerulosclerosis.[68]

The modus operandi of AGEs in DKD involves, on the one hand, an alteration in the function of the glycated proteins. For example, ECM proteins may become less susceptible to enzymatic hydrolysis by matrix metalloproteinases (MMPs), facilitating their accumulation in the extracellular space.[69] Furthermore, glycation of sulfated proteoglycans modifies the charge-selective properties of the basement membrane and contributes to the development of microalbuminuria.[70] On the other hand, AGEs act as signaling molecules either by directly acting intracellularly or by interacting with their receptor RAGE that is expressed on the surfaces of podocytes

and tubular epithelia. AGEs induce intracellular oxidant stress and activate NF-κB by redox-sensitive signaling pathways.[71] AGEs also activate PKC and regulate the expression of diverse growth factors and cytokines such as angiotensin II (Ang II) and TGF-β1.[72]

Protein Kinase C Signaling

The activation of the PKC signaling pathway is a direct product of glucotoxicity in DKD. In fact, the channeling of glycolytic metabolites to react with glycerol phosphate leads to the *de novo* formation of diacylglycerol (DAG), the major endogenous activator of PKC.[73] Further activation of PKC occurs secondary to activation of the polyol metabolites, AGE accumulation, RAGE activation, reactive oxygen species (ROS) production, and Ang II stimulation.[74] On the other hand, altered lipid metabolism and particularly the imbalance between lipid delivery and intracellular oxidation of fatty acids could lead to accumulation of DAG.[75]

It appears that the PKC isoforms may cooperate in the pathogenesis of DKD. While PKC-beta can lead to renal hypertrophy and glomerulosclerosis, PKC-alpha appears to contribute primarily to diabetic albuminuria by acting through vascular endothelial growth factor (VEGF) and by affecting nephrin expression.[76] Animal experiments with double knockouts of PKC-alpha and PKC-beta, or the administration of an inhibitor of both PKC isoforms, confirmed this hypothesis.[76] However, a randomized, double-blind, placebo-controlled pilot study found that type 2 diabetic patients receiving renin–angiotensin system inhibitors failed to respond to the addition of a PKC-beta inhibitor, ruboxistaurin, and did not have a significant reduction in their albumin:creatinine ratios.[77]

Oxidative Stress

Oxidative stress has long been considered a central pathogenic mechanism in diabetes that synthesizes and amplifies the metabolic dysregulations of hyperglycemia.[56] Diabetes is accompanied by the increased generation of superoxide, hydroxyl radicals, hydrogen peroxide, and peroxynitrite, all commonly referred to as ROS. The ROS along with associated oxidized proteins, lipids, nucleic acids, and carbohydrates contributes to glomerular hypertrophy, causes injury to the podocyte, and promotes fibrogenesis in the glomeruli and tubules.[78,79]

The notable sources of ROS production in the diabetic kidney are the mitochondria, the cytosolic NADPH oxidase (NOX), nitric oxide (NO) synthases, xanthine oxidase, and lipoxygenase.[75,80] The prevailing hypothesis in diabetic microvascular complications was that glucose metabolism increased mitochondrial electron transport chain activity, a high proton gradient, and a high electrochemical potential difference that enhance the generation of mitochondrial superoxide.[56] However, more recent evidence from metabolomic studies suggest decreased efficiency of the electron transport chain. Moreover, measuring mitochondrial superoxide is difficult and has yielded inconsistent conclusions, with some groups finding a decrease in mitochondrial ROS.[54,75,80,81] Some level of mitochondrial superoxide may in fact be beneficial and may retard organ dysfunction.[80,81]

While more sensitive spatiotemporal ROS measurements are being pursued to elucidate the role of mitochondrial ROS in DKD, NOX4 has been consistently shown to be upregulated in animal models of DKD.[68] Various mediators of the diabetic milieu are now known to alter the activity or expression of the Nox proteins, including hyperglycemia, Ang II, TGF-β, AGEs, VEGF, endothelin, and aldosterone.[78] NOX4-mediated stimulation of PKC-alpha may contribute to many of the NOX4-dependent effects in DKD.[82] In addition, NOX4 has been shown to drive the accumulation of fumarate by inhibiting fumarate hydratase.[83] Fumarate, a TCA cycle metabolite with oncogenic properties, has been linked to stimulation of hypoxia-inducible factor 1-alpha, TGF-β, and other matrix genes promoting fibrosis.[83]

GLOMERULAR HEMODYNAMICS

One of the earliest pathophysiologic features of DKD is hyperfiltration. It is particularly pronounced in newly diagnosed T1D patients and during periods of poor glycemic control. There are four factors that determine the GFR: (a) the glomerular plasma flow, (b) the systemic oncotic pressure, (c) glomerular transcapillary hydraulic pressure difference, and (d) the glomerular ultrafiltration (permeability) coefficient, K_f. Several mechanisms have been proposed to explain glomerular hyperfiltration. First, as diabetic glomeruli become hypertrophied, filtration surface area increases, leading to increased ultrafiltration coefficient.[84] Second, and more importantly, abnormal vascular control in diabetic nephropathy leads to differential reduction in afferent glomerular arteriolar resistance and a net increase in efferent arteriolar resistance. This results in increased renal blood flow and glomerular capillary hypertension, all resulting in an elevated single nephron GFR.[85] This intraglomerular hemodynamic stress occurs in response to an imbalance of a variety of vasoactive substances and growth factors including the RAAS, atrial natriuretic peptide, insulin-like growth factor-1, endothelin, prostanoids, eicosanoids, and the NO system secondary to endothelial dysfunction.[86,87] The rise in glomerular capillary

pressure accelerates renovascular complications of DKD. Induced by the diabetic milieu, this hemodynamic stress promotes the production of various mediators of DKD.[88] Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers lower glomerular pressure and limit hyperfiltration by blocking the effect of Ang II on the efferent arteriole.[89–92]

Some studies have suggested that glomerular hyperfiltration is a result of increased proximal tubular reabsorption of glucose and sodium (Na).[93] Hyperglycemia, tubular growth, and increased SGLT2 expression in the proximal tubule increase Na/glucose reabsorption *via* SGLT2 and SGLT1, as well as increase Na reabsorption *via* NHE3.[94] This causes decreased sodium delivery to the macula densa, suppresses tubuloglomerular feedback, and results in facilitated dilation of the afferent arteriole. Indeed, glomerular hyperfiltration is blunted in diabetic mice deficient in the adenosine receptor A1, which lack the tubuloglomerular feedback mechanism.[95] However, there have been conflicting results using this mouse model.[96] In addition, the decreased distal delivery lowers the tubular back pressure in Bowman's space, which increases the effective glomerular filtration pressure and may explain a significant portion of diabetic hyperfiltration.[97,98]

More importantly, the tubule-centric hypothesis of diabetic hyperfiltration has been proposed as one mechanism for the renoprotective effects of the Na-glucose cotransporter SGLT2 inhibitors. Indeed gene-targeted SGLT2 knockout and pharmacologic inhibition of SGLT2 prevent glomerular hyperfiltration in animal models of diabetes.[99] Treatment of T1D and T2D patients with the sodium glucose cotransporter 2 inhibitor empagliflozin has been shown to attenuate renal hyperfiltration, as reflected by eGFR.[100,101] This effect appears to be independent of lowering blood glucose.[102,103]

Overall, clinical trials are building evidence that SGLT2 inhibitors can lower the risk of kidney failure in patients with diabetes. The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial emphasized the preliminary findings from previous cardiovascular outcome trials.[104–107] This randomized, double-blind, placebo-controlled, multicenter clinical trial was designed to assess the effects of the SGLT2 inhibitor canagliflozin on renal outcomes in patients with T2DM and albuminuric CKD.[104] The result was a 30% relative risk reduction of the composite primary outcome of ESRD, doubling of the serum creatinine level, or death from renal or cardiovascular causes.[104] Moreover, Canagliflozin decreased the average urinary albumin:creatinine ratio by 31% (95% CI, 26–35), and reduced the rate of eGFR loss by 1.52 mL/min/1.73 m^2/yr (95% CI, 1.11–1.93).[104] This effect appears to be additive to ACEIs and ARBs. Further studies are being conducted to determine whether the renoprotection is consistent across the class of SGLT2 inhibitors, and to better understand the side effect profile of these medications.

CELLULAR AND MOLECULAR MECHANISMS OF GLOMERULOPATHY

Glomerular hyperfiltration and hypertension exert a biomechanical stress on the endothelial cells, the mesangial cells, and the podocytes. Laminar shear stress that occurs in the setting of glomerular hyperfiltration likely further promotes endothelial nitric oxide synthase dysfunction initiated by hyperglycemia and metabolic dysregulation.[108] In parallel, the mesangial cells respond to increased mechanical stretch by upregulating GLUT1, thus indirectly promoting the metabolic derangements of DKD.[109] Stretched mesangial cells have also been shown to promote fibrosis either by directly expressing ECM proteins or by activating TGF-β1.[110]

The podocytes rely on complex interactions between their intricate actin-based cytoskeleton, cell–cell, and cell–matrix contact proteins to maintain the glomerular filtration barrier in the face of mechanical challenges resulting from pulsatile blood flow and filtration of this blood flow.[111,112] In the setting of diabetes, glomerular hypertrophy, thickening and stiffening of the GBM, and glomerular hyperfiltration and hypertension result in shear and tensile stress on the podocyte that challenge the cell's attachment to the GBM.[111] Meanwhile, the hyperglycemic milieu further compromises the cytoskeletal architecture of the podocytes. Podocytes downregulate the expression of nephrin under the effect of glucotoxicity, Ang II, TGF-β, VEGF, and other signaling pathways.[4] Nephrin is not only a key slit diaphragm protein but is also important in podocyte cytoskeletal function and insulin signaling, as well as in maintaining overall podocyte health.[4] Moreover, hyperglycemia, AGEs, ROS, and others result in dysregulation of the Rho family GTPases.[4] This family of enzymes is a key regulator of actin cytoskeleton remodeling. Lastly, studies have shown that podocyte integrin expression is decreased in diabetes, compromising cell–matrix interactions.[4] All these stressors together result in effacement of the foot processes, detachment, and loss of a number of podocytes in the urinary space. Another fate of the podocytes in diabetes is apoptosis under the effect of hyperglycemia, ROS, and on activation of the TGF-β pathway.[113] For the remaining podocytes to cover the newly denuded GBM, they have to adapt by hypertrophy with activation of mammalian target of rapamycin.[114] However, once podocyte loss reaches 20%, the remaining cells die and glomerulosclerosis develops.[115]

Overall, the metabolic and hemodynamic dysregulation in the diabetic kidney interact to activate second

messenger signaling pathways, transcription factors, and cytokines, including the RAAS, TGF-β, VEGF, and others, all of which can lead to the development of albuminuria and glomerulosclerosis characteristic of diabetic nephropathy.

The RAAS is one of the most important pathways in DKD pathophysiology. Intriguingly, intrinsic renal cells such as mesangial cells and podocytes and even tubular cells synthesize Ang II and express receptors for this humoral mediator, which may contribute to the regional activation of RAAS.[109,116] In the setting of diabetes, various factors stimulate the RAAS. Hyperglycemia by itself has been shown to directly upregulate the expression of renin and angiotensinogen in mesangial cells.[81] Further stimulation occurs secondary to the ROS and AGEs.[117,118] As Ang II builds up in the kidney, it exerts its effects not only by sustaining the hemodynamic changes of DKD but also by independently activating a multitude of cytokines such as TGF-β, connecting tissue growth factor, interleukin-6, monocyte chemoattractant protein-1 (MCP-1), and VEGF-A. Accordingly, high levels of Ang II can contribute to the early hyperplasia and hypertrophy of the renal cells observed in diabetes and modulate glomerular ECM deposition in the later stages of diabetes.[119]

VEGF has been proposed to be one of the cornerstones of the all-important crosstalk between glomerular endothelium and podocytes. In healthy glomeruli, VEGF-A is mainly produced by podocytes and binds to vascular endothelial growth factor receptor 2 (VEGFR2) located on the endothelium, maintaining the cell's structure and function.[120] Targeted genetic deletion of all VEGF-A isoforms from podocytes causes glomerular disease in healthy animals.[121] In diabetes, there were conflicting findings initially. Some studies reported increased VEGF-A activity in diabetic glomeruli, with improvement of DKD on inhibition of VEGF-A or VEGFR2.[122–125] Other research showed that total glomerular VEGF-A levels decrease as diabetic nephropathy progresses, and that targeted genetic deletion of all VEGF-A isoforms from podocytes accelerated nephropathy in diabetic animals.[123] In fact, VEGF balance is tightly controlled in the glomeruli, and too much or too little is likely to be pathogenic.[126] Moreover, other crosstalk signals such as NO and angiopoietins can also feed into this paracrine signaling and tip the balance toward pathogenesis. More recent evidence has also shown that the isoforms of VEGF-A may have different roles in health and disease. VEGF-A_{165a} is a potent vasoactive agent, increasing vasodilation, vascular permeability, and angiogenesis.[127] Meanwhile, VEGF-A_{165b} is a protective factor in diabetic nephropathy.[128] The $VEGF_{165b}$ isoform was higher in the kidneys of patients that were protected from advanced nephropathy.[128] In diabetic mice, podocyte-specific $VEGF_{165b}$ overexpression or $VEGF_{165b}$ administration reduced albuminuria, likely by maintaining the glycocalyx and preventing endothelial and podocyte cell death.[128]

Other components of podocyte and endothelial cell crosstalk may serve as potential treatment targets in DKD. New insights have revealed that endothelin-1 (ET-1), an endothelial-derived vasoconstrictor, can signal to the podocyte and then back to the endothelial cell.[129] Atrasentan, an ET-1 receptor antagonist, has been shown to ameliorate early microalbuminuric DKD.[130]

TGF-β has been shown to play an essential role in the pathogenesis of DKD and appears to be a common pathway that leads to the early hypertrophic and later prosclerotic changes in all stages of DKD.[131,132] TGF-β is activated by a multitude of mediators that are generated secondary to the metabolic and hemodynamic forces in DKD. These include high glucose concentration[133]; AGE-modified proteins[134]; ROS[56]; cyclical stretch/relaxation of mesangial cells in culture[135]; PKC activation[136]; and Ang II.[137] All these factors depend on TGF-β to stimulate the synthesis of ECM proteins and prevent their degradation, leading to their deposition and accumulation. Experimental evidence has shown that this cytokine increases the expression of type I collagen, type IV collagen, fibronectin, and laminin. Furthermore, TGF-β inhibits MMPs and can also stimulate the inhibitors of proteases.[138] Blocking the renal TGF-β system in diabetic animals has ameliorated DKD, providing proof of the cytokine's central role. Whether TGF-β is inhibited upstream of its receptor or downstream in the intracellular signaling cascade, numerous studies have demonstrated marked improvement in glomerulosclerosis, ECM deposition, GBM thickening, and other histological and molecular parameters of diabetic renal disease.[86,125,139,140]

TUBULOPATHY IN DIABETES

While glomerulopathy is of great importance in the pathophysiology of DKD, it may not be the sole determinant of renal prognosis. There is growing clinical and pathological data suggesting that tubular damage plays a critical role in the pathogenesis of DKD.[141] For instance, elevated baseline plasma biomarkers of tubular injury such as KIM-1 have been significantly associated with the risk of early decline of kidney function, independent of albuminuria.[142] Moreover, in DKD, significant numbers of glomeruli are attached to dilated and atrophic tubules and may even be atubular.[143,144] Such tubular dysfunction and tubulointerstitial fibrosis are known to correlate significantly with GFR and the progression of kidney disease.

Various mechanisms come into play in diabetic tubulopathy.[145] First, diabetes promotes a hypoxic environment for the proximal tubule. Indeed, the increase in SGLT2 and NHE3 reabsorptive capacity in diabetes results in a commensurate demand for ATP to maintain the Na^+/K^+ ATPase activity.[145] Moreover, proximal tubular epithelial cells are unique in their ability to undertake gluconeogenesis, an energy-requiring process that is increased in the setting of diabetes.[145] However, because of the metabolic dysfunction of hyperglycemia and the mitochondrial injury, the proximal tubular cells consume more O_2 for each molecule of ATP generated. This increased demand and inefficient utilization of O_2 is met with reduced blood supply due to concomitant endothelial injury, intrinsic capillary loss within the tubulointerstitium, and as a consequence of glomerular capillary occlusion.[145]

As a result of hypoxia, proximal tubular epithelial cells not only undergo apoptosis but also promote tubulointerstitial fibrosis *via* TGF-β and other mechanisms.[145] The expansion of the ECM results in further hypoxia and microvascular rarefaction, starting the spiral of fibrosis and CKD.

In addition to hypoxia, several other pathomechanisms target the proximal tubule in DKD. These include the RAAS and the toxic effects of albuminuria and albumin-bound fatty acids among others.[145,146]

The role of the tubules in DKD is likely to be further studied in light of the recently demonstrated protective effects of the SGLT2 inhibitors. Moreover, recent animal studies have shown that selective proximal tubular injury can lead to podocytopathy and extensive glomerular injury reminiscent of diabetes.[147] Indeed, there is evidence of retrograde crosstalk between the proximal tubules and the podocytes. Tubular epithelial cells can protect against albuminuria in diabetes by maintaining nicotinamide mononucleotide concentrations around glomeruli and influencing podocyte function.[148]

INFLAMMATION

Hypoxia and inflammation frequently coexist in injured tissues and have been shown to modulate each other. Furthermore, in diabetes, metabolic and hemodynamic abnormalities, including hyperglycemia, AGEs, ROS, Ang II, and TGF-β, precipitate a proinflammatory state.[149]

Multiple components of the immune system are involved in the pathophysiology of DKD.[150] First, from an innate immunity standpoint, the kidney is home to mononuclear phagocytic cells that are activated in diabetes and are joined by renal cells in the release of proinflammatory cytokines and paracrine signals.[151] Consequently, additional monocytes and macrophages are recruited into the kidney, and there is further amplification of cytokine and chemokine release from the kidney.[152,153] Another type of innate immune cell that infiltrates the tubulointerstitium in DKD is the mast cell. Its degranulation releases inflammatory mediators such as TGF-β and proteolytic enzymes, the most notable of which is chymase.[150] Mast cell chymase is 40 times more potent than ACE at converting Ang I into Ang II.[154,155]

Essential to proper function of the innate immune system are pattern recognition receptors (PRRs), including Toll-like receptors and nucleotide-binding oligomerization domain-like receptors. PRRs are upregulated in mononuclear phagocytic cells, as well as in endothelial cells and podocytes.[150] They recognize pathogen-associated molecular patterns and endogenous stress signals or damage-associated molecular patterns that indicate cellular stress and injury, including uric acid, extracellular ATP, and glucose and ROS. On sensitization of PRRs, there is activation of the inflammasome and, among other effects, release of inflammatory cytokines.

Numerous cytokines have been implicated in the pathogenesis of DKD. For instance, IL-1, IL-6, and IL-18 correlate with morphological changes of DKD, such as GBM thickening, and are associated with increasing albuminuria and more rapid loss of GFR.[150] Early in diabetes, both glomerular and tubular cells increase expression of TNF-α.[156] This cytokine has been demonstrated to be cytotoxic to glomerular mesangial and epithelial cells, to increase vascular endothelial permeability, induce oxidative stress, and affect glomerular hemodynamics and GFR.[157,158] Its receptors, TNFR1 and TNFR2, are candidate biomarkers of DKD. Serum level of TNFR1 was a predictor of ESRD, even after adjustment for clinical covariates in a cohort of T1D.[159]

Chemokines mediate the migration of monocytes and macrophages into kidney tissue and are also upregulated in DKD. Of particular interest is the CC-chemokine ligand 2 (CCL2; also known as MCP-1). Its expression is upregulated in response to metabolic and hemodynamic features of the diabetic milieu, including Ang II.[160] Because its receptor CCR2 is also expressed on podocytes, the effects extend beyond the recruitment of macrophages to the tubulointerstitium.[161] Several studies have implicated CCR2 in effacement of the foot processes, podocytopenia, and damage to the slit diaphragm leading to albuminuria.[162] CCR2 inhibitors are being evaluated for the management of DKD.[163]

Another therapeutic target in DKD is the Janus kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathway. This pathway transduces inflammatory signals from cytokines and chemokines as well as AGEs, growth factors, and hormones.[164] The JAK-STAT pathway has been shown to be upregulated

in DKD, including in intrinsic renal cells. Baricitinib, an oral, reversible, selective inhibitor of JAK1 and JAK2, is showing promise as an intervention to slow the progression of DKD.[164] Overall, the activation of the innate immune system in DKD is a concerted effort between resident immune cells, infiltrating cells, and resident renal cells. The involvement of renal cells arises from the production of cytokines and chemokines and the expression of adhesion molecules that facilitate adhesion of the inflammatory cells.[149,150] Eventually, the adaptive immune system is also involved in diabetes, as T cells infiltrate kidneys in DKD, albeit not as prominently as macrophages.[150] T helper phenotype in DKD appears to be shifted toward Th1/Th17 cells rather than Tregs.[150,165] This promotes further macrophage-induced injury rather than repair of the kidney. There is limited evidence for involvement of B cells in DKD.

GENETIC AND EPIGENETIC PROGRAMMING OF DKD

Nephropathy is not an inevitable complication of diabetes. Only 25–35% of type 1 or type 2 diabetes ultimately develop kidney disease. Differences in the control of glycemia and blood pressure by themselves do not explain this unequal distribution. The propensity for DKD appears to be driven, at least in part, by familial and genetic factors.

The initial evidence for genetic predisposition comes from familial clustering studies. Having a sibling or parent with DKD increases the risk of diabetic family members to develop elevated UAE or ESRD. The finding was consistent across families with various ethnic backgrounds and was, to a large extent, independent of blood glucose concentration.[166–168] It was also validated in larger multicenter trials such as the ESRD network and the Diabetes Control and Complications Trial.[169,170]

Because family members often share environmental factors and habits, nurture may be difficult to tease apart from nature in the study of DKD. A better analysis comes from the calculation of the heritability factor h^2, which estimates the proportion of total variation of a trait caused by genetic effects. In the case of albuminuria, h^2 was between 0.27 and 0.39 in families with type 2 diabetes.[171–175] On the other hand, GFR was found to be as strong a heritable trait, with an h^2 ranging from 0.29 to 0.75.[173,174] Because a heritability factor of 1 indicates Mendelian transmission of a trait, these h^2 values suggest a strong genetic component in the susceptibility to DKD.

Since the advent and evolution of genomics, multiple studies have attempted to localize the genetic drivers of DKD. Based on the known or theorized roles in the mechanisms of disease, numerous genes were tested for polymorphisms in patients with kidney disease compared to controls. One notable example is that of the ACE insertion/deletion (I/D) polymorphism. Patients homozygous for the D allele have stronger ACE activity and appear to be at a higher risk for DKD progression. Multiple studies have attempted to prove this effect with variable results. These were recently pooled into a meta-analysis that somewhat confirmed the association of the D allele with DKD, with the evidence being stronger in the Asian subgroup.[176]

Another level of evidence comes from linkage analysis, which hunts for human disease genes relative to known genetic markers. The technique is based on the principle that markers in proximity to DKD susceptibility genes are unlikely to be segregated and are therefore "linked," thereby narrowing the genomic region that needs to be searched.[177] Genome-wide association studies (GWASs) cast a wider and, arguably, unbiased net across the genome and allow the analysis of population-based samples. They offer a better screen for genetic associations.[178] Whole exome sequencing methods are emerging for DKD. They help investigate low-frequency and rare variants not detected on GWAS platforms. Data on candidate genes is starting to appear, such as RREB1 gene, an upstream regulator of RAAS, and COL4A3 which encodes the α3 collagen chain subunit of type IV collagen, which is the major structural component in the mature GBM.[179,180] Although multiple areas of interest have been noted, no significant genes have been pinpointed as specific mediators of DKD. Diabetic nephropathy continues to be a complex disease, so its inheritance is most likely polygenic. Moreover, environmental factors influence its incidence and progression.

Environmental factors from intrauterine environment to diet and hyperglycemic control can modify genome expression through epigenetic mechanisms. These include changes in DNA methylation, histone modification by methylation and acetylation, among others.[181] Epigenetic modifications can shape the transcription of specific genes, and therefore affect disease pathogenesis. Accumulation of TCA intermediates and other metabolic dysregulations in diabetes may result in epigenetic modifications of renal and immune cells, potentially explaining some of the gene expression in DKD.[182] Such epigenetic modifications may persist, perpetuating some of the glomerulopathy, tubulopathy, and inflammation in DKD, even after normoglycemia is reestablished.[182]

Researchers have also been conducting epigenome-wide association studies to identify epigenetic marks associated with disease across the whole genome. For example, looking at differentially methylated genes in

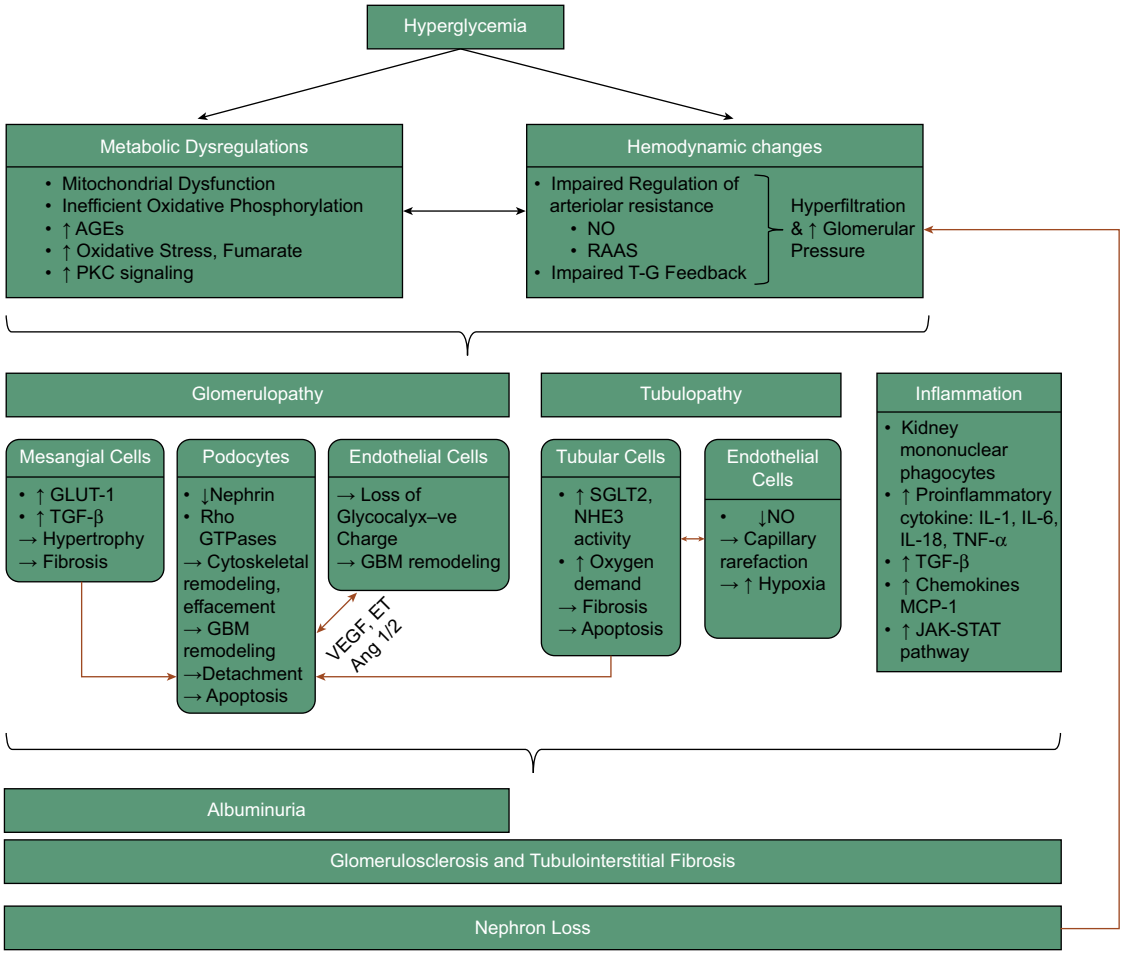


FIGURE 19.3 Conceptual model of the pathogenesis of diabetic kidney disease.

DKD cases vs. controls without renal complications is a new approach toward understanding predisposition to DKD.[181]

Because the epigenome is responsive to internal and external stimuli, harnessing this plasticity has fast become a new line of investigation to assessing dysregulated gene function. However, the broader utility for individual patients beyond conventional risk factors, such as glycemia, nutrition, and exercise, remains to be established.[182]

CONCLUSION

The pathogenesis of DKD is complex (Figure 19.3). Engendered by glucotoxicity and glomerular hypertension, deleterious combinations of toxic metabolites, growth factors, and cytokines are foisted on the various compartments of the kidney, and the damage manifests clinically as albuminuria and progressive loss of renal function. Although we discussed DKD pathogenic mechanisms separately, in reality, they intersect/overlap and occur simultaneously and perhaps even act synergistically. The reductionist approach is powerful but needs to be balanced by a desire to synthesize the "big picture," as unifying the theories of DKD remain a laudable goal. There is some suggestion that many of the inciting factors may converge on a final, common pathway. The armamentarium for the treatment and prevention of DKD in clinical practice had long remained limited to the blockade of the renin-angiotensin-aldosterone system (RAAS) and the control of hypertension and hyperglycemia. The SGLT2 inhibitors offer hope for additional nephroprotective effects. Overall we are optimistic that newer and more effective therapies will be on the horizon, and that progress will be made possible by further elucidating the pathophysiology of DKD.

References

1. Fioretto P, Mauer M. Histopathology of diabetic nephropathy. *Semin Nephrol* 2007;**27**:195–207.
2. Zhu D, Kim Y, Steffes MW, Groppoli TJ, Butkowski RJ, Mauer SM. Glomerular distribution of type IV collagen in diabetes by high resolution quantitative immunochemistry. *Kidney Int* 1994;**45**: 425–33.
3. Caramori ML, Kim Y, Huang C, et al. Cellular basis of diabetic nephropathy: 1. Study design and renal structural-functional relationships in patients with long-standing type 1 diabetes. *Diabetes* 2002;**51**:506–13.
4. Lin JS, Susztak K. Podocytes: the weakest link in diabetic kidney disease? *Curr Diabetes Rep* 2016;**16**:45.
5. Toyoda M, Najafian B, Kim Y, Caramori ML, Mauer M. Podocyte detachment and reduced glomerular capillary endothelial fenestration in human type 1 diabetic nephropathy. *Diabetes* 2007;**56**: 2155–60.
6. Meyer TW, Bennett PH, Nelson RG. Podocyte number predicts long-term urinary albumin excretion in Pima Indians with Type II diabetes and microalbuminuria. *Diabetologia* 1999;**42**:1341–4.
7. Kashihara N, Watanabe Y, Makino H, Wallner EI, Kanwar YS. Selective decreased de novo synthesis of glomerular proteoglycans under the influence of reactive oxygen species. *Proc Natl Acad Sci USA* 1992;**89**:6309–13.
8. Osterby R. Morphometric studies of the peripheral glomerular basement membrane in early juvenile diabetes. I. Development of initial basement membrane thickening. *Diabetologia* 1972;**8**: 84–92.
9. Drummond K, Mauer M. The early natural history of nephropathy in type 1 diabetes: II. Early renal structural changes in type 1 diabetes. *Diabetes* 2002;**51**:1580–7.
10. Saito Y, Kida H, Takeda S, et al. Mesangiolysis in diabetic glomeruli: its role in the formation of nodular lesions. *Kidney Int* 1988;**34**:389–96.
11. Bader R, Bader H, Grund KE, Markensen-Haen S, Christ H, Bohle A. Structure and function of the kidney in diabetic glomerulosclerosis: correlations between morphologic and functional parameters. *Pathol Res Pract* 1980;**167**:204–16.
12. Lane PH, Steffes MW, Fioretto P, Mauer SM. Renal interstitial expansion in insulin-dependent diabetes mellitus. *Kidney Int* 1993;**43**:661–7.
13. Ziyadeh FN, Goldfarb S. The renal tubulointerstitium in diabetes mellitus. *Kidney Int* 1991;**39**:464–75.
14. Tervaert TW, Mooyaart AL, Amann K, et al. Pathologic classification of diabetic nephropathy. *J Am Soc Nephrol* 2010;**21**:556–63.
15. Ponchiardi C, Mauer M, Najafian B. Temporal profile of diabetic nephropathy pathologic changes. *Curr Diabetes Rep* 2013;**13**: 592–9.
16. Fioretto P, Mauer M, Brocco E, et al. Patterns of renal injury in NIDDM patients with microalbuminuria. *Diabetologia* 1996;**39**: 1569–76.
17. Gambara V, Mecca G, Remuzzi G, Bertani T. Heterogeneous nature of renal lesions in type II diabetes. *J Am Soc Nephrol* 1993;**3**: 1458–66.
18. Mogensen CE, Christensen CK, Vittinghus E. The stages in diabetic renal disease. With emphasis on the stage of incipient diabetic nephropathy. *Diabetes* 1983;**32**(Suppl. 2):64–78.
19. Olivarius Nde F, Andreasen AH, Keiding N, Mogensen CE. Epidemiology of renal involvement in newly-diagnosed middle-aged and elderly diabetic patients. Cross-sectional data from the population-based study "Diabetes Care in General Practice", Denmark. *Diabetologia* 1993;**36**:1007–16.
20. Mogensen CE, Steffes MW, Deckert T, Christiansen JS. Functional and morphological renal manifestations in diabetes mellitus. *Diabetologia* 1981;**21**:89–93.
21. Ficociello LH, Perkins BA, Roshan B, et al. Renal hyperfiltration and the development of microalbuminuria in type 1 diabetes. *Diabetes Care* 2009;**32**:889–93.
22. Myers BD, Nelson RG, Williams GW, et al. Glomerular function in Pima Indians with noninsulin-dependent diabetes mellitus of recent onset. *J Clin Investig* 1991;**88**:524–30.
23. Magee GM, Bilous RW, Cardwell CR, Hunter SJ, Kee F, Fogarty DG. Is hyperfiltration associated with the future risk of developing diabetic nephropathy? A meta-analysis. *Diabetologia* 2009;**52**:691–7.
24. Ruggenenti P, Porrini EL, Gaspari F, et al. Glomerular hyperfiltration and renal disease progression in type 2 diabetes. *Diabetes Care* 2012;**35**:2061–8.
25. Cederholm J, Eliasson B, Nilsson PM, Weiss L, Gudbjörnsdottir S, Register SCotSND. Microalbuminuria and risk factors in type 1 and type 2 diabetic patients. *Diabetes Res Clin Pract* 2005;**67**: 258–66.
26. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 1984;**310**:356–60.
27. Caramori ML, Fioretto P, Mauer M. The need for early predictors of diabetic nephropathy risk: is albumin excretion rate sufficient? *Diabetes* 2000;**49**:1399–408.
28. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. *N Engl J Med* 2003;**348**:2285–93.
29. Ninomiya T, Perkovic V, Verdon C, et al. Proteinuria and stroke: a meta-analysis of cohort studies. *Am J Kidney Dis* 2009;**53**: 417–25.
30. Perkovic V, Verdon C, Ninomiya T, et al. The relationship between proteinuria and coronary risk: a systematic review and meta-analysis. *PLoS Med* 2008;**5**:1486–95.
31. Deckert T, Yokoyama H, Mathiesen E, et al. Cohort study of predictive value of urinary albumin excretion for atherosclerotic vascular disease in patients with insulin dependent diabetes. *BMJ* 1996;**312**:871–4.
32. Damsgaard EM, Froland A, Jorgensen OD, Mogensen CE. Microalbuminuria as predictor of increased mortality in elderly people. *Br Med J* 1990;**300**:297–300.
33. Mathiesen ER, Feldt-Rasmussen B, Hommel E, Deckert T, Parving HH. Stable glomerular filtration rate in normotensive IDDM patients with stable microalbuminuria. A 5-year prospective study. *Diabetes Care* 1997;**20**:286–9.
34. Gaede P, Tarnow L, Vedel P, Parving H-H, Pedersen O. Remission to normoalbuminuria during multifactorial treatment preserves kidney function in patients with type 2 diabetes and microalbuminuria. *Nephrol Dial Transplant* 2004;**19**:2784–8.
35. Remuzzi G, Bertani T. Is glomerulosclerosis a consequence of altered glomerular permeability to macromolecules? *Kidney Int* 1990;**38**:384–94.
36. Mauer SM, Steffes MW, Ellis EN, Sutherland DE, Brown DM, Goetz FC. Structural-functional relationships in diabetic nephropathy. *J Clin Investig* 1984;**74**:1143–55.
37. Yamada T, Komatsu M, Komiya I, et al. Development, progression, and regression of microalbuminuria in Japanese patients with type 2 diabetes under tight glycemic and blood pressure control: the Kashiwa study. *Diabetes Care* 2005;**28**:2733–8.
38. Macisaac RJ, Jerums G. Diabetic kidney disease with and without albuminuria. *Curr Opin Nephrol Hypertens* 2011;**20**:246–57.
39. Costacou T, Ellis D, Fried L, Orchard TJ. Sequence of progression of albuminuria and decreased GFR in persons with type 1 diabetes: a cohort study. *Am J Kidney Dis* 2007;**50**:721–32.
40. Parving HH, Lewis JB, Ravid M, Remuzzi G, Hunsicker LG, et al. Prevalence and risk factors for microalbuminuria in a referred cohort of type II diabetic patients: a global perspective. *Kidney Int* 2006;**69**:2057–63.

41. Tsalamandris C, Allen TJ, Gilbert RE, et al. Progressive decline in renal function in diabetic patients with and without albuminuria. *Diabetes* 1994;**43**:649–55.
42. Perkins BA, Nelson RG, Ostrander BE, et al. Detection of renal function decline in patients with diabetes and normal or elevated GFR by serial measurements of serum cystatin C concentration: results of a 4-year follow-up study. *J Am Soc Nephrol* 2005;**16**: 1404–12.
43. Writing Team for the Diabetes C, Complications Trial/Epidemiology of Diabetes I, Complications Research G. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *J Am Med Assoc* 2003;**290**:2159–67.
44. Group UPDSU. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;**352**:837–53.
45. Fioretto P, Steffes MW, Sutherland DER, Goetz FC, Mauer M. Reversal of lesions of diabetic nephropathy after pancreas transplantation. *N Engl J Med* 1998;**339**:69–75.
46. Barbosa J, Steffes MW, Sutherland DE, Connett JE, Rao KV, Mauer SM. Effect of glycemic control on early diabetic renal lesions. A 5-year randomized controlled clinical trial of insulin-dependent diabetic kidney transplant recipients. *J Am Med Assoc* 1994;**272**:600–6.
47. Group DCCTR, Nathan DM, Genuth S, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977–86.
48. Heilig CW, Brosius FC, Henry DN. Glucose transporters of the glomerulus and the implications for diabetic nephropathy. *Kidney Int Suppl* 1997;**60**:S91–9.
49. Zhang G, Darshi M, Sharma K. The Warburg effect in diabetic kidney disease. *Semin Nephrol* 2018;**38**:111–20.
50. Tanner LB, Goglia AG, Wei MH, et al. Four key steps control glycolytic flux in mammalian cells. *Cell Systems* 2018;**7**:49–62 e8.
51. Sas KM, Kayampilly P, Byun J, et al. Tissue-specific metabolic reprogramming drives nutrient flux in diabetic complications. *JCI Insight* 2016;**1**:e86976.
52. Sharma K, Karl B, Mathew AV, et al. Metabolomics reveals signature of mitochondrial dysfunction in diabetic kidney disease. *J Am Soc Nephrol* 2013;**24**:1901–12.
53. Bhargava P, Schnellmann RG. Mitochondrial energetics in the kidney. *Nat Rev Nephrol* 2017;**13**:629–46.
54. Galvan DL, Green NH, Danesh FR. The hallmarks of mitochondrial dysfunction in chronic kidney disease. *Kidney Int* 2017;**92**: 1051–7.
55. Dunlop M. Aldose reductase and the role of the polyol pathway in diabetic nephropathy. *Kidney Int* 2000;**58**:S3–12.
56. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001;**414**:813–20.
57. Du XL, Edelstein D, Rossetti L, et al. Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosamine pathway and induces plasminogen activator inhibitor-1 expression by increasing Sp1 glycosylation. *Proc Natl Acad Sci USA* 2000;**97**:12222–6.
58. Qi W, Li Q, Gordin D, King GL. Preservation of renal function in chronic diabetes by enhancing glomerular glucose metabolism. *J Mol Med (Berl)* 2018;**96**:373–81.
59. Qi W, Keenan HA, Li Q, et al. Pyruvate kinase M2 activation may protect against the progression of diabetic glomerular pathology and mitochondrial dysfunction. *Nat Med* 2017;**23**:753–62.
60. Kimmelstiel P, Wilson C. Intercapillary lesions in the glomeruli of the kidney. *Am J Pathol* 1936;**12**. 83–98.7.
61. Kang HM, Ahn SH, Choi P, et al. Defective fatty acid oxidation in renal tubular epithelial cells has a key role in kidney fibrosis development. *Nat Med* 2015;**21**:37–46.
62. Martinez-Garcia C, Izquierdo-Lahuerta A, Vivas Y, et al. Renal lipotoxicity-associated inflammation and insulin resistance affects actin cytoskeleton organization in podocytes. *PLoS One* 2015;**10**: e0142291.
63. Jakus V, Rietbrock N. Advanced glycation end-products and the progress of diabetic vascular complications. *Physiol Res* 2004;**53**: 131–42.
64. Horie K, Miyata T, Maeda K, et al. Immunohistochemical colocalization of glycoxidation products and lipid peroxidation products in diabetic renal glomerular lesions. Implication for glycoxidative stress in the pathogenesis of diabetic nephropathy. *J Clin Investig* 1997;**100**:2995–3004.
65. Schleicher ED, Wagner E, Nerlich AG. Increased accumulation of the glycoxidation product N(epsilon)-(carboxymethyl)lysine in human tissues in diabetes and aging. *J Clin Investig* 1997;**99**:457–68.
66. Cooper ME. Interaction of metabolic and haemodynamic factors in mediating experimental diabetic nephropathy. *Diabetologia* 2001;**44**:1957–72.
67. Vlassara H, Striker LJ, Teichberg S, Fuh H, Li YM, Steffes M. Advanced glycation end products induce glomerular sclerosis and albuminuria in normal rats. *Proc Natl Acad Sci USA* 1994;**91**: 11704–8.
68. Busch M, Franke S, Rüster C, Wolf G. Advanced glycation end-products and the kidney. *Eur J Clin Investig* 2010;**40**:742–55.
69. Catania JM, Chen G, Parrish AR. Role of matrix metalloproteinases in renal pathophysiologies. *Am J Physiol Renal Physiol* 2007;**292**:F905–11.
70. Wautier JL, Guillausseau PJ. Advanced glycation end products, their receptors and diabetic angiopathy. *Diabetes Metab* 2001;**27**: 535–42.
71. Yamagishi S, Inagaki Y, Okamoto T, et al. Advanced glycation end product-induced apoptosis and overexpression of vascular endothelial growth factor and monocyte chemoattractant protein-1 in human-cultured mesangial cells. *J Biol Chem* 2002;**277**:20309–15.
72. Fukami K, Ueda S, Yamagishi S, et al. AGEs activate mesangial TGF-beta-Smad signaling via an angiotensin II type I receptor interaction. *Kidney Int* 2004;**66**:2137–47.
73. Studer RK, Craven PA, DeRubertis FR. Role for protein kinase C in the mediation of increased fibronectin accumulation by mesangial cells grown in high glucose medium. *Diabetes* 1993;**42**:118–26.
74. Thallas-Bonke V, Thorpe SR, Coughlan MT, et al. Inhibition of NADPH oxidase prevents advanced glycation end product-mediated damage in diabetic nephropathy through a protein kinase C-alpha-dependent pathway. *Diabetes* 2008;**57**:460–9.
75. Hallan S, Sharma K. The role of mitochondria in diabetic kidney disease. *Curr Diabetes Rep* 2016;**16**:61.
76. Menne J, Shushakova N, Bartels J, et al. Dual inhibition of classical protein kinase C-α and protein kinase C-β isoforms protects against experimental murine diabetic nephropathy. *Diabetes* 2013;**62**:1167–74.
77. Tuttle KR, Bakris GL, Toto RD, McGill JB, Hu K, Anderson PW. The effect of ruboxistaurin on nephropathy in type 2 diabetes. *Diabetes Care* 2005;**28**:2686–90.
78. Gorin Y, Block K. Nox4 and diabetic nephropathy: with a friend like this, who needs enemies? *Free Radic Biol Med* 2013;**61**:130–42.
79. Baynes JW. Role of oxidative stress in development of complications in diabetes. *Diabetes* 1991;**40**:405–12.
80. Coughlan MT, Sharma K. Challenging the dogma of mitochondrial reactive oxygen species overproduction in diabetic kidney disease. *Kidney Int* 2016;**90**:272–9.
81. Sharma K. Mitochondrial dysfunction in the diabetic kidney. In: Santulli G, editor. *Mitochondrial dynamics in cardiovascular*

medicine. Cham: Springer International Publishing; 2017. p. 553–62.
82. Thallas-Bonke V, Jha JC, Gray SP, et al. Nox-4 deletion reduces oxidative stress and injury by PKC-α -associated mechanisms in diabetic nephropathy. *Physiol Rep* 2014;**2**.
83. You YH, Quach T, Saito R, Pham J, Sharma K. Metabolomics reveals a key role for fumarate in mediating the effects of NADPH oxidase 4 in diabetic kidney disease. *J Am Soc Nephrol* 2016;**27**: 466–81.
84. Christiansen JS, Gammelgaard J, Frandsen M, Parving HH. Increased kidney size, glomerular filtration rate and renal plasma flow in short-term insulin-dependent diabetics. *Diabetologia* 1981; **20**:451–6.
85. Tonneijck L, Muskiet MH, Smits MM, et al. Glomerular hyperfiltration in diabetes: mechanisms, clinical significance, and treatment. *J Am Soc Nephrol* 2017;**28**:1023–39.
86. De Vriese AS, Stoenoiu MS, Elger M, et al. Diabetes-induced microvascular dysfunction in the hydronephrotic kidney: role of nitric oxide. *Kidney Int* 2001;**60**:202–10.
87. Goligorsky MS. Endothelial cell dysfunction and nitric oxide synthase. *Kidney Int* 2000;**58**:1360–76.
88. Hostetter TH, Rennke HG, Brenner BM. The case for intrarenal hypertension in the initiation and progression of diabetic and other gomerulopathies. *Am J Med* 1982;**72**:375–80.
89. Anderson S, Rennke HG, Brenner BM. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Investig* 1986;**77**:1993–2000.
90. Lambers Heerspink HJ, de Borst MH, Bakker SJL, Navis GJ. Improving the efficacy of RAAS blockade in patients with chronic kidney disease. *Nat Rev Nephrol* 2012;**9**:112–21.
91. Holtkamp FA, de Zeeuw D, Thomas MC, et al. An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. *Kidney Int* 2011;**80**:282–7.
92. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor–associated elevations in serum creatinine. *Arch Intern Med* 2000;**160**.
93. Vallon V, Thomson SC. Renal function in diabetic disease models: the tubular system in the pathophysiology of the diabetic kidney. *Annu Rev Physiol* 2012;**74**:351–75.
94. Wang XX, Levi J, Luo Y, et al. SGLT2 protein expression is increased in human diabetic nephropathy: SGLT2 protein inhibition decreases renal lipid accumulation, inflammation, and the development of nephropathy in diabetic mice. *J Biol Chem* 2017; **292**:5335–48.
95. Vallon V, Schroth J, Satriano J, Blantz RC, Thomson SC, Rieg T. Adenosine A(1) receptors determine glomerular hyperfiltration and the salt paradox in early streptozotocin diabetes mellitus. *Nephron Physiol* 2009;**111**:p30–8.
96. Carmines PK. The renal vascular response to diabetes. *Curr Opin Nephrol Hypertens* 2010;**19**:85–90.
97. Vallon V, Richter K, Blantz RC, Thomson S, Osswald H. Glomerular hyperfiltration in experimental diabetes mellitus: potential role of tubular reabsorption. *J Am Soc Nephrol* 1999;**10**:2569–76.
98. Hallow KM, Gebremichael Y, Helmlinger G, Vallon V. Primary proximal tubule hyperreabsorption and impaired tubular transport counterregulation determine glomerular hyperfiltration in diabetes: a modeling analysis. *Am J Physiol Renal Physiol* 2017; **312**:F819–35.
99. Vallon V, Rose M, Gerasimova M, et al. Knockout of Na-glucose transporter SGLT2 attenuates hyperglycemia and glomerular hyperfiltration but not kidney growth or injury in diabetes mellitus. *Am J Physiol Renal Physiol* 2013;**304**:F156–67.
100. Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014;**129**:587–97.
101. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;**375**:323–34.
102. Thomson SC, Rieg T, Miracle C, et al. Acute and chronic effects of SGLT2 blockade on glomerular and tubular function in the early diabetic rat. *Am J Physiol Regul Integr Comp Physiol* 2012;**302**:R75–83.
103. Skrtic M, Yang GK, Perkins BA, et al. Characterisation of glomerular haemodynamic responses to SGLT2 inhibition in patients with type 1 diabetes and renal hyperfiltration. *Diabetologia* 2014; **57**:2599–602.
104. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 2019; **380**:2295–306.
105. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017; **377**:644–57.
106. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2019;**380**:347–57.
107. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015;**373**:2117–28.
108. Chade AR. Renal vascular structure and rarefaction. *Comp Physiol* 2013;**3**:817–31.
109. Gnudi L, Thomas SM, Viberti G. Mechanical forces in diabetic kidney disease: a trigger for impaired glucose metabolism. *J Am Soc Nephrol* 2007;**18**:2226–32.
110. Gruden G, Zonca S, Hayward A, et al. Mechanical stretch-induced fibronectin and transforming growth factor-beta1 production in human mesangial cells is p38 mitogen-activated protein kinase-dependent. *Diabetes* 2000;**49**:655–61.
111. Endlich K, Kliewe F, Endlich N. Stressed podocytes-mechanical forces, sensors, signaling and response. *Pflügers Archiv* 2017;**469**: 937–49.
112. Kriz W, Lemley KV. A potential role for mechanical forces in the detachment of podocytes and the progression of CKD. *J Am Soc Nephrol* 2015;**26**:258–69.
113. Schiffer M, Bitzer M, Roberts IS, et al. Apoptosis in podocytes induced by TGF-beta and Smad7. *J Clin Investig* 2001;**108**: 807–16.
114. Inoki K, Mori H, Wang J, et al. mTORC1 activation in podocytes is a critical step in the development of diabetic nephropathy in mice. *J Clin Investig* 2011;**121**:2181–96.
115. Wharram BL, Goyal M, Wiggins JE, et al. Podocyte depletion causes glomerulosclerosis: diphtheria toxin-induced podocyte depletion in rats expressing human diphtheria toxin receptor transgene. *J Am Soc Nephrol* 2005;**16**:2941–52.
116. Durvasula RV, Petermann AT, Hiromura K, et al. Activation of a local tissue angiotensin system in podocytes by mechanical strain. *Kidney Int* 2004;**65**:30–9.
117. Thomas MC, Tikellis C, Burns WM, et al. Interactions between renin angiotensin system and advanced glycation in the kidney. *J Am Soc Nephrol* 2005;**16**:2976–84.
118. Tan ALY, Forbes JM, Cooper ME. AGE, RAGE, and ROS in diabetic nephropathy. *Semin Nephrol* 2007;**27**:130–43.
119. Wolf G. New insights into the pathophysiology of diabetic nephropathy: from haemodynamics to molecular pathology. *Eur J Clin Investig* 2004;**34**:785–96.
120. Tufro A, Veron D. VEGF and podocytes in diabetic nephropathy. *Semin Nephrol* 2012;**32**:385–93.
121. Eremina V, Sood M, Haigh J, et al. Glomerular-specific alterations of VEGF-A expression lead to distinct congenital and acquired renal diseases. *J Clin Investig* 2003;**111**:707–16.
122. Sung SH, Chen S, Laping NJ, Ziyadeh FN. Albuminuria is ameliorated by an inhibitor of VEGF receptors, SU5416, in diabetic db/db mice but is unaffected in Smad3-knockout mice rendered diabetic with streptozotocin. *J Am Soc Nephrol* 2004 [Abstract].

123. Sivaskandarajah GA, Jeansson M, Maezawa Y, Eremina V, Baelde HJ, Quaggin SE. VEGF-A protects the glomerular microvasculature in diabetes. *Diabetes* 2012;**61**:2958–66.
124. De Vriese AS, Tilton RG, Elger M, Stephan CC, Kriz W, Lameire NH. Antibodies against vascular endothelial growth factor improve early renal dysfunction in experimental diabetes. *J Am Soc Nephrol* 2001;**12**:993–1000.
125. Flyvbjerg A, Dagnaes-Hansen F, De Vriese AS, Schrijvers BF, Tilton RG, Rasch R. Amelioration of long-term renal changes in obese type 2 diabetic mice by a neutralizing vascular endothelial growth factor antibody. *Diabetes* 2002;**51**:3090–4.
126. Majumder S, Advani A. VEGF and the diabetic kidney: more than too much of a good thing. *J Diabet Complicat* 2017;**31**:273–9.
127. Bates DO. Vascular endothelial growth factors and vascular permeability. *Cardiovasc Res* 2010;**87**:262–71.
128. Oltean S, Qiu Y, Ferguson JK, et al. Vascular endothelial growth factor-A165b is protective and restores endothelial glycocalyx in diabetic nephropathy. *J Am Soc Nephrol* 2015;**26**:1889–904.
129. Garsen M, Lenoir O, Rops AL, et al. Endothelin-1 induces proteinuria by heparanase-mediated disruption of the glomerular glycocalyx. *J Am Soc Nephrol* 2016;**27**:3545–51.
130. de Zeeuw D, Coll B, Andress D, et al. The endothelin antagonist atrasentan lowers residual albuminuria in patients with type 2 diabetic nephropathy. *J Am Soc Nephrol* 2014;**25**:1083–93.
131. Reeves WB, Andreoli TE. Transforming growth factor beta contributes to progressive diabetic nephropathy. *Proc Natl Acad Sci USA* 2000;**97**:7667–9.
132. Ziyadeh FN. Evidence for the involvement of transforming growth factor-beta in the pathogenesis of diabetic kidney disease: are Koch's postulates fulfilled? *Curr Pract Med* 1998;**1**:87–9.
133. Ziyadeh FN, Sharma K, Ericksen M, Wolf G. Stimulation of collagen gene expression and protein synthesis in murine mesangial cells by high glucose is mediated by autocrine activation of transforming growth factor-beta. *J Clin Investig* 1994;**93**:536–42.
134. Yang CW, Vlassara H, Peten EP, He C-J, Striker GE, Striker LJ. Advanced glycation end products up-regulate gene expression found in diabetic glomerular disease. *Proc Natl Acad Sci USA* 1994;**91**:9436–40.
135. Riser BL, Cortes P, Yee J, et al. Mechanical strain- and high glucose-induced alterations in mesangial cell collagen metabolism: role of TGF-beta. *J Am Soc Nephrol* 1998;**9**:827–36.
136. Fumo P, Kuncio GS, Ziyadeh FN. PKC and high glucose stimulate collagen alpha1(IV)transcriptional activity in a reporter mesangial cell line. *Am J Physiol* 1994;**267**:F632–8.
137. Wolf G, Neilson EG. Angiotensin II as a hypertrophogenic cytokine for proximal tubular cells. *Kidney Int Suppl* 1993;**39**:S100–7.
138. Sharma K, Ziyadeh FN, Alzahabi B, et al. Increased renal production of transforming growth factor-beta1 in patients with type II diabetes. *Diabetes* 1997;**46**:854–9.
139. Ziyadeh FN, Hoffman BB, Han DC, et al. Long-term prevention of renal insufficiency, excess matrix gene expression and glomerular mesangial matrix expression by treatment with monoclonal anti-TGF-bantibody indb/dbdiabetic mice. *Proc Natl Acad Sci USA* 2000:8015–20.
140. Chen S, Kasama Y, Lee JS, Jim B, Marin M, Ziyadeh FN. Podocyte-derived vascular endothelial growth factor mediates the stimulation of alpha3(IV) collagen production by transforming growth factor-beta1 in mouse podocytes. *Diabetes* 2004;**53**:2939–49.
141. Yu SM, Bonventre JV. Acute kidney injury and progression of diabetic kidney disease. *Adv Chron Kidney Dis* 2018;**25**:166–80.
142. Sabbisetti VS, Waikar SS, Antoine DJ, et al. Blood kidney injury molecule-1 is a biomarker of acute and chronic kidney injury and predicts progression to ESRD in type I diabetes. *J Am Soc Nephrol* 2014;**25**:2177–86.
143. White KE, Marshall SM, Bilous RW. Prevalence of atubular glomeruli in type 2 diabetic patients with nephropathy. *Nephrol Dial Transplant* 2008;**23**:3539–45.
144. Najafian B. Atubular glomeruli and glomerulotubular junction abnormalities in diabetic nephropathy. *J Am Soc Nephrol* 2003;**14**:908–17.
145. Gilbert RE. Proximal tubulopathy: prime mover and key therapeutic target in diabetic kidney disease. *Diabetes* 2017;**66**:791–800.
146. Ziyadeh FN, Snipes ER, Watanabe M, Alvarez RJ, Goldfarb S, Haverty TP. High glucose induces cell hypertrophy and stimulates collagen gene transcription in proximal tubule. *Am J Physiol* 1990;**259**:F704–14.
147. Grgic I, Campanholle G, Bijol V, et al. Targeted proximal tubule injury triggers interstitial fibrosis and glomerulosclerosis. *Kidney Int* 2012;**82**:172–83.
148. Hasegawa K, Wakino S, Simic P, et al. Renal tubular Sirt1 attenuates diabetic albuminuria by epigenetically suppressing Claudin-1 overexpression in podocytes. *Nat Med* 2013;**19**:1496–504.
149. Alicic RZ, Johnson EJ, Tuttle KR. Inflammatory mechanisms as new biomarkers and therapeutic targets for diabetic kidney disease. *Adv Chron Kidney Dis* 2018;**25**:181–91.
150. Pichler R, Afkarian M, Dieter BP, Tuttle KR. Immunity and inflammation in diabetic kidney disease: translating mechanisms to biomarkers and treatment targets. *Am J Physiol Renal Physiol* 2017;**312**:F716–31.
151. Nelson PJ, Rees AJ, Griffin MD, Hughes J, Kurts C, Duffield J. The renal mononuclear phagocytic system. *J Am Soc Nephrol* 2012;**23**:194–203.
152. Nguyen D, Ping F, Mu W, Hill P, Atkins RC, Chadban SJ. Macrophage accumulation in human progressive diabetic nephropathy. *Nephrology* 2006;**11**:226–31.
153. Furuta T, Saito T, Ootaka T, et al. The role of macrophages in diabetic glomerulosclerosis. *Am J Kidney Dis* 1993;**21**:480–5.
154. Wintroub BU, Schechter NB, Lazarus GS, Kaempfer CE, Schwartz LB. Angiotensin I conversion by human and rat chymotryptic proteinases. *J Investig Dermatol* 1984;**83**:336–9.
155. Reilly CF, Tewksbury DA, Schechter NM, Travis J. Rapid conversion of angiotensin I to angiotensin II by neutrophil and mast cell proteinases. *J Biol Chem* 1982;**257**:8619–22.
156. Navarro-Gonzalez JF, Jarque A, Muros M, Mora C, Garcia J. Tumor necrosis factor-alpha as a therapeutic target for diabetic nephropathy. *Cytokine Growth Factor Rev* 2009;**20**:165–73.
157. Awad AS, You H, Gao T, et al. Macrophage-derived tumor necrosis factor-alpha mediates diabetic renal injury. *Kidney Int* 2015;**88**:722–33.
158. McCarthy ET, Sharma R, Sharma M, et al. TNF-alpha increases albumin permeability of isolated rat glomeruli through the generation of superoxide. *J Am Soc Nephrol* 1998;**9**:433–8.
159. Gohda T, Niewczas MA, Ficociello LH, et al. Circulating TNF receptors 1 and 2 predict stage 3 CKD in type 1 diabetes. *J Am Soc Nephrol* 2012;**23**:516–24.
160. Brosius FC, Khoury CC, Buller CL, Chen S. Abnormalities in signaling pathways in diabetic nephropathy. *Expert Rev Endocrinol Metab* 2010;**5**:51–64.
161. Lee EY, Chung CH, Khoury CC, et al. The monocyte chemoattractant protein-1/CCR2 loop, inducible by TGF-beta, increases podocyte motility and albumin permeability. *Am J Physiol Renal Physiol* 2009;**297**:F85–94.
162. You H, Gao T, Raup-Konsavage WM, et al. Podocyte-specific chemokine (C-C motif) receptor 2 overexpression mediates diabetic renal injury in mice. *Kidney Int* 2017;**91**:671–82.
163. de Zeeuw D, Bekker P, Henkel E, et al. The effect of CCR2 inhibitor CCX140-B on residual albuminuria in patients with type 2 diabetes and nephropathy: a randomised trial. *Lancet Diabetes Endocrinol* 2015;**3**:687–96.

164. Tuttle KR, Brosius 3rd FC, Adler SG, et al. JAK1/JAK2 inhibition by baricitinib in diabetic kidney disease: results from a Phase 2 randomized controlled clinical trial. *Nephrol Dial Transplant* 2018;**33**(11):1950−9.
165. Zeng C, Shi X, Zhang B, et al. The imbalance of Th17/Th1/Tregs in patients with type 2 diabetes: relationship with metabolic factors and complications. *J Mol Med (Berl)* 2012;**90**:175−86.
166. Freedman BI, Tuttle AB, Spray BJ. Familial predisposition to nephropathy in African-Americans with non-insulin-dependent diabetes mellitus. *Am J Kidney Dis* 1995;**25**:710−3.
167. Pettitt DJ, Saad MF, Bennett PH, Nelson RG, Knowler WC. Familial predisposition to renal disease in two generations of Pima Indians with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1990;**33**:438−43.
168. Fioretto P, Steffes MW, Barbosa J, Rich SS, Miller ME, Mauer M. Is diabetic nephropathy inherited? Studies of glomerular structure in type 1 diabetic sibling pairs. *Diabetes* 1999;**48**:865−9.
169. Freedman BI, Volkova NV, Satko SG, et al. Population-based screening for family history of end-stage renal disease among incident dialysis patients. *Am J Nephrol* 2005;**25**:529−35.
170. Clustering of long-term complications in families with diabetes in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. *Diabetes* 1997;**46**: 1829−39.
171. Forsblom CM, Kanninen T, Lehtovirta M, Saloranta C, Groop LC. Heritability of albumin excretion rate in families of patients with Type II diabetes. *Diabetologia* 1999;**42**:1359−66.
172. Fogarty DG, Rich SS, Hanna L, Warram JH, Krolewski AS. Urinary albumin excretion in families with type 2 diabetes is heritable and genetically correlated to blood pressure. *Kidney Int* 2000; **57**:250−7.
173. Placha G, Canani LH, Warram JH, Krolewski AS. Evidence for different susceptibility genes for proteinuria and ESRD in type 2 diabetes. *Adv Chron Kidney Dis* 2004;**12**:155−69.
174. Langefeld CD, Beck SR, Bowden DW, Rich SS, Wagenknecht LE, Freedman BI. Heritability of GFR and albuminuria in Caucasians with type 2 diabetes mellitus. *Am J Kidney Dis* 2004;**43**:796−800.
175. Krolewski AS, Poznik GD, Placha G, et al. A genome-wide linkage scan for genes controlling variation in urinary albumin excretion in type II diabetes. *Kidney Int* 2006;**69**:129−36.
176. Mooyaart AL, Valk EJ, van Es LA, et al. Genetic associations in diabetic nephropathy: a meta-analysis. *Diabetologia* 2011;**54**: 544−53.
177. Thomas MC, Groop PH, Tryggvason K. Towards understanding the inherited susceptibility for nephropathy in diabetes. *Curr Opin Nephrol Hypertens* 2012;**21**:195−202.
178. Li M, Pezzolesi MG. Advances in understanding the genetic basis of diabetic kidney disease. *Acta Diabetol* 2018;**55**:1093−104.
179. Bonomo JA, Guan M, Ng MC, et al. The ras responsive transcription factor RREB1 is a novel candidate gene for type 2 diabetes associated end-stage kidney disease. *Hum Mol Genet* 2014;**23**: 6441−7.
180. Wang Y, Zhang J, Zhao Y, et al. COL4A3Gene variants and diabetic kidney disease in MODY. *Clin J Am Soc Nephrol* 2018;**13**: 1162−71.
181. Keating ST, van Diepen JA, Riksen NP, El-Osta A. Epigenetics in diabetic nephropathy, immunity and metabolism. *Diabetologia* 2018;**61**:6−20.
182. Rosen ED, Kaestner KH, Natarajan R, et al. Epigenetics and epigenomics: implications for diabetes and obesity. *Diabetes* 2018;**67**: 1923−31.

QUESTIONS AND ANSWERS

Question 1

A 48-year-old man with a past medical history of 6 years of diabetes mellitus and poor medical follow-up presents with generalized edema and is found to have nephrotic-range proteinuria. He undergoes kidney biopsy that shows PAS-positive nodules in some of the glomeruli. These lesions are best known as?

A. Arteriolar hyalinosis
B. Hyaline caps
C. Exudative lesions
D. Kimmelstiel–Wilson bodies
E. Collapsed glomeruli

Answer: D

Kimmelstiel–Wilson bodies are nodular deposits of extracellular material that develop due to continued mesangial matrix expansion or to mesangiolysis and the formation of capillary aneurysms. They are present in up to 25% of diabetic patients at postmortem examination.

Question 2

Which of the following diabetic nephropathy mediators exerts its effects by direct modification of molecules as well as by activation of signaling pathways?

A. TGF-β
B. PKC
C. The polyols
D. Angiotensin II
E. AGE and ROS

Answer: E

AGEs are generated both intracellularly and extracellularly in the setting of hyperglycemia. They are at higher levels in vascular organs like the kidney. They induce their effects *via* direct modification of molecules and alteration of their function or by transformation into signaling molecules that act *via* the receptor RAGE. ROS generation is tightly linked to AGE formation and signaling. ROS oxidize a host of proteins, lipids, and carbohydrates in the cells affecting the cell's normal function, eventually leading to cell death. ROS can also affect DNA contributing to the differential gene expression in DKD.

Question 3

The rise in intraglomerular pressure can best be explained by which of the following effects?

A. The sole translation of systemic hypertension into the kidney
B. Abnormal autoregulation of the glomerular arterioles
C. Increased oncotic pressure
D. Increased glomerular filtration coefficient
E. Shift in pressure distribution with progressive loss of nephrons

Answer: B

Intraglomerular hypertension is best explained by alteration in autoregulation of the glomerular arterioles. While systemic blood pressure will likely be increased in later stages of diabetes, early glomerular hypertension has been described as an isolated phenomenon. Oncotic pressure and filtration coefficient have not been found to contribute to the hemodynamic changes in the kidney.

Question 4

Which of the following mediators and signaling pathways likely represents the best link between the hemodynamic and metabolic mechanisms of diabetic nephropathy?

A. The RAAS pathway
B. TGF-β
C. ROS
D. AGE
E. PKC

Answer: A

The RAAS pathway is activated by various metabolic drivers in diabetic nephropathy, including glucose, AGE, and others, and in turn activates TGF-β signaling among other pathways. It is likely one of the main drivers of glomerular hypertension *via* its selective vasoconstrictive effect on the efferent arteriole.

Question 5

A 46-year-old woman with a past medical history of diabetes mellitus is initiated on empagliflozin, an SGLT2i. Her GFR measured by inulin clearance was 185 mL/min/1.73 m^2 prior to the initiation of therapy and decreased to 150 mL/min/1.73 m^2 after two weeks on empagliflozin. Her volume status, glycemic control, and overall clinical condition remained relatively stable during this period. The decrease in GFR can best be explained by?

A. An acute kidney injury secondary to empagliflozin-related tubulointerstitial nephritis
B. Impairment of tubuloglomerular feedback as a result of glycation of the macula densa from increased distal delivery of glucose

C. Day-to-day variation in GFR measurement
D. Increased sodium chloride delivery to the macula densa results in afferent vasoconstriction *via* the tubuloglomerular feedback
E. Decreased pressure in the tubules and Bowman's space with SGLT2i therapy

Answer: D

In diabetes, there is an increase in sodium and glucose absorption in the proximal tubule, thus impairing the tubuloglomerular feedback and contributing to hyperfiltration by persistent afferent arteriolar dilation. SGLT2i has the opposite effect. Sodium and glucose that are not absorbed proximally *via* SGLT2 and the NHE3 transporters are delivered distally. There is increased delivery of NaCl to the macula densa, triggering tubuloglomerular feedback and inducing afferent arteriolar vasoconstriction. Simultaneously, the osmotic effect of glucose and sodium also increases the pressure in the tubules and Bowman's space, thus reducing the transglomerular filtration pressure and the GFR.

Question 6

Genetic predisposition to the development of diabetic nephropathy is likely due to which of the following?

A. Acquired mutations as a result of ROS modifications of DNA
B. Mendelian single gene inheritance
C. Epigenetic pathways
D. Mitochondrial inheritance of overactive glucose metabolism pathways
E. Multifactorial genetic inheritance

Answer: E

Only a proportion of diabetic patients ever develop diabetic nephropathy. The predisposition to diabetic nephropathy is likely due to a multifactorial inheritance, with involvement of multiple genes being associated with the disease. Environmental factors may contribute to epigenetic modifications of DNA. That said, the analysis of genetic predisposition to diabetes is largely affected by the difficulty in separating predisposition to renal involvement from tendency to poorly controlled diabetes.

CHAPTER

20

Prenatal Antecedents of Chronic Kidney Disease

Valerie A. Luyckx[a,b]

[a]Institute of Biomedical Ethics and the History of Medicine, University of Zurich, Zurich, Switzerland;
[b]Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

Abstract

Hypertension and chronic kidney disease are common in disadvantaged communities, where maternal health is also suboptimal and risk factors for poor pregnancy outcomes are common. Multiple exposures during pregnancy and early childhood impact fetal and infant growth and nephrogenesis, which in turn affect the risk of hypertension and kidney disease throughout the life course. Being small for gestational age is the strongest risk predictor for renal programming, but being born preterm, of low birth weight, large for gestational age, or being exposed to gestational diabetes and preeclampsia are also risk markers. This programmed risk could be mitigated by optimization of maternal health before pregnancy, education about healthy lifestyles, and screening of individuals who may have experienced developmental programming, to permit early diagnosis and intervention. Given that millions of babies are born too small, too early, or in complicated pregnancies, increased awareness of programmed risk of hypertension and kidney disease should provide a window of opportunity to reduce the global burden of these conditions across the life course through prevention, early diagnosis and treatment, and education.

SCOPE OF THE PROBLEM

Chronic kidney disease (CKD) has been called a "silent epidemic," affecting around 10% of adults and an estimated 750 million people worldwide.[1] Individual susceptibility to kidney disease varies but tends to be higher among disadvantaged populations and those of certain ethnicities, including Aboriginal Australians, Native Americans, and people of African descent.[2] CKD also tends to manifest earlier, i.e. prematurely, in these populations compared with Caucasians and other nondisadvantaged populations. In addition to some monogenic disorders, multiple risk factors underlie the susceptibility to CKD including hypertension, diabetes, genetic factors such as ApoL1, lifestyle, socioeconomics, environmental factors in certain world regions, acute kidney injury (AKI), and infections such as hepatitis and HIV. Not every individual who has such risk factors, however, develops CKD. Increasingly, developmental factors occurring during fetal life are recognized as modulators of individuals' risk of CKD throughout their life course.[3] Multiple adverse circumstances experienced *in utero*, some of which are manifest by extremes of birth weight or preterm delivery, affect development of the fetal kidney, which then impacts lifetime risk of CKD.

The Developmental Programming Paradigm

The phenomenon of intrauterine exposures translating into lifelong risk for chronic disease, termed developmental programming, was first proposed by Barker and colleagues[4] who observed an increase in premature cardiac deaths among adults who had been born with low birth weight (LBW), decades earlier. Since then, evidence has shown that programming occurs in multiple organ systems, including the kidney, and has been recognized by the World Health Organization as an important pathway in the pathogenesis of noncommunicable diseases.[5] LBW (birth weight under 2.5 kg), being small for gestational age (SGA, birth weight <10th percentile for gestational age), or being born preterm (birth before 37 weeks of gestation) are the most obvious surrogate markers for adverse fetal developmental circumstances.[6] High birth weight (HBW, >4 kg) may also reflect suboptimal intrauterine exposures.[3,7]

Infants born with LBW, SGA, and preterm are at increased risk for premature CKD.[3] Globally 10–15%

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00020-6

of babies are born with LBW, SGA, or preterm (Table 20.1). Other developmental risk factors which have been associated with increased risk of hypertension and CKD in the offspring include maternal hyperglycemia, preeclampsia, and maternal obesity, which occur in around 15%, 4%, and up to 30% of pregnant women, respectively (Table 20.1). Many babies born each year are therefore at potential risk of CKD, which may be consistent with the estimated prevalence of CKD of around 10%.[1] Poor maternal nutrition is associated with LBW, SGA, and preterm birth in offspring; however, birth weight and prematurity are also affected by many other circumstances, including maternal age, access to antenatal care, maternal chronic disease, maternal infections, and social stress, among others.[3] HBW often results from maternal diabetes or obesity.[3] More subtle exposures that may affect fetal kidney development may not be easily detectable by history or clinically at birth but are important to consider regarding an individual's lifelong risk of CKD.[3,8]

This chapter discusses the impact of developmental programming on the kidney in terms of structure and function and the associations with long-term levels of blood pressure and kidney function. Risk factors for developmental programming are discussed in terms of global prevalence and the potential to modify these as targets for CKD prevention. Developmental programming of related conditions, such as cardiovascular disease, diabetes, and obesity, that may impact kidney function are expertly reviewed elsewhere.[3]

TABLE 20.1 Global Prevalence of Birth Weights, Preterm Birth, and Risk Factors

	Global	Ref.
Low birth weight (birth weight <2.5 kg, % live births)	15	106
Preterm birth (births, <37 weeks of gestation, %, range)	11.1 (9.1–13.4)	a
Term small for gestational age (% SGA, birth weight <10th percentile)	13.8	107
Preterm small for gestational age (% SGA, birth weight <10th percentile for gestational age)	26.6	107
High birth weight (birth weight >4 kg, %)	Up to 20	7
Preeclampsia (% deliveries)	4.6	108
Hyperglycemia in pregnancy (%)	17	109
Teenage pregnancy (adolescent births 15–19 years per 1000 deliveries)	44.1 (2015)	b
Obesity in pregnancy (BMI >30 kg/m^2 %)	Up to 32	47
Maternal iron deficiency anemia (<110 g/L, %, range)	19.2 (17.1–21.5)	110
Maternal vitamin A deficiency (serum retinol <0.70 μmol/L, %, range) 2005	7.8 (6.0–24.6)	110
Antenatal clinic attendance (% ≥four visits)	62	c

[a] http://data.un.org/Data.aspx?d=WHO&f=MEASURE_CODE%3aWHS_PBR.
[b] https://data.worldbank.org/indicator/SP.ADO.TFRT.
[c] https://data.unicef.org/topic/maternal-health/antenatal-care/.

PATHOPHYSIOLOGY

Developmental Programming in the Kidney

The Nephron Number Hypothesis

It is generally accepted that under normal circumstances nephrogenesis in humans continues *in utero* until 36 weeks of gestation, and that no new nephrons develop in term infants after birth.[9] In preterm infants, however, some nephrogenesis may continue for up to 40 days postnatally, but the nephrons formed may not be normal.[9] How nephrogenesis is modulated by preterm birth is not yet understood. Growth restriction *in utero*, the change in neonatal redox state which occurs at birth, suboptimal nutrition, and the many pharmacologic interventions required in postnatal care may all play pathogenic roles.[10] As early as 1968, Zeman[11] noted a reduction in nephron number in kidneys of LBW offspring of pregnant rats fed on a protein-deficient diet. Subsequently, building on the Barker hypothesis, Brenner and colleagues proposed that LBW may be associated with a reduced number of nephrons, and that this in turn may predispose to subsequent hypertension and kidney disease.[12] It was postulated that kidneys with fewer nephrons would be less efficient in excreting salt, and less able to withstand kidney injury, thereby contributing to a higher risk of hypertension and CKD.[12] This hypothesis could plausibly explain, at least in part, the higher rates of hypertension and CKD seen in disadvantaged populations where LBW is more prevalent.[8,13]

Experimental Corroboration of the Nephron Number Hypothesis

Many animal studies have since shown a link between various developmental exposures, including maternal dietary restrictions, reduction in uterine perfusion during gestation, maternal hyperglycemia and corticosteroid or other drug administration in pregnancy, and reduced nephron number in offspring (Table 20.2).[14,15] In many of these models, reduced

TABLE 20.2 Experimental Conditions Associated With Programming of Low Nephron Number and Kidney Function and Blood Pressure

Experimental Model	Renal Phenotype	Nephron Endowment
Uteroplacental insufficiency	↑ Apoptosis	↓
Vitamin A-deficient diet from 3 weeks before mating throughout pregnancy	Not evaluated	↓
Low sodium diet (0.07%) during pregnancy and lactation	Hypertension at 5 months	↓
High sodium diet (3%) during pregnancy and lactation	Glomerular hypertrophy, hypertension at 5 month	↓
Partial ligation of uterine ligation	↓ GFR, glomerular hypertrophy	↓
Ethanol (1 g/kg/day) at gestational day 13.5 and 14.5	↓ GFR at 6 months	↓
Lipopolysaccharide (0.79 mg/kg/day) i.p. at gestational day 8, 10, and 12	↓ GFR	↓
Dexamethasone (0.1 mg/kg/day) throughout pregnancy	↓ GFR, glomerular hypertrophy	↓
Dexamethasone (0.2 mg/kg/day) at gestational days 15 and 16 or 17 and 18	↔ GFR, unchanged glomerular morphology	↓
Low protein diet (8% protein) during lactation	Hypertension at 5 months	↓
Cyclosporine (3.3 mg/kg/day) from gestational day 10 to postnatal day 7	↔ GFR, glomerular hypertrophy	↓
50% caloric restriction during pregnancy and lactation	↔ GFR, glomerular hypertrophy, hypertension, tubulointerstitial injury	↓
Streptozotocin-induced diabetes during pregnancy	↔ GFR, hypertension, tuburointerstitial injury	↓
Multideficient diet during pregnancy	↑ GFR, glomerular hypertrophy	↓
Dexamethasone (0.1 mg/kg/day) from gestational day 16–22	Hypertension	↓
Low protein diet (85% protein) during pregnancy	↔ GFR, hypertension	↓
Iron restriction diet (3 mg/kg diet) from 1 week before mating and through pregnancy	Glomerular hypertrophy, hypertension	↓

Studies tabulated according to age at evaluation. GFR = glomerular filtration rate, ↑ = increased, ↓ = decreased, ↔ = unaltered.
Table adapted under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/) from reference 15.

nephron number in turn is associated with higher blood pressure and kidney dysfunction in later life (Table 20.2).[15,16] These associations tend to be stronger in males.[17] Although the pathophysiology of this sexual dimorphism is not yet fully understood, it may relate to differences in placental size and function, and differential growth rates of male and female fetuses, which may affect susceptibility to programming exposures.[18,19] There is, however, also varying susceptibility to gestational perturbations depending on the animal species and experimental model, as well as varying effects of the degree to which nephron number is reduced, suggesting a complex interplay of factors likely determines final nephron number.[3,14,15]

A pathophysiologic link between reduced nephron number and CKD is plausible. In the setting of a reduced nephron number, filtration surface area has been observed to be relatively preserved as a result of compensatory glomerular hypertrophy.[20] Whole-kidney glomerular filtration rate (GFR) therefore may not change in the setting of a mild or moderately reduced nephron number; however, single nephron GFR (SNGFR) should be increased. Indeed, in the Munich Wistar Fromter rat, which develops spontaneous glomerular injury, nephron numbers are reduced and SNGFR is increased compared with control rats.[21] Sustained hyperfiltration would be expected to increase susceptibility to further renal injury, as illustrated in Figure 20.1.

Consistent also with the nephron number hypothesis, experimental salt-sensitivity (increase in systemic blood pressure in response to a sodium load) has been

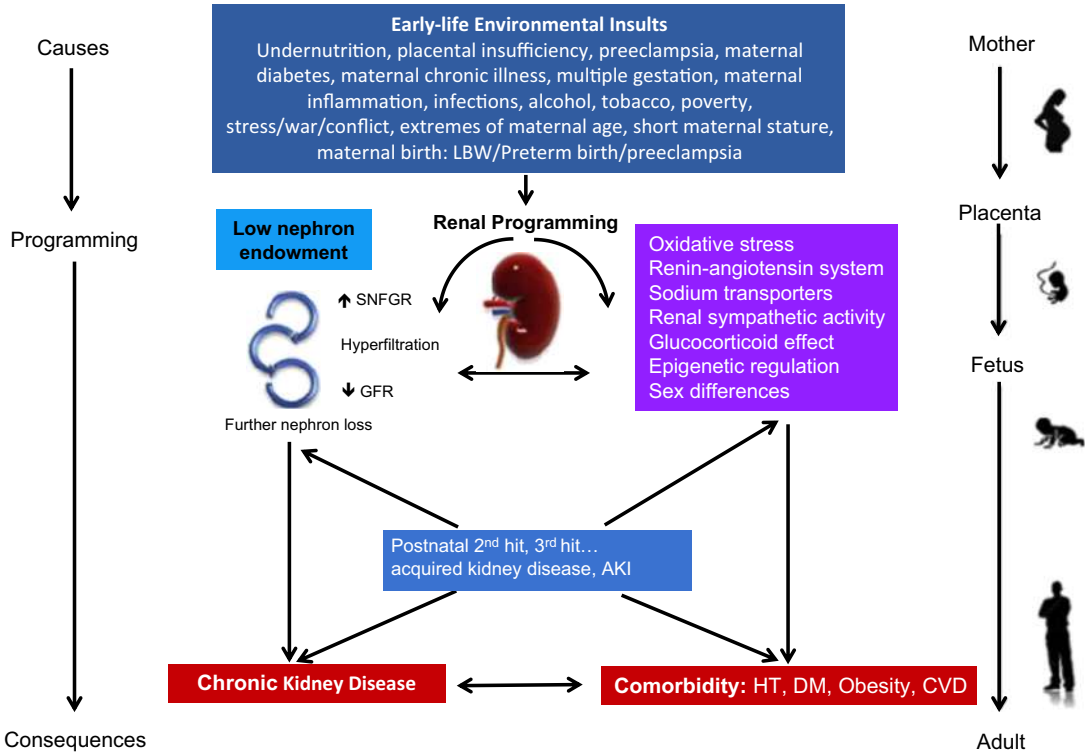


FIGURE 20.1 Representation of interactions between risk factors and pathophysiology of developmental programming in the kidney and modulation of renal disease risk by events accumulating over the life course. *Adapted under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/) from reference 15.*

reported in association with LBW and low nephron number or exposure to diabetes *in utero*.[22,23] This, however, is not universal, and in some models is only inducible with aging. Interestingly, in glial cell line-derived neurotrophic factor (GDNF) heterozygous mice, which have either 65% or 25% fewer nephrons than wild-type mice, depending on whether they have one or two kidneys, the degree of salt sensitivity was found to be proportional to the nephron endowment.[24] Consistent with this, having 30% more nephrons protected transforming growth factor-β2 heterozygous mice from developing high blood pressure with chronic salt loading.[25] Nephron number and filtration surface area therefore appear to be factors predisposing to programmed hypertension.

That not all experimental programming interventions lead to lower nephron number, hypertension or kidney disease, however, may explain some of the variability in hypertension and CKD risk observed in humans.[3] It is likely that programming of nephron number may be the first "hit," which increases susceptibility of the kidney to subsequent "hits" such as a primary kidney disease, programmed hypertension, or diabetes, which then leads to premature CKD (Figure 20.1).[3,26] It is not yet known whether a reduced nephron number *per se* affects the risk of AKI, or a kidney's capacity to recover from AKI, beyond a recognized significantly increased risk of AKI among preterm neonates.[3] LBW rats were, however, more susceptible to ischemia reperfusion injury than normal birth weight (NBW) rats, suggesting increased susceptibility to AKI.[27]

Experimental Evidence of Additional Programmed Changes in the Kidney

In some experimental models, modulation of the amino acid composition of maternal low protein diets abrogated the development of hypertension in rat offspring, despite persistence of low nephron numbers; in other models, augmentation or nephron number through postnatal hypernutrition did not prevent hypertension.[28,29] A recent report found that the salt-sensitive hypertension observed in GDNF heterozygous mice was associated with an increase in total body chloride, but not in total body sodium.[30] This finding remains unexplained but suggests that sodium retention may not be the only mechanism contributing to programmed hypertension. Taken together, these observations suggest that a reduction in nephron number does not explain all programmed hypertension; therefore, other potential programming effects in the kidney have been investigated.[16]

Altered Renal Sodium Transport In various LBW models and offspring of diabetic rats, expression of the tubule sodium transporters Na-K-2Cl (NKCC2) and Na-Cl and sodium-hydrogen exchanger type III was significantly increased, and activity of both NKCC2 and ENaC was significantly increased.[16] A programmed increase in sodium transport in all segments of the renal tubule therefore seems likely, although it is not known whether this is related to glomerulotubular balance required in the setting of fewer nephrons or is intrinsic to the transporters.

Renin–Angiotensin–Aldosterone System Dysregulation of elements of the renal renin–angiotensin–aldosterone system (RAAS) has been described in various programming models. Inhibition of this system during kidney development is often associated with system upregulation in adulthood and changes in blood pressure.[31] Such changes are model- and timing-dependent and are differentially regulated by sex hormones.[31] For example, aldosterone levels were higher among adolescent male offspring of mothers who had preeclampsia who had been preterm and very LBW, although the effect was attenuated when adjusted for body mass index (BMI).[32] Plasma angiotensin II/Ang-(1-7) and urinary angiotensin II/Ang-(1-7) levels were increased in adolescents who had been born preterm; however, these differences were variably modulated by gender, obesity, or prenatal corticosteroid exposure.[33,34] Among matched 18- to 29-year-old subjects who had been born preterm or at term, renin and alamandine levels were significantly higher among those born preterm, which correlated with higher blood pressure, smaller kidneys, and higher urine albumin excretion.[35] When stratified by gender, renin levels were higher in males in both birth groups, but alamandine levels were significantly higher among preterm males.[35] The interactions of multiple developmental exposures and offspring gender on programmed changes in the RAAS is highly complex and requires further investigation, especially to understand the utility of medications that modulate this system.

Sympathetic Nervous System and Renal Vascular Reactivity The sympathetic nervous system contributes to blood pressure regulation through modulation of RAAS activity, sodium transport, and vascular tone.[36] Renal denervation modulates blood pressure and sodium transporter expression in LBW rats and is associated with differential age and gender effects.[37,38]

Factors Impacting Renal Programming

Maternal Nutrition

Maternal nutrition, preconception and throughout pregnancy, has an important impact on pregnancy outcomes and fetal growth.[3,5] Mothers who themselves may have been born small, as reflected by short maternal stature or maternal underweight, are anemic, smoke, drink alcohol, or consume caffeine during pregnancy have a higher risk of having a LBW, SGA, or preterm infant.[3,16] Maternal diets deficient in calories, protein, Vitamin A, sodium, zinc, or iron have been associated with reduced nephron numbers in offspring of experimental animals (Table 20.2).[8] Maternal vitamin A deficiency was associated with smaller newborn kidney size in Indian neonates.[39] Optimization of maternal nutrition is therefore important for fetal kidney development.

In humans, exposure to famine at the time of conception or at various stages of gestation has also been associated with higher risk of hypertension, proteinuria, and renal dysfunction in offspring in later life.[8] In these studies, blood pressures were higher and rose earlier in Nigerian compared with Caucasian and Chinese populations.[8,40,41,42] Fasting during Ramadan has not been found to affect offspring birth weight, which may suggest that intermittent fasting may not affect fetal growth.[43]

Maternal Diabetes and Obesity

HBW is associated with an increased risk of later life hypertension, obesity, diabetes, and kidney disease.[3] HBW is often a complication of maternal obesity or diabetes in pregnancy, which are becoming increasingly common worldwide (Table 20.1).[5] Infants of diabetic mothers have an increased risk of congenital abnormalities, including of the kidney.[44] In experimental animals, offspring of diabetic mothers have reduced nephron numbers in proportion to the degree of maternal hyperglycemia; however, control of maternal glucose with insulin in the latter half of pregnancy failed to restore nephron number in mice, suggesting a very early effect of hyperglycemia.[45,46] These observations emphasize the importance of good and early control of maternal blood sugar, ideally before conception, and the need to screen for gestational diabetes.

Maternal obesity is associated with a higher risk of pregnancy complications including gestational diabetes, hypertensive disorders of pregnancy, preterm birth, HBW and LBW, and perinatal mortality.[3,47] Nephron numbers were found unchanged or increased in rat and mice offspring of high-fat fed mothers, although in some blood pressures were high and renal injury and proteinuria were evident.[48,49] Studies of children of obese mothers have shown an increased risk of ischemic heart disease, type 2 diabetes, and obesity, suggesting a potential indirect, if not direct, impact on CKD risk in these individuals.[47]

Uteroplacental Insufficiency

Reduction in uteroplacental blood flow restricts nutrient transfer to the fetus and induces LBW, low

nephron number, and hypertension in rat offspring, which is more evident in males.[50] In high-income countries, placental insufficiency is a common cause of fetal growth restriction, given increasing pregnancies at advanced maternal age, maternal chronic illness, and use of assisted reproduction technologies. Therefore, even in settings where nutrition may be adequate, fetal nutrition may not be optimal.[3] Recent evidence points to differences in male and female placentas which may enhance male susceptibility to developmental programming and may explain some of the observed sexual dimorphism in developmentally programmed risk for CKD.[19] Preeclampsia and gestational hypertension are common and are common causes of placental insufficiency (Table 20.1). Higher blood pressures have been observed in children born in preeclamptic pregnancies, but systematic study of renal function in such patients has not been performed.[51]

Fetal Exposure to Glucocorticoids

Under conditions of maternal stress or exogenous therapy, fetal exposure to glucocorticoids can increase.[52] The effect of maternal dietary protein restriction on offspring nephron number and blood pressures in rats has also been found to be mediated at least in part by increased fetal steroid exposure.[52] Fetal glucocorticoid exposure is associated with reduced nephron numbers and higher blood pressures in experimental animals (Table 20.2).[14,15] Short-term perinatal exposure to corticosteroids is common in human infants at low gestational age, but so far there has been no consistent evidence of increased blood pressure or kidney dysfunction long term.[53] Follow-up of children of mothers treated with steroids throughout pregnancy has not been systematically performed.

Fetal Exposure to Medication

Exposure to exogenous medications or substances during fetal life may affect nephrogenesis (Table 20.2).[3] Medications including aminoglycosides, ampicillin, ceftriaxone, and cyclosporine, which may be commonly used during pregnancy or early postnatally, especially in preterm infants, impact nephrogenesis in animals.[3,16] Caution with use of these medications in humans is therefore advised. Longer follow-up studies of individuals exposed to these medications are required.

Congenital Obstruction of the Kidney

Congenital obstruction is a major cause of childhood end-stage renal disease (ESRD).[54] Congenital abnormalities of the urinary tract are frequently associated with obstruction and impaired nephrogenesis, which may be further impacted by associated fetal growth restriction.[54] Animal studies have also shown that long-term changes also occur in the contralateral unobstructed kidney, suggesting that relief of obstruction should occur as early as possible to rescue both kidneys. Long-term follow-up of such patients is required.[54]

Common Genetic Variants

Many genes implicated in congenital abnormalities of the kidney and urinary tract are associated with branching morphogenesis. Compared with wild-type alleles, common polymorphisms[16,55] in *PAX2* and *RET* and *BMPR1A* which regulate ureteric bud signaling and branching, *OSR1*, which interferes with mRNA splicing, and the angiotensin-converting enzyme (ACE) gene were all associated with approximately 10% reductions in newborn kidney volume and nephron number. In contrast, a common variant of the *ALHD1A2* gene, which modulates RET expression in the ureteric epithelium, was associated with 22% larger newborn kidneys. Such polymorphisms may therefore contribute to population variance in nephron number, although interactions with birth weight remain to be studied.

Epigenetics

Dietary composition, the degree of nutrient restriction, specific amino acid content, and source of carbohydrate may all affect nephrogenesis through epigenetic DNA methylation, increased fetal exposure to glucocorticoids, angiogenesis, and global downregulation of gene expression.[8,15] In addition, diabetes and obesity-associated programming effects are mediated *via* inflammation, oxidative stress, and epigenetic processes.[15,47] Epigenetic processes therefore may be modifiable, but further work is required to understand their role in determining organ structure and the premature aging and organ dysfunction observed in programmed animals.[15]

Nephron Number in Human Kidneys

Thus far, it has only been possible to estimate nephron number in human kidneys *post mortem*, using the physical disector/fractionator technique.[56] New techniques are being developed to estimate nephron number *in vivo* based on kidney biopsies combined with CT scan measurements of kidney volume or measurements which appear relatively consistent with post-mortem estimates.[57] Promising MRI techniques are also being investigated, which may permit direct correlation of nephron number with kidney function.[58]

Overall, the average number of nephrons per kidney is around 1,000,000, but this ranges from 210,000 to 2.7 million per kidney.[59] This high interindividual variability likely contributes to the interindividual susceptibility to CKD. Much of this variability already exists at birth, pointing to a programming effect.[60,61] Nephron number in humans increases with gestational age and is therefore reduced in infants born preterm compared

with term infants.[9,62] Whether the reduced nephron number observed in preterm infants reflects cessation of nephrogenesis at the time of birth, the impact of factors which may have predisposed to preterm birth, the frequent accompanying growth restriction, deranged nephrogenesis which can continue for a few weeks after birth, or a combination of these is unknown.[10] Growth restriction *in utero* is also associated with reduced nephron number, which has been found to be lower in infants with LBW or born SGA, compared with those born with appropriate birth weights for gestational age (AGA).[9,63,64]

In a population of 58 Caucasian and African Americans, aged 1.5–50 years and having birth weights ranging from 2.18 kg to over 4 kg, Hughson and colleagues[65] reported a correlation between birth weight and glomerular numbers, predicting an increase of 257,426 glomeruli per kg increase in birth weight ($r = 0.423$, $p = 0.0012$, Figure 20.2). When the analysis was confined to 11 individuals who had died under 18 years of age, to control for the known decline in nephron number with age, the regression coefficient predicted a steeper increase of 518,038 glomeruli per kg increase in birth weight ($r = 0.773$, $p = 0.0053$).[65] In this study, females had a nonsignificant 9% fewer glomeruli than men, but the association with birth weight was stronger in men. There was no difference in glomerular number between Caucasian and African-American subjects.[65] Only African-American subjects had birth weights <2.5 kg ($n = 4$). Four of six subjects with birth weights >3.8 kg were African American, which may explain the wide range of nephron numbers seen in these subjects.[65] In further studies, the highest and lowest observed nephron numbers have been seen among African Americans, with the range approaching 13-fold, compared with 2- to 7-fold in other populations.[59]

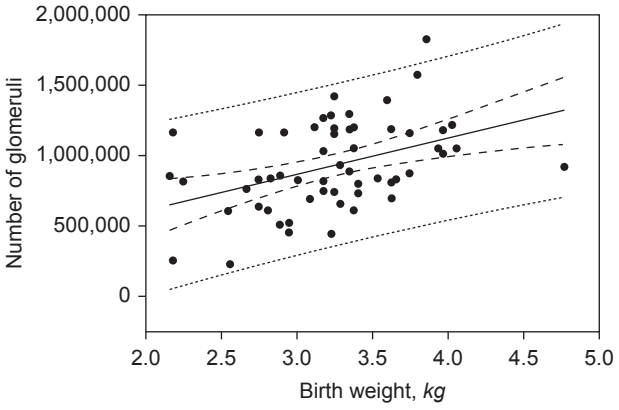


FIGURE 20.2 The relationship between birth weight and total glomerular number. Symbols are (•) Nglom vs. birth weight; (——) Nglom vs. birth weight regression; (– –) 95% regression CI; and (……) regression prediction interval. The regression coefficient predicts a gain of 257,426 glomeruli per kg increase in birth weight, $r = 0.423$, $p = 0.0012$, $N = 56$, all ages included (Nglom—glomerular number). *Figure reproduced with permission from reference 65.*

Clinical Correlates for Nephron Number and Renal Programming

As nephron number cannot currently be measured *in vivo*, potential clinical markers highlighting risk of reduced nephron numbers include female gender, shorter adult height, maternal vitamin A deficiency, and Australian Aboriginal or Japanese ethnicity, in addition to LBW, SGA, preterm birth, and possibly HBW.[13,39,66] Glomerular hypertrophy increases inversely with nephron number. Therefore, glomerulomegaly on biopsy may be a crude indicator of reduced nephron numbers.[59] Kidney weight/size correlates positively with glomerular number, although more strongly in infants than in adults.[67]

DIAGNOSIS

Developmental Associations with Blood Pressure

Systematic reviews have found associations between LBW,[68] preterm birth,[69] HBW (in children but not adults),[70] being born to mothers with diabetes (in males but not females)[71] or preeclampsia,[51] and subsequent risk of higher blood pressures and hypertension.[3] All of these observations strongly suggest a developmental programming impact on lifelong risk of hypertension.[3]

Among children who had been born with LBW or preterm, blood pressures may be higher but are generally still within the normal range. As these populations age, blood pressures reach hypertensive ranges.[68] Male gender, BMI, and rate of "catch-up" growth in early childhood appear to modify the relationship between blood pressure and birth circumstances in childhood and adolescence.[72] These associations between developmental exposures and blood pressure have been most frequently studied in Caucasian populations, although evidence from other ethnic groups is largely similar.[72] The association is, however, less consistent among children of African origin, suggesting that birth weight may be one of several factors contributing to the overall higher risk of hypertension in this population.[72,73] Recent data from a multiethnic cohort of adolescents participating in the NHANES study (aged 12–15 years) found an increased odds of hypertension (blood pressure ≥95th percentile for age, height, and sex) among those who had been LBW (OR 2.90, 95% CI 1.48–5.71) or very low birth weight (VLBW, <1500 g at birth: OR 5.23, 95% CI 1.11–24.74).[74] Large twin studies, which permit controlling for genetic contributors to

blood pressure, have corroborated the association between lower birth weights and higher blood pressures, suggesting an important role for the intrauterine environment in programming risk of hypertension.[75]

Nephron Number and Blood Pressure

Nephron numbers have been found to be lower in adults with essential hypertension compared with normotensive subjects.[13,66,76] Although the birth weights were unknown in these studies, the association supports a role for lower nephron number in development of hypertension. In a cohort of subjects where blood pressures and birth weights were available in the same individuals, a significant correlation was found between birth weight and nephron number, blood pressure and nephron number, and blood pressure and birth weight among Caucasian subjects.[77] These relationships did not reach significance among African-American subjects; however, hypertension was twice as prevalent among African Americans with nephron numbers below the mean, suggesting that developmental programming likely contributes to the risk of hypertension in this population.[77] The observation that salt sensitivity is more prevalent among subjects with lower birth weights (<3050 g vs. higher) is consistent with a likely role for nephron number in blood pressure regulation.[78]

Developmental Associations with Kidney Function

Nephron Number and CKD

One study has examined nephron numbers in subjects with known CKD. Among Japanese men with CKD, glomerular numbers were significantly lower than among matched men without CKD (mean nephron numbers 298,348 ± 116,526 in CKD vs. 666,140 ± 159,775 without CKD, $p < 0.001$).[66] Lower nephron numbers were associated with greater glomerular hypertrophy. The authors suggested these findings are unlikely to reflect loss of nephrons secondary to CKD, as the number of sclerosed glomeruli was similar in both groups.

Birth Weight, Preterm Birth, and Kidney Function

Individuals born with a severe reduction in nephron number, such as those with renal hypoplasia or unilateral renal agenesis, develop early and progressive proteinuria and renal dysfunction.[79] A frequent argument against the nephron number hypothesis, however, is that loss of a single kidney through kidney donation, although associated with higher risks of hypertension and proteinuria, has infrequently been associated with long-term kidney failure.[80] This risk has, however, recently been found to be higher than previously thought, especially in African Americans compared with Caucasians, and in overweight individuals, which may suggest a programming effect.[81] How many nephrons are enough to protect an individual from future CKD is not known and may depend on the degree of nephron deficit and the severity of the subsequent "hits," including the development of hypertension and obesity after being born small. Intriguingly, the timing of nephron loss may also be important. In experimental animals, uninephrectomy before nephrogenesis was completed, compared with uninephrectomy in adulthood, and was associated with later-life higher blood pressure and accelerated loss of kidney function.[82,83]

Glomerular Filtration Rate

As discussed above, because of compensatory glomerular hypertrophy, filtration surface area in kidneys with fewer nephrons is similar to that in kidneys with normal nephron numbers.[20] GFR at baseline would therefore be expected to be preserved. If kidneys with fewer nephrons are constantly hyperfiltering, however, they would have less functional reserve capacity in the face of superimposed injury or injury accruing over time, and GFRs would decline. Indeed, LBW and preterm birth are now recognized risk factors for reduced GFR.[3] Meta-analysis of five studies including data from over 27,000 subjects reported an overall odds ratio of 1.79 (95% CI, 1.31−2.45) for eGFR <60 mL/min/1.73 m^2 and/or eGFR 10th percentile for sex with LBW (Table 20.3).[84] The odds of a reduced GFR were nonsignificantly higher in males. A distinction between LBW resulting from growth restriction or preterm birth was not made in this analysis, and studies on very preterm (<32 weeks gestation) and VLBW (<1500 g birth weight) subjects were excluded. Preterm birth has, however, also been associated with lower renal function compared with subjects born at term.[10,85,86] Measured GFRs were lower in children aged 7 years who had been born preterm and experienced intrauterine growth restriction or growth restriction immediately postbirth, compared with those who maintained appropriate weights for their gestation age, suggesting an additional effect of growth restriction on longer-term kidney function.[87] Consistent with this, a trend toward reduced renal functional reserve capacity was observed in young adults born preterm with SGA, compared with preterm AGA and term with NBW.[88] Indeed, in the NHANES cohort described above, the odds of a reduced GFR was higher among those born with VLBW (OR 2.49, 95% CI 1.20−5.18) than with LBW (OR 1.49, 95% CI 1.06−2.10), suggesting a compounding effect of growth restriction (Table 20.3).[74] This study estimated a population attributable fraction among adolescents with systolic blood pressures ≥95th percentile and/or eGFR <90 mL/min/1.73 m^2 of 1 in 13 for LBW or 1 in

TABLE 20.3 Associations Between Birth Weight and Preterm Birth and Later Risk of CKD[§]

Age	Subject Number	Study Design	Renal Outcome	Programming Risk Marker	Risk Ration	Ref.
12–75 years	46,249 subjects	Systematic review and meta-analysis (18 studies)	CKD	Low birth weight (BW <2.5 kg)	OR 1.73 (1.44–2.08)	84
			ESRD		OR 1.58 (1.33–1.88)	
			Albuminuria		OR 1.81 (1.19–2.77)	
			↓ GFR*		OR 1.79 (1.31–2.45)	
<21 years	1994 cases 20,032 controls	Case–control study (USA)	Childhood CKD[#]	Low birth weight (BW <2.5 kg)	OR 2.88 (2.28–3.63)	44
				Maternal diabetes	OR 1.54 (1.13–2.09)	
				Maternal overweight	OR 1.24 (1.05–1.48)	
				Maternal obesity	OR 1.26 (1.05–1.52)	
				High birth weight (BW >4.0 kg)	OR 0.97 (0.79–1.21)	
Birth 1992–2010	447 cases 20,619,622 controls	Pediatric population (Japan)	Childhood CKD	LBW childhood (<2.5 kg)	PAF 21.1% (16.0–26.1)	94
				Preterm birth	PAF 18.2 % (16.5–25.6)	
			CAKUT	LBW childhood (<2.5 kg)	RR 3.31 (2.40–4.56)	
12–15 years	5352	NHANES (USA)	↓ GFR[¶]	LBW (<2.5 kg)	OR 1.49 (1.06–2.10)	74
				VLBW (<1.5 kg)	OR 5.23 (1.11–24.74)	
			Albuminuria	LBW (<2.5 kg)	OR 0.98 (0.64–1.51)	
				VLBW (<1.5 kg)	OR 0.53 (0.20–1.46)	
1–42 years	1,852,080 subjects (527 developed ESRD)	Population/Renal registry (Norway)	ESRD	LBW (BW <10th percentile)	HR 1.63 (1.29–2.06)	97
				LBW (BW <2.5 kg)	2.25 (1.59–3.19)	
				Term/SGA	1.54 (1.2–1.96)	
				Preterm/AGA	1.09 (0.69–1.73)	
				Preterm/SGA	4.03 (2.08–7.8)	
				Preterm/LBW	1.89 (1.25–2.86)	
29.3 ± 7.0 (ESRD) 35.1 ± 8.1 (no ESRD)	471 with IgA (74 developed ESRD)	Population/IgA nephropathy (Norway)	ESRD	LBW, male (BW <10th percentile)	HR 2.2 (1.1–4.4)	26
				LBW, female (BW <10th percentile)	HR 1.3 (0.3–5.8)	
				SGA, male (<10th percentile for GA)	HR 2.7 (1.4–5.5)	
				SGA, female (<10th percentile for GA)	HR 0.8 (0.1–5.9)	
Birth 1924–1944	20,431 (followed until death or 86 years)	Helsinki Birth Cohort (Finland)	CKD	Per increase SD of birth weight, male	HR 0.73 (0.64–0.83)	18
				Per increase SD of birth weight, male	HR 0.99 (0.84–1.16)	
				Preterm birth (<34 week), male	HR 2.1 (0.9–4.9)	
				Preterm birth (<34 week), female	HR 3.2 (1.4–7.4)	

HBW, high birth weight; *HR*, hazard ratio; *LBW*, low birth weight; *OR*, odds ratio; *PAF*, population attributable fraction; *RR*, relative risk; *SGA*, small for gestational age.
[§]*Included studies population-based, registries, or meta-analyses.*
* *eGFR <60 mL/min/1.73 m^2 or and eGFR 10th percentile for sex.*
[#]*Including reduced renal function, renal dysplasia and/or aplasia, and obstructive uropathy.*
[¶]*eGFR <90 mL/min/1.73 m^2.*

5 for VLBW.[74] Twin studies have also demonstrated a consistent association between lower birth weight and lower creatinine clearances, highlighting the impact of feto-placental factors in renal programming.[89] Renal functional reserve capacity was also reduced in young adults who were born in diabetic pregnancies compared with those with diabetic fathers, again pointing to an environmental impact during gestation rather than genetic factors.[90]

Reduced renal function may, however, not only reflect reduced glomerular filtration but may also reflect abnormal renal tubular function. Whether tubular function may be independently programmed or result from congenital obstruction or perinatal AKI in individuals born with LBW or preterm remains to be elucidated.[54,85]

Proteinuria

If kidneys with low nephron numbers do indeed hyperfilter at baseline, over time this may manifest as proteinuria. Across eight studies and 6758 individuals, a meta-analysis reported an odds ratio of 1.81 (95% CI, 1.19−2.77) for albuminuria with LBW (Table 20.3).[84] The prevalence of albuminuria was also increased among 4-year-old children with normal height who had been born preterm.[91] Albuminuria was not significantly increased among preterm children who remained short, suggesting exacerbation of risk of albuminuria with catch-up growth in height. Among 19-year olds who had been preterm with VLBW, albuminuria was highest among those who had been SGA compared with AGA, again suggesting an additional programming effect of growth restriction.[86] LBW and VLBW, however, were not associated with increased albuminuria in the NHANES cohort despite reduced GFRs, which may be a true observation or may reflect potential inaccuracy introduced by a single-spot measurement for albuminuria.[74]

Among Pima Indians, a U-shaped relationship was observed between birth weight and proteinuria, with the risk being elevated at birth weights below 2.5 kg or over 4.5 kg. Proteinuria was most strongly associated with having been exposed to diabetes during gestation.[92]

Developmental Associations with CKD

Chronic Kidney Disease

Meta-analysis of 18 studies including over 2 million subjects reported an odds ratio for a composite endpoint of CKD (albuminuria, decreased GFR, or ESRD) of 1.73 (95% CI, 1.44−2.08) with LBW (Table 20.3).[84] A recent Finnish study examined this association across the life course (Table 20.3).[18] Among men, the hazard ratio for CKD was found to decrease by 0.73 (95% CI, 0.64−0.83) for every increase in standard deviation of birth weight and by 0.81 (95% CI, 0.7−0.93) for birth length. This increased risk in men was seen at all ages but was higher among those under 60 years of age and for hypertensive CKD (HR 0.57, 95% CI 0.40−0.80).[18] Among women, the risk of CKD was significantly higher if they had been born before 34 weeks of gestation (HR3 3.2, 95% CI 1.4−7.4).[18]

Among children born preterm, case series have shown evidence of secondary focal and segmental glomerulosclerosis (FSGS) and glomerulomegaly in kidney biopsies performed for proteinuria.[93] This observation suggests a programmed predisposition to hyperfiltration and glomerulosclerosis. LBW and preterm birth are associated with CKD in children, with a population attributable fraction around 20% (Table 20.3).[44,94] Exposure to maternal diabetes, overweight, and obesity is also associated with a higher risk of childhood CKD, including dysplasia/aplasia and congenital obstruction (Table 20.3).[44]

Preterm birth is a major risk factor for neonatal AKI.[3,10] The long-term impact of this on pediatric and adult CKD is not yet known.

It is unlikely that developmental alterations in kidney development alone are enough to cause CKD, but a smaller kidney, which may be hyperfiltering at baseline, may be more susceptible to superimposed kidney stresses or injury, and lose function more quickly (Figure 20.1). Indeed, several studies have reported associations of greater severity or more rapid progression of a variety of primary kidney disorders in individuals who had LBW.[3]

Conceivably, hyperfiltration injury would also be exacerbated in the face of increased BMI. Consistent with this, among children born preterm who had experienced neonatal AKI or who had proteinuric kidney disease, obesity and excessive weight gain were associated with more rapid loss of kidney function.[8,95] A recent study of young Australian Aboriginal adults also illustrates the likelihood of the "multihit" hypothesis in programmed CKD. Albuminuria levels were highest among individuals who simultaneously had been of LBW, had poststreptococcal glomerulonephritis, and had higher BMIs.[96]

End-Stage Renal Disease

In a meta-analysis of four studies reporting associations of birth weight with ESRD, the odds of ESRD with LBW were found to be 1.58 (95% CI, 1.33−1.88) (Table 20.3).[84] A subsequent Norwegian registry study, restricted to subjects under 42 years, reported a hazard ratio for ESRD of 1.63 (95% CI 1.29−2.06) for LBW (defined as birth weight <10th percentile) (2.87 kg for males, 2.8 kg for females) and of 2.25 (95% CI 1.59−3.19) for LBW defined as < 2.5 kg (Table 20.3).[97] Overall, the risk of ESRD was increased in all those

born SGA (HR 1.67, 95% CI 1.30−2.07), but not in those born preterm (HR 1.36, 95% CI 0.91−1.99). When both preterm birth and SGA coexisted, however, the risk was markedly increased (HR 4.03, 95% CI 2.08−7.80).[97] When the analysis was restricted to subjects between 18 and 42 years, in an attempt to control for potential confounding from congenital causes of early ESRD, SGA remained the only significant association with ESRD in both term (HR 1.53, 95% CI 1.15−2.03) and preterm (HR 4.2, 95% CI 1.79−9.03) individuals.[97] These findings suggest that growth restriction (SGA) may be the most important risk marker for renal programming.

The incidence rate ratio of developing ESRD after exposure to diabetes during gestation was found to be 4.12 (95% CI 1.54−11.02) compared with nonexposure in a cohort of Pima Indians younger than 45 years.[98] Birth weights were not reported in this study, but this effect appeared to be largely driven by earlier onset of diabetes in these subjects compared with those whose mothers had not been diabetic during pregnancy, demonstrating that renal disease risk can be indirectly impacted through developmental programming of related disorders, in this case diabetes. In a multiracial US dialysis cohort, HBW was associated with a significantly increased risk of ESRD among those with diabetes (OR 2.4, 95% CI 1.3−4.2).[99] HBW may have resulted from exposure to maternal diabetes.

TREATMENT

Optimization of Maternal Health and Nutrition

Given the associations between fetal growth restriction, preterm birth, maternal diabetes and obesity, and preeclampsia with developmental programming of hypertension and kidney disease, optimization of maternal health and maternal and fetal nutrition during pregnancy may have a long-term impact on offspring blood pressure and kidney function.[8] Potential experimental strategies to rescue nephron number are reviewed in reference 16.

In humans, routine micronutrient supplementation, as a means to improve fetal growth and early childhood outcomes, has been introduced in many countries. Overall, from a comprehensive global review, iron and folate supplementation reduced the incidence of LBW by 19%, multiple micronutrient supplements reduced LBW by 11−13%, and balanced energy supplementation reduced SGA births by 34%.[100] Vitamin A supplementation did not change birth weights.[100] In terms of impact on blood pressure and kidney function, as recently reviewed by Lee and colleagues[101] from 10 studies, blood pressure and microalbuminuria at age 10 years were not affected by maternal vitamin A supplementation. Maternal supplementation with folate was associated with a reduction in microalbuminuria in 6- to 8-year-old Nepalese children, higher maternal blood folate levels were associated with larger kidney size in Dutch children, and GFR in 4- to year-old children in Bangladesh was higher among those whose mothers had received higher dose iron supplementation.[101] Given the relatively young ages and the diverse settings of these studies, firm conclusions regarding supplementation strategies cannot yet be drawn.

Optimization of maternal health prior to and during pregnancy through optimizing nutrition, socioeconomic support, education, ensuring access to health care, planned pregnancy, and attendance at antenatal clinic are all associated with improved pregnancy outcomes.[3] Treatment or prophylaxis for infections such as syphilis, malaria, and lower genital infections in pregnant women are associated with reductions in SGA and preterm births.[102] Management of maternal diabetes and obesity before and during pregnancy can improve outcomes.[3,5] Prophylaxis with aspirin and calcium can prevent preeclampsia.[3]

Intergenerational Effects of Programming

The risk of gestational diabetes and/or preeclampsia is increased in women who themselves had been preterm, and, in turn, preeclampsia is a major risk factor for preterm delivery and fetal growth restriction.[3,103] The risk of gestational diabetes is increased in women who themselves had a low or a high birth weight.[104] Having herself been born from a preeclamptic pregnancy increases a woman's risk for preeclampsia.[105] All these factors contribute to pregnancy outcomes and affect the infant's subsequent risks for the same outcomes.[3] Careful identification of these risks in such women may permit attenuation of the risk and reduction of risk in subsequent generations.[3,16]

Optimization of Infant and Child Health to Preserve Kidney Function

Documentation of birth weight and gestational age is important to identify children who may have experienced developmental programming. Careful avoidance of nephrotoxins and optimization of growth and nutrition in preterm infants may reduce AKI and permit nephrogenesis to proceed.[3] Close attention should be paid to timely management of congenital obstruction.[54] In children born small, avoidance of rapid catch-up growth and overweight/obesity through nutrition and physical exercise can reduce the long-term risks of development of hypertension and CKD.[3] In children with FSGS and proteinuria, response to inhibitors of the renin−angiotensin system has been favorable.[93]

CONCLUSIONS

Hypertension and CKD are common in disadvantaged communities, which are often the same communities where maternal health is suboptimal and risk factors for poor pregnancy outcomes are highly prevalent.[2,3,16] Diverse environmental exposures during gestation impact fetal growth and nephrogenesis, which in turn affect the risk of hypertension and kidney disease throughout the life course.[3] Being SGA is the strongest risk predictor for renal programming. Worldwide millions of babies are born each year who may have experienced developmental programming. Infants and mothers of infants who are growth restricted, preterm, of HBW, or who experienced preeclampsia or gestational diabetes require lifelong follow-up. Their programmed risk promises to be mitigated by adherence to healthy lifestyles, and early diagnosis and treatment of high blood pressure, diabetes, overweight, or kidney dysfunction. Prevention of developmental programming is the most proximal form of primary prevention. A holistic, multisectoral approach to optimize health of women and girls from birth throughout childbearing and beyond is therefore required to improve their socioeconomic and physical circumstances and improve pregnancy outcomes globally.

References

1. Bikbov B, Perico N, Remuzzi G, on behalf of the GBDGDEG. Disparities in chronic kidney disease prevalence among males and females in 195 countries: analysis of the global burden of disease 2016 study. *Nephron* 2018;**139**(4):313–8.
2. Garcia-Garcia G, Jha V, World Kidney Day Steering C. CKD in disadvantaged populations. *Kidney Int* 2015;**87**(2):251–3.
3. Low Birth Weight and Nephron Number Working Group. The impact of kidney development on the life course: a consensus document for action. *Nephron* 2017;**136**(1):3–49.
4. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *Br Med J* 1989;**298**(6673):564–7.
5. World Health Organisation Regional Office for Europe. *Good maternal nutrition. The best start in life*. 2016. http://www.euro.who.int/__data/assets/pdf_file/0008/313667/Good-maternal-nutrition-The-best-start-in-life.pdf?ua=1.
6. Lee AC, Katz J, Blencowe H, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. *Lancet Glob Health* 2013;**1**(1):e26–36.
7. Koyanagi A, Zhang J, Dagvadorj A, et al. Macrosomia in 23 developing countries: an analysis of a multicountry, facility-based, cross-sectional survey. *Lancet* 2013;**381**(9865):476–83.
8. Luyckx VA, Brenner BM. Birth weight, malnutrition and kidney-associated outcomes–a global concern. *Nat Rev Nephrol* 2015;**11**(3):135–49.
9. Rodriguez MM, Gomez AH, Abitbol CL, Chandar JJ, Duara S, Zilleruelo GE. Histomorphometric analysis of postnatal glomerulogenesis in extremely preterm infants. *Pediatr Dev Pathol* 2004;**7**(1):17–25.
10. Luyckx VA. Preterm birth and it's impact on renal health. *Semin Nephrol* 2017;**37**(4):311–9.
11. Zeman FJ. Effects of maternal protein restriction on the kidney of the newborn young of rats. *J Nutr* 1968;**94**(2):111–6.
12. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? *Am J Hypertens* 1988;**1**(4 Pt 1):335–47.
13. Hoy WE, Bertram JF, Denton RD, Zimanyi M, Samuel T, Hughson MD. Nephron number, glomerular volume, renal disease and hypertension. *Curr Opin Nephrol Hypertens* 2008;**17**(3):258–65.
14. Luyckx VA, Brenner BM. The clinical importance of nephron mass. *J Am Soc Nephrol* 2010;**21**(6):898–910.
15. Tain YL, Hsu CN. Developmental origins of chronic kidney disease: should we focus on early life? *Int J Mol Sci* 2017;**18**(2).
16. Luyckx VA, Moritz KM, Bertram JF. Developmental programming of blood pressure and renal function through the life-course. In: Yu AS, Chertow GM, Taal HR, Marsden PA, Skorecki K, Luyckx VA, editors. *The kidney*. Philadelphia: Elsevier; 2019.
17. Ojeda NB, Intapad S, Alexander BT. Sex differences in the developmental programming of hypertension. *Acta Physiologica* 2014;**210**(2):307–16.
18. Eriksson JG, Salonen MK, Kajantie E, Osmond C. Prenatal growth and CKD in older adults: longitudinal findings from the Helsinki birth cohort study, 1924-1944. *Am J Kidney Dis* 2018;**71**(1):20–6.
19. Dearden L, Bouret SG, Ozanne SE. Sex and gender differences in developmental programming of metabolism. *Mol Metab* 2018;**15**:8–19.
20. Hoy WE, Douglas-Denton RN, Hughson MD, Cass A, Johnson K, Bertram JF. A stereological study of glomerular number and volume: preliminary findings in a multiracial study of kidneys at autopsy. *Kidney Int Suppl* 2003;(83):S31–7.
21. Macconi D, Bonomelli M, Benigni A, et al. Pathophysiologic implications of reduced podocyte number in a rat model of progressive glomerular injury. *Am J Pathol* 2006;**168**(1):42–54.
22. Salazar F, Reverte V, Saez F, Loria A, Llinas MT, Salazar FJ. Age- and sodium-sensitive hypertension and sex-dependent renal changes in rats with a reduced nephron number. *Hypertension* 2008;**51**(4):1184–9.
23. Nehiri T, Duong Van Huyen JP, Viltard M, et al. Exposure to maternal diabetes induces salt-sensitive hypertension and impairs renal function in adult rat offspring. *Diabetes* 2008;**57**(8):2167–75.
24. Ruta LA, Dickinson H, Thomas MC, Denton KM, Anderson WP, Kett MM. High-salt diet reveals the hypertensive and renal effects of reduced nephron endowment. *Am J Physiol Renal Physiol* 2010;**298**(6):F1384–92.
25. Walker KA, Cai X, Caruana G, Thomas MC, Bertram JF, Kett MM. High nephron endowment protects against salt-induced hypertension. *Am J Physiol Renal Physiol* 2012;**303**(2):F253–8.
26. Ruggajo P, Svarstad E, Leh S, Marti HP, Reisaether AV, Vikse BE. Low birth weight and risk of progression to end stage renal disease in IgA nephropathy–A retrospective registry-based cohort study. *PLoS One* 2016;**11**(4):e0153819.
27. Ojeda NB. Low birth weight increases susceptibility to renal injury in a rat model of mild ischemia-reperfusion. *Am J Physiol Renal Physiol* 2011;**301**(2):F420–6.
28. Langley-Evans S, Langley-Evans A, Marchand M. Nutritional programming of blood pressure and renal morphology. *Arch Physiol Biochem* 2003;**111**(1):8–16.
29. Boubred F, Buffat C, Feuerstein JM, et al. Effects of early postnatal hypernutrition on nephron number and long-term renal function and structure in rats. *Am J Physiol Renal Physiol* 2007;**293**(6):F1944–9.
30. Benz K, Schlote J, Daniel C, et al. Mild salt-sensitive hypertension in genetically determined low nephron number is associated with chloride but not sodium retention. *Kidney Blood Press Res* 2018;**43**(1):1–11.

31. Moritz KM, Cuffe JS, Wilson LB, et al. Review: sex specific programming: a critical role for the renal renin-angiotensin system. *Placenta* 2010;**31**(Suppl. l):S40−6.
32. Washburn LK, Brosnihan KB, Chappell MC, et al. The renin-angiotensin-aldosterone system in adolescent offspring born prematurely to mothers with preeclampsia. *J Renin Angiotensin Aldosterone Syst* 2015;**16**(3):529−38.
33. South AM, Nixon PA, Chappell MC, et al. Antenatal corticosteroids and the renin-angiotensin-aldosterone system in adolescents born preterm. *Pediatr Res* 2017;**81**(1−1):88−93.
34. South AM, Nixon PA, Chappell MC, et al. Association between preterm birth and the renin-angiotensin system in adolescence: influence of sex and obesity. *J Hypertens* 2018;**36**(10):2092−101.
35. Paquette K, Fernandes RO, Xie LF, et al. Kidney size, renal function, ang (angiotensin) peptides, and blood pressure in young adults born preterm. *Hypertension* 2018;**72**(4):918−28.
36. Kett MM, Denton KM. Renal programming: cause for concern? *Am J Physiol Regul Integr Comp Physiol* 2011;**300**(4):R791−803.
37. Dagan A, Kwon HM, Dwarakanath V, Baum M. Effect of renal denervation on prenatal programming of hypertension and renal tubular transporter abundance. *Am J Physiol Renal Physiol* 2008; **295**(1):F29−34.
38. Intapad S, Tull FL, Brown AD, et al. Renal denervation abolishes the age-dependent increase in blood pressure in female intrauterine growth-restricted rats at 12 months of age. *Hypertension* 2013; **61**(4):828−34.
39. Goodyer P, Kurpad A, Rekha S, et al. Effects of maternal vitamin A status on kidney development: a pilot study. *Pediatr Nephrol* 2007;**22**(2):209−14.
40. Hult M, Tornhammar P, Ueda P, et al. Hypertension, diabetes and overweight: looming legacies of the Biafran famine. *PLoS One* 2010;**5**(10):e13582.
41. Huang C, Guo C, Nichols C, Chen S, Martorell R. Elevated levels of protein in urine in adulthood after exposure to the Chinese famine of 1959-61 during gestation and the early postnatal period. *Int J Epidemiol* 2014;**43**(6):1806−14.
42. Stein AD, Zybert PA, van der Pal-de Bruin K, Lumey LH. Exposure to famine during gestation, size at birth, and blood pressure at age 59 y: evidence from the Dutch Famine. *Eur J Epidemiol* 2006; **21**(10):759−65.
43. Savitri AI, Amelia D, Painter RC, et al. Ramadan during pregnancy and birth weight of newborns. *J Nutr Sci* 2018;**7**:e5.
44. Hsu CW, Yamamoto KT, Henry RK, De Roos AJ, Flynn JT. Prenatal risk factors for childhood CKD. *J Am Soc Nephrol* 2014;**25**(9): 2105−11.
45. Amri K, Freund N, Van Huyen JP, Merlet-Benichou C, Lelievre-Pegorier M. Altered nephrogenesis due to maternal diabetes is associated with increased expression of IGF-II/mannose-6-phosphate receptor in the fetal kidney. *Diabetes* 2001;**50**(5): 1069−75.
46. Hokke S, Arias N, Armitage JA, et al. Maternal glucose intolerance reduces offspring nephron endowment and increases glomerular volume in adult offspring. *Diabetes Metab Res Rev* 2016;**32**(8):816−26.
47. Poston L, Caleyachetty R, Cnattingius S, et al. Preconceptional and maternal obesity: epidemiology and health consequences. *Lancet Diabetes Endocrinol* 2016;**4**(12):1025−36.
48. Hokke S, Puelles VG, Armitage JA, Fong K, Bertram JF, Cullen-McEwen LA. Maternal fat feeding augments offspring nephron endowment in mice. *PLoS One* 2016;**11**(8):e0161578.
49. Jackson CM, Alexander BT, Roach L, et al. Exposure to maternal overnutrition and a high-fat diet during early postnatal development increases susceptibility to renal and metabolic injury later in life. *Am J Physiol Renal Physiol* 2012;**302**(6):F774−83.
50. Wlodek ME, Mibus A, Tan A, Siebel AL, Owens JA, Moritz KM. Normal lactational environment restores nephron endowment and prevents hypertension after placental restriction in the rat. *J Am Soc Nephrol* 2007;**18**(6):1688−96.
51. Davis EF, Lazdam M, Lewandowski AJ, et al. Cardiovascular risk factors in children and young adults born to preeclamptic pregnancies: a systematic review. *Pediatrics* 2012;**129**(6):e1552−61.
52. Langley-Evans SC. Fetal programming of CVD and renal disease: animal models and mechanistic considerations. *Proc Nutr Soc* 2013;**72**(3):317−25.
53. Painter RC, Roseboom TJ, de Rooij SR. Long-term effects of prenatal stress and glucocorticoid exposure. *Birth Defects Res C Embryo Today* 2012;**96**(4):315−24.
54. Chevalier RL. Congenital urinary tract obstruction: the long view. *Adv Chron Kidney Dis* 2015;**22**(4):312−9.
55. Luyckx VA, Bertram JF, Brenner BM, et al. Effect of fetal and child health on kidney development and long-term risk of hypertension and kidney disease. *Lancet* 2013;**382**(9888):273−83.
56. Puelles VG, Bertram JF. Counting glomeruli and podocytes: rationale and methodologies. *Curr Opin Nephrol Hypertens* 2015;**24**(3): 224−30.
57. Denic A, Lieske JC, Chakkera HA, et al. The substantial loss of nephrons in healthy human kidneys with aging. *J Am Soc Nephrol* 2017;**28**(1):313−20.
58. Baldelomar EJ, Charlton JR, Beeman SC, Bennett KM. Measuring rat kidney glomerular number and size in vivo with MRI. *Am J Physiol Renal Physiol* 2018;**314**(3):F399−406.
59. Puelles VG, Hoy WE, Hughson MD, Diouf B, Douglas-Denton RN, Bertram JF. Glomerular number and size variability and risk for kidney disease. *Curr Opin Nephrol Hypertens* 2011; **20**(1):7−15.
60. Sutherland MR, Gubhaju L, Moore L, et al. Accelerated maturation and abnormal morphology in the preterm neonatal kidney. *J Am Soc Nephrol* 2011;**22**(7):1365−74.
61. Faa G, Gerosa C, Fanni D, et al. Marked interindividual variability in renal maturation of preterm infants: lessons from autopsy. *J Matern Fetal Neonatal Med* 2010;**23**(Suppl. 3):129−33.
62. Hinchliffe SA, Sargent PH, Howard CV, Chan YF, van Velzen D. Human intrauterine renal growth expressed in absolute number of glomeruli assessed by the disector method and Cavalieri principle. *Lab Invest* 1991;**64**(6):777−84.
63. Manalich R, Reyes L, Herrera M, Melendi C, Fundora I. Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. *Kidney Int* 2000;**58**(2):770−3.
64. Hinchliffe SA, Lynch MR, Sargent PH, Howard CV, Van Velzen D. The effect of intrauterine growth retardation on the development of renal nephrons. *Br J Obstet Gynaecol* 1992;**99**(4):296−301.
65. Hughson M, Farris AB, Douglas-Denton R, Hoy WE, Bertram JF. Glomerular number and size in autopsy kidneys: the relationship to birth weight. *Kidney Int* 2003;**63**(6):2113−22.
66. Kanzaki G, Puelles VG, Cullen-McEwen LA, et al. New insights on glomerular hyperfiltration: a Japanese autopsy study. *JCI Insight* 2017;**2**(19).
67. Zhang Z, Quinlan J, Hoy W, et al. A common RET variant is associated with reduced newborn kidney size and function. *J Am Soc Nephrol* 2008;**19**(10):2027−34.
68. Mu M, Wang SF, Sheng J, et al. Birth weight and subsequent blood pressure: a meta-analysis. *Arch Cardiovasc Dis* 2012;**105**(2):99−113.
69. de Jong F, Monuteaux MC, van Elburg RM, Gillman MW, Belfort MB. Systematic review and meta-analysis of preterm birth and later systolic blood pressure. *Hypertension* 2012;**59**(2):226−34.
70. Zhang Y, Li H, Liu SJ, et al. The associations of high birth weight with blood pressure and hypertension in later life: a systematic review and meta-analysis. *Hypertens Res* 2013;**36**(8):725−35.
71. Aceti A, Santhakumaran S, Logan KM, et al. The diabetic pregnancy and offspring blood pressure in childhood: a systematic review and meta-analysis. *Diabetologia* 2012;**55**(11):3114−27.

72. Richardson LJ, Hussey JM, Strutz KL. Origins of disparities in cardiovascular disease: birth weight, body mass index, and young adult systolic blood pressure in the national longitudinal study of adolescent health. *Ann Epidemiol* 2011;**21**(8):598–607.
73. Lule SA, Elliott AM, Smeeth L, Webb EL. Is birth weight associated with blood pressure among African children and adolescents? A systematic review. *J Dev Orig Health Dis* 2018;**9**(3):270–80.
74. Khalsa DD, Beydoun HA, Carmody JB. Prevalence of chronic kidney disease risk factors among low birth weight adolescents. *Pediatr Nephrol* 2016;**31**(9):1509–16.
75. Bergvall N, Iliadou A, Johansson S, et al. Genetic and shared environmental factors do not confound the association between birth weight and hypertension: a study among Swedish twins. *Circulation* 2007;**115**(23):2931–8.
76. Keller G, Zimmer G, Mall G, Ritz E, Amann K. Nephron number in patients with primary hypertension. *N Engl J Med* 2003;**348**(2):101–8.
77. Hughson MD, Douglas-Denton R, Bertram JF, Hoy WE. Hypertension, glomerular number, and birth weight in African Americans and white subjects in the southeastern United States. *Kidney Int* 2006;**69**(4):671–8.
78. Perala MM, Moltchanova E, Kaartinen NE, et al. The association between salt intake and adult systolic blood pressure is modified by birth weight. *Am J Clin Nutr* 2011;**93**(2):422–6.
79. Schreuder MF, Langemeijer ME, Bokenkamp A, Delemarre-Van de Waal HA, Van Wijk JA. Hypertension and microalbuminuria in children with congenital solitary kidneys. *J Paediatr Child Health* 2008;**44**(6):363–8.
80. Ibrahim HN, Foley R, Tan L, et al. Long-term consequences of kidney donation. *N Engl J Med* 2009;**360**(5):459–69.
81. Massie AB, Muzaale AD, Luo X, et al. Quantifying postdonation risk of ESRD in living kidney donors. *J Am Soc Nephrol* 2017;**28**(9):2749–55.
82. Lankadeva YR, Singh RR, Tare M, Moritz KM, Denton KM. Loss of a kidney during fetal life: long-term consequences and lessons learned. *Am J Physiol Renal Physiol* 2014;**306**(8):F791–800.
83. Nyengaard JR. Number and dimensions of rat glomerular capillaries in normal development and after nephrectomy. *Kidney Int* 1993;**43**(5):1049–57.
84. White SL, Perkovic V, Cass A, et al. Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. *Am J Kidney Dis* 2009;**54**(2):248–61.
85. Stritzke A, Thomas S, Amin H, Fusch C, Lodha A. Renal consequences of preterm birth. *Mol Cell Pediatr* 2017;**4**(1):2.
86. Keijzer-Veen MG, Schrevel M, Finken MJ, et al. Microalbuminuria and lower glomerular filtration rate at young adult age in subjects born very premature and after intrauterine growth retardation. *J Am Soc Nephrol* 2005;**16**(9):2762–8.
87. Bacchetta J, Harambat J, Dubourg L, et al. Both extrauterine and intrauterine growth restriction impair renal function in children born very preterm. *Kidney Int* 2009;**76**(4):445–52.
88. Keijzer-Veen MG, Kleinveld HA, Lequin MH, et al. Renal function and size at young adult age after intrauterine growth restriction and very premature birth. *Am J Kidney Dis* 2007;**50**(4):542–51.
89. Gielen M, Pinto-Sietsma SJ, Zeegers MP, et al. Birth weight and creatinine clearance in young adult twins: influence of genetic, prenatal, and maternal factors. *J Am Soc Nephrol* 2005;**16**(8):2471–6.
90. Abi Khalil C, Travert F, Fetita S, et al. Fetal exposure to maternal type 1 diabetes is associated with renal dysfunction at adult age. *Diabetes* 2010;**59**(10):2631–6.
91. Vieux R, Hascoet JM, Franck P, Guillemin F. Increased albuminuria in 4-year-old preterm-born children with normal height. *J Pediatr* 2012;**160**(6):923–928 e1.
92. Nelson RG, Morgenstern H, Bennett PH. Birth weight and renal disease in Pima Indians with type 2 diabetes mellitus. *Am J Epidemiol* 1998;**148**(7):650–6.
93. Hayashi A, Santo Y, Satomura K. Proteinuria and glomerular hypertrophy in extremely low-birthweight children. *Pediatr Int* 2014;**56**(6):860–4.
94. Hirano D, Ishikura K, Uemura O, et al. Association between low birth weight and childhood-onset chronic kidney disease in Japan: a combined analysis of a nationwide survey for paediatric chronic kidney disease and the National Vital Statistics Report. *Nephrol Dial Transplant* 2016;**31**(11):1895–900.
95. Abitbol CL, Rodriguez MM. The long-term renal and cardiovascular consequences of prematurity. *Nat Rev Nephrol* 2012;**8**(5):265–74.
96. Hoy WE, White AV, Tipiloura B, et al. The influence of birthweight, past poststreptococcal glomerulonephritis and current body mass index on levels of albuminuria in young adults: the multideterminant model of renal disease in a remote Australian Aboriginal population with high rates of renal disease and renal failure. *Nephrol Dial Transplant* 2016;**31**(6):971–7.
97. Ruggajo P, Skrunes R, Svarstad E, Skjaerven R, Reisaether AV, Vikse BE. Familial factors, low birth weight, and development of ESRD: a nationwide registry study. *Am J Kidney Dis* 2016;**67**(4):601–8.
98. Pavkov ME, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Nelson RG. Effect of intrauterine diabetes exposure on the incidence of end-stage renal disease in young adults with type 2 diabetes. *Diabetes Care* 2010;**33**(11):2396–8.
99. Lackland DT, Bendall HE, Osmond C, Egan BM, Barker DJ. Low birth weights contribute to high rates of early-onset chronic renal failure in the Southeastern United States. *Arch Intern Med* 2000;**160**(10):1472–6.
100. Bhutta ZA, Das JK, Rizvi A, et al. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? *Lancet* 2013;**382**(9890):452–77.
101. Lee YQ, Collins CE, Gordon A, Rae KM, Pringle KG. The relationship between maternal nutrition during pregnancy and offspring kidney structure and function in humans: a systematic review. *Nutrients* 2018;**10**(2).
102. Bhutta ZA, Das JK, Bahl R, et al. Can available interventions end preventable deaths in mothers, newborn babies, and stillbirths, and at what cost? *Lancet* 2014;**384**(9940):347–70.
103. Boivin A, Luo ZC, Audibert F, et al. Pregnancy complications among women born preterm. *CMAJ* 2012;**184**(16):1777–84.
104. Innes KE, Byers TE, Marshall JA, Baron A, Orleans M, Hamman RF. Association of a woman's own birth weight with subsequent risk for gestational diabetes. *JAMA* 2002;**287**(19):2534–41.
105. Skjaerven R, Vatten LJ, Wilcox AJ, Ronning T, Irgens LM, Lie RT. Recurrence of pre-eclampsia across generations: exploring fetal and maternal genetic components in a population based cohort. *BMJ* 2005;**331**(7521):877.
106. World Health Organisation. *Global nutrition targets 2025: low birth weight policy brief (WHO/NMH/NHD/14.5)*. 2014. http://www.who.int/nutrition/publications/globaltargets2025_policybrief_lbw/en/.
107. Ota E, Ganchimeg T, Morisaki N, et al. Risk factors and adverse perinatal outcomes among term and preterm infants born small-for-gestational-age: secondary analyses of the WHO multi-country survey on maternal and newborn health. *PLoS One* 2014;**9**(8):e105155.
108. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol* 2013;**170**(1):1–7.
109. Goldenberg RL, McClure EM, Harrison MS, Miodovnik M. Diabetes during pregnancy in low- and middle-income countries. *Am J Perinatol* 2016;**33**(13):1227–35.
110. Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* 2013;**382**(9890):427–51.

QUESTIONS AND ANSWERS

Question 1

Which of the following are known factors which impact nephron number?

A. Growth restriction
B. Preterm birth
C. LBW
D. HBW
E. Male gender

Answer: A, B, and E

Nephron number is proportional to gestational age, and babies born preterm have fewer nephrons than babies born at term. Growth restriction in preterm infants was associated with lower nephron numbers and therefore impacts nephrogenesis. Females tend to have fewer nephrons than males. Answers C and D are incorrect, because birth weight *per se* does not impact nephrogenesis, but is rather a marker for developmental programming.

Question 2

As nephron number cannot be measured *in vivo*, which of the following are clinical surrogates that may serve to identify an individual who may have a lower nephron number?

A. Shorter adult height
B. HBW
C. Small glomeruli on kidney biopsy
D. Being a twin
E. Being born to a teenage mother

Answer: A, D, and E

It has been estimated that nephron numbers increase by around 28,000 nephrons per cm adult height. Being born in a twin pregnancy or to a teenage mother increases the likelihood of preeclampsia, preterm birth, and lower birth weight, and therefore lower nephron numbers. HBW is associated with higher nephron numbers. Kidneys with fewer nephrons have glomerular hypertrophy which most likely occurs as a compensatory response to preserve GFR.

Question 3

Programmed hypertension is associated with which of the following?

A. Salt sensitivity
B. Maternal preeclampsia
C. Maternal diabetes during pregnancy
D. HBW
E. Preterm birth

Answer: All of the above

Salt sensitivity has been found to increase with decreasing birth weight below 3050 g. From multiple meta-analyses, it has emerged that blood pressures are higher in children and adolescents born in preeclamptic pregnancies; male children of mothers who had diabetes during pregnancy; children who had a HBW; and individuals born preterm. Exposure to maternal diabetes was not associated with higher blood pressure in females and HBW was not associated with higher blood pressure in adulthood.

Question 4

Factors which may be implicated in developmental programming of hypertension include which of the following?

A. Altered activity of the RAAS
B. Reduced sympathetic tone
C. Catch-up growth
D. Low current BMI
E. Reduced renal tubular sodium transporter activity

Answer: A and C

Modulation of the activity of the RAAS has been shown in many programming models, although magnitude and specificity of changes vary with time and model studied. In adult animals, however, the RAAS tends to be upregulated. Catch-up growth and an increased BMI have been associated with higher blood pressures in children born small or preterm. Sympathetic tone and activity of renal sodium transporters have been shown to be increased by developmental programming and therefore may contribute to hypertension.

Question 5

A 29-year-old woman who was born preterm is planning a pregnancy and comes to you for a consultation to discuss potential risks for her and her child should she get pregnant. Which of the following factors are important to ascertain?

A. Her gestational age
B. Whether she had AKI postnatally
C. Her current BMI
D. Precipitant of her own preterm birth
E. Smoking history

Answer: All of the above

Women who were born preterm have a higher risk of having a preterm delivery as well as preeclampsia and gestational diabetes, and this is proportional to the degree of prematurity. AKI is common in preterm

infants. If the patient had experienced AKI, it is possible she may have some subtle residual renal dysfunction, which may affect her pregnancy outcomes. Individuals who were born preterm and become overweight or obese have a higher risk of hypertension and renal dysfunction. Overweight and obesity are risk factors for poorer pregnancy outcomes, including LBW, HBW, preterm birth, preeclampsia, and gestational diabetes. Smoking increases the risk of preterm birth, which declines on cessation of smoking.

Question 6

The mother of a 9-month-old boy who had been born at 36 weeks with a birth weight on the eighth percentile of normal (SGA) brings him in for a routine vaccination. What will you recommend to his mother to preserve the child's kidney health?

A. Start an ACE inhibitor now
B. Ensure that he catches up in weight to his peers
C. Encourage a balanced healthy diet
D. Suggest yearly checkups for microalbuminuria and blood pressure
E. Educate her about a healthy lifestyle for the whole family

Answer: C, D, and E

The child has a high risk of developing kidney dysfunction having been both preterm and SGA. Maintaining a healthy weight and BMI through healthy diet and lifestyle are likely the best strategies to mitigate against programmed hypertension and kidney disease, by reducing the avoidable second "hits" such as obesity, which may be a consequence of rapid catch-up growth. The child does require life-long follow up, but the frequency and intensity of such care has not been established. It is reasonable to monitor blood pressures, and once the child is old enough, to consider screening for microalbuminuria at least at well-baby and well-child/vaccination visits. If proteinuria becomes evident, it may be beneficial to consider initiation of an ACEI. It is important to emphasize the preventive nature of such activities, and that they do not mean the child is sick or will become sick.

CHAPTER

21

Pathophysiology of Hypertension in Chronic Kidney Disease

Raymond R. Townsend

Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States

Abstract

Elevated blood pressure is a ubiquitous finding in patients with chronic kidney diseases. The kidney, recognized as both a villain and a victim when it comes to high blood pressure, has a significant regulatory role in many aspects of blood pressure. When kidney function is impaired, the ability of the kidney to maintain balance in the internal milieu of electrolytes, hormones, adrenergic activity, and endothelial function, particularly in the presence of comorbidities such as diabetes and prevalent cardiovascular disease, contributes greatly to hypertension. In this chapter the reader will be presented with the epidemiology of hypertension in chronic kidney disease, a summary of what we know about the dysregulation of traditional factors in blood pressure maintenance, and information on the emerging roles of inflammation, immune system influence, the gut microbiome, and arterial stiffness, which should aid in the evaluation and management of elevated blood pressure.

SCOPE OF THE PROBLEM AND PUBLIC HEALTH IMPLICATIONS

The prevalence of chronic kidney disease (CKD) continues to increase among certain groups, such as African Americans and Hispanics, while it appears to have stabilized among Caucasians, with an estimated prevalence of 13–14% adults in the US.[1,2] Hypertension using older definitions (usually >140/>90 mm Hg) is a common occurrence in CKD, with more than 80% of patients with CKD having coexistent hypertension. More severe stages of CKD are associated with more severe hypertension,[3] that is usually more difficult to control and requires a greater number of medications to reach target blood pressure (BP) goals.[4] This prevalence may be even higher as the newer ACC/AHA guidelines lowered the definition to 130/80 mm Hg.[5] Patients with more severe hypertension are also more likely to develop CKD.[6] Based on data from the USRDS, it is estimated that hypertension occurs in 23.3% of individuals without CKD and 35.8% of stage 1, 48.1% of stage 2, 59.9% of stage 3, and 84.1% of stages 4–5 CKD patients. Most patients with CKD require multiple antihypertensive agents to control BP.[7] Nonadherence to antihypertensive medications does not appear to be more common in CKD patients compared with the general population.[7]

Rates of awareness and control of hypertension have improved in the general population and appear to be improving in patients with CKD. Recent studies have shown that both awareness and control of hypertension in the general population have improved from 69% to 80% and 27% to 50%, respectively, compared with earlier decades.[8] Reports from CKD patients enrolled in prospective observational studies have shown similar improvements in the rates of awareness and BP control in the CKD population.[4,7] CKD patients have also been shown to be more likely to receive adequate treatment for hypertension when compared with prior decades.[9,10]

Ambulatory blood pressure monitoring (ABPM) provides superior BP measurements compared with office BP measurements in CKD patients. ABPM measurements are often abnormal in CKD, with CKD patients frequently showing an altered circadian rhythm with an increased rate of nondipping and reverse dipping.[11] The prevalence of nondipping and reverse dipping increases progressively as stage of CKD progresses. Masked hypertension is common in CKD, occurring in 28% of participants enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study.[12] In the African American Study of Kidney (AASK) Disease Cohort Study, of the 61% of participants with controlled clinic BP, 70% had masked hypertension.[13] Target organ damage (proteinuria and left ventricular hypertrophy) was more

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00021-8

common in those with elevated night time BP, masked hypertension, or sustained hypertension.[12,13] Masked hypertension, particularly nocturnal BP control, may account for the disappointing results from the AASK study, where progression of kidney disease occurred despite excellent in-office BP control.[14]

The likelihood of hypertension in CKD patients is also influenced by the type of underlying renal disease. Tubulointerstitial diseases typically have a lower prevalence of elevated BP compared with glomerular diseases.[15] Hypertension was reported in one study to be present in 93% of patients with renal artery stenosis, 87% of patients with diabetic nephropathy (87%), and 74% of patients with polycystic kidney disease.[16]

African Americans have a higher incidence of hypertension and CKD than Caucasians and are at greater risk of developing progressive CKD and end-stage renal disease (ESRD) than any other racial group in the US.[17] African Americans develop cardiovascular disease approximately 5 years earlier and have higher mortality rates compared with Caucasians of similar ages.[18,19] This is largely due to the increased prevalence and severity of both hypertension and CKD. African Americans with risk variants of the APOL1 gene that encodes apolipoprotein L1 have been linked to higher risk of hypertension-attributable kidney disease.[20,21]

Treatment of hypertension in the patient with CKD can often be challenging, as CKD patients often have severe hypertension requiring the use of multiple medications to achieve target BP goals. Target BP goals have traditionally been set lower in patients with CKD than in the general population. The goal BP for patients with CKD is currently recommended to be <130/80 mm Hg.[5]

Hypertension is also very common among patients treated with either peritoneal dialysis or hemodialysis, as well as in patients who have had a renal transplant. Because of fluid accumulation between hemodialysis sessions, the definition of hypertension and goal BP in this population is difficult to define, as there are large differences between pre-, post-, and interdialytic BPs.[22] It has been suggested that a predialysis BP of 150/85 mm Hg be the target BP in hemodialysis patients, as data have shown that with a predialysis BP greater than 150/85 mm Hg, there is an 80% sensitivity in predicting elevated interdialytic ambulatory BP.[23] Based on this definition, one study showed that 86% of hemodialysis patients had hypertension, of whom only 30% had adequate control.[24] The prevalence of hypertension in peritoneal dialysis patients is similar, and greater than 70% of renal transplant recipients have hypertension.[25,26] There is controversy surrounding the benefit of BP control in dialysis patients. Similar to the general population, dialysis patients with higher BPs have increased cardiovascular mortality, but there is also an increased mortality of dialysis patients with lower BPs, presumed to be due to poor underlying cardiac function. In the Frequent Hemodialysis Network Daily Trial, patients receiving more frequent dialysis had improved BP control and improved outcomes with respect to LV mass and CV death.[27] In renal transplant recipients, posttransplant hypertension is an independent risk factor for graft failure and death. The risk is improved by adequate BP control.[28,29]

PATHOPHYSIOLOGY OF HYPERTENSION IN CHRONIC KIDNEY DISEASE

The pathogenesis of hypertension in CKD is complex. There is a remarkable breadth of factors implicated in BP dysregulation in CKD. A compilation of factors discussed in this chapter that contribute to hypertension in CKD is shown in Figure 21.1.

Hypertension in CKD patients results from four basic interrelated mechanisms by which BP is regulated: (1) sodium and fluid retention, (2) hormonal factors such as the renin–angiotensin–aldosterone axis, (3) the activity of the sympathetic nervous system, and (4) endothelial autoregulation. These four basic servos for BP control are shown in Figure 21.2. The factors affecting these servos are often modifiable, and treatment of hypertension in CKD takes this into account when lifestyle measures and medications are selected. Each of these mechanisms are discussed separately below.

SODIUM AND FLUID RETENTION

The maintenance of sodium and fluid homeostasis by the kidneys has long been implicated as the key regulator of BP. A defect in kidney function is a common element in the development of hypertension.[30] Intact kidneys are very sensitive to BP changes, which, in the range of 1–3 mm Hg in mean arterial pressure, result in prompt changes in sodium and fluid excretion or retention. In normal kidneys, this regulatory mechanism accurately adjusts sodium and fluid balance across a wide range of BP. The rapid response of the kidneys in handling sodium and fluid are the results of changes in tubular sodium and fluid reabsorption, rather than total renal blood flow or glomerular filtration rate (GFR). In CKD, however, the tubular reabsorption of sodium and fluid is often not suppressed adequately, resulting in inappropriate sodium and fluid retention and the development of elevated BP.

The kidneys are very effective in handling of sodium and fluid balance by excretion during the periods of surplus and retention during the periods of deficit. In normal kidneys, variations in dietary sodium intake usually result in less than 10% fluctuation in

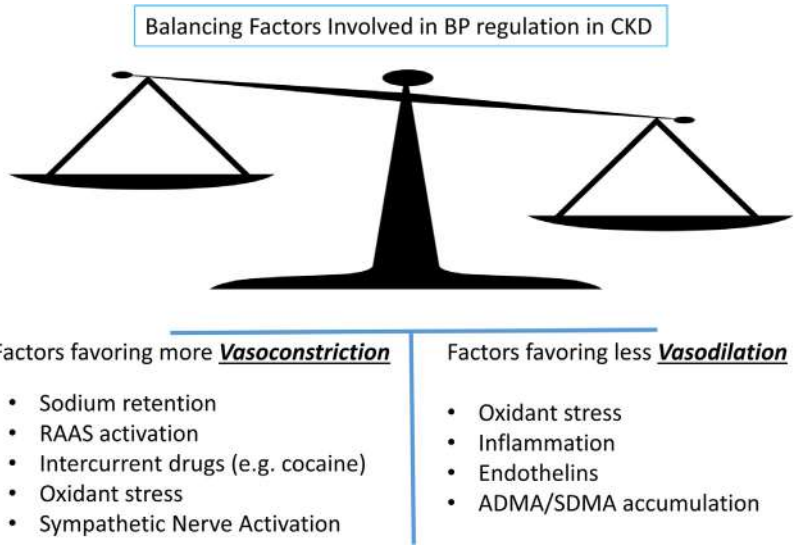


FIGURE 21.1 The balance of factors covered in the text and their effects to promote vasoconstriction, impair vasodilation, or act through both mechanisms. *ADMA*, asymmetric dimethylarginine; *BP*, blood pressure; *CKD*, chronic kidney disease; *RAAS*, renin–angiotensin–aldosterone system; *SDMA*, symmetric dimethylarginine.

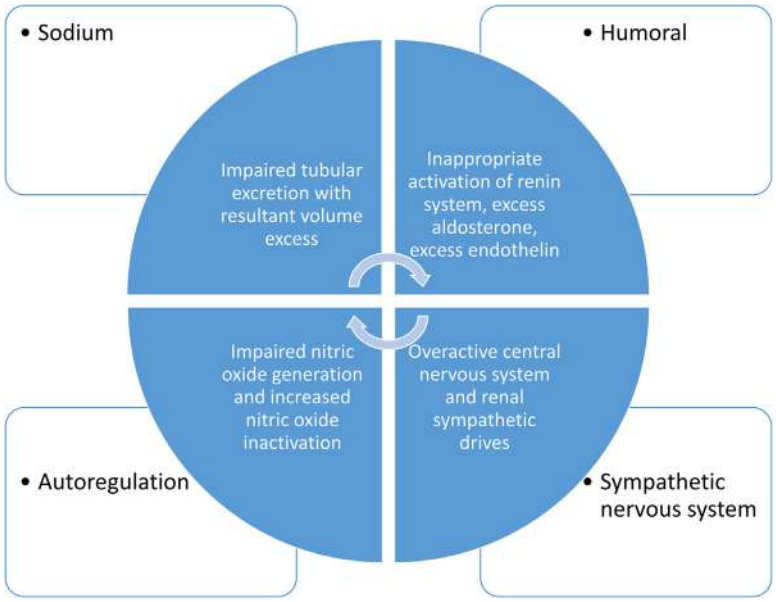


FIGURE 21.2 The major domains of blood pressure regulation in the outer squares with specific contributors to the pathogenesis of hypertension in chronic kidney disease in the areas within the circles.

extracellular fluid and intravascular volume, and only subtle changes in BP. In CKD, however, BP becomes more responsive to variations in dietary sodium intake and often increases significantly with increasing dietary sodium intake. This "salt-sensitive" component of BP increases progressively as the GFR declines.

Sodium retention and volume expansion are common concomitants in the hypertension of CKD. The ability to eliminate sodium and fluid decreases progressively as kidney function declines. Heart failure in CKD further challenges the maintenance of volume status. Sodium intake increases BP to a great extent as kidney function declines, and to an even greater extent than simple volume expansion alone would predict at the lowest levels of kidney function.[31] This finding suggests that the effect of sodium intake on BP is enhanced by the CKD milieu.

Independent of the effect of increasing BP through effects on volume, high sodium intake also results in

increased arterial stiffness, reductions in vascular nitric oxide (NO), and promotion of inflammatory processes.[32] Moreover, sodium intake is well known to abet the prohypertensive effects of angiotensin II[33] and norepinephrine.[34]

RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM ACTIVATION

The renin–angiotensin–aldosterone system (RAAS) is recognized as an important humoral regulator of BP. Renin activity and angiotensin II production are regulated closely in response to changes in dietary sodium intake. Increased sodium intake leads to suppressed renin activity and reduced angiotensin II production, resulting in a prompt and effective elimination of sodium by the kidneys to maintain normal BP. Inappropriate activation of RAAS has been implicated in the hypertension associated with CKD.[35] The presence of volume expansion in CKD further potentiates the vasoactive effects of RAAS activation. Some of the increase in RAAS activation appears to be the result of increased sympathetic input into the juxtaglomerular apparatus through the β_1-adrenoreceptor.[33]

Increased RAAS activation in CKD is supported by several lines of evidence. First, CKD patients often do not have normal suppression of plasma renin activity given their usual state of sodium retention and volume expansion. Secondly, CKD patients often have a good antihypertensive response to both angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. In addition, bilateral nephrectomy results in BP normalization in many of these patients. Thirdly, a direct relationship between plasma renin activity and BP is often seen in CKD. Aside from the hemodynamic consequences of renin activation, the excess angiotensin II produced likely contributes to progressive renal function loss and other target organ damage, through its stimulation of aldosterone release, potentiation of the effects of various growth factors, and in particular its stimulating effects on the fibrogenesis-promoting cytokine transforming growth factor-β.[36,37]

A component related to renin system activation is aldosterone. A large increase in aldosterone occurs in the five-sixth (5/6) nephrectomy rat model.[38] Aldosterone contributes to BP in CKD through its effects to stimulate sodium reabsorption, which occur both through epithelial sodium transport channels and through upregulation of sodium absorption in the sodium-chloride channels of the distal tubule.[39] Other actions of aldosterone that contribute to increased BP in CKD include inhibition of NO action, hyperfiltration and proteinuria, inflammation and hypertrophy at the glomerular level, and podocyte injury related to reactive oxygen species generated by aldosterone.[40]

SYMPATHETIC NERVOUS SYSTEM ACTIVATION

The neural control of the kidneys is mainly sympathetic,[41] and the sympathetic nervous system appears to be overactive in CKD.[42] As with the RAAS, the kidneys are both the source and target of neurogenic activity.[43] Activation of the renal efferent sympathetic nerves, which carry central sympathetic input into kidneys, results in increased renin secretion and tubular sodium reabsorption. There is an extensive network of sensory nerve fibers in the kidneys, and much laboratory data indicate that renal sympathetic activation plays a role in hypertension in CKD through direct vascular constriction and interactions with the RAAS and salt handling. The recent results of impressive BP reduction in drug-resistant hypertension with renal nerve ablation support the importance of sympathetic system in hypertension.[44–47] In addition, pilot studies showing similarly impressive BP lowering with renal sympathetic denervation in patients with CKD[48] and ESRD[49] further support the important role of sympathetic overactivity in hypertension associated with CKD.

Sympathetic activation in CKD is manifested in several ways. Direct measures of muscle sympathetic activity through microneurography in dialysis patients shows increased neuronal firing consistent with activation.[50] Bilateral nephrectomy dramatically reduces both BP in drug-resistant hypertensives on dialysis and muscle sympathetic nerve activity.[50] A relatively new aspect in catecholamine metabolism has emerged from the work of Desir and colleagues who have isolated an enzyme, renalase, from the kidney which degrades catecholamines. Reduced kidney function is associated with less renalase activity, reducing catecholamine clearance and potentially allowing more effect because of greater catecholamine exposure.[51]

Another sympathetic mechanism involved in BP control is an increase in renin secretion, induced by renal sympathetic activity mediated by β_1-adrenoreceptors, which can be offset by beta-blocking drugs. Several studies attest to the efficacy of beta-blocker therapy in hypertensive patients with CKD.[52,53]

Although increases in tubular sodium reabsorption and renal vascular resistance are mediated by α_1-adrenoreceptors and can be offset in the short term by alpha-blocking drugs, the exacerbation of heart failure with longer-term use of these agents suggests that the interaction of α adrenoreceptors in the kidney is complex.[54] As a result, enthusiasm for use of α_1-blocking drugs has relegated their use largely to men with prostate hypertrophy. Centrally acting antihypertensive agents such as clonidine reduce renal sympathetic activity and renin activity.

ENDOTHELIAL FUNCTION

A great deal of effort has gone into understanding the role of disordered endothelial function in the pathogenesis of atherosclerosis and hypertension in the setting of impaired kidney function. The endothelium is a large organ, having both an antithrombotic function and a significant role in regulating vascular smooth muscle tone through a series of locally acting mediators. One of the most potent vasoactive mediators generated by the endothelium is NO. Asymmetric dimethylarginine, an inhibitor of NO production and availability, is elevated in CKD and ESRD and is an independent predictor of death in ESRD patients.[55] NO activity is impaired by oxidative stress, which is commonly found in CKD.[56] Oxidative stress denatures NO into peroxynitrite ($ONOO^-$) and dissociates tetrahydrobiopterin (BH4), a necessary cofactor for NO action, from NO. The intracellular substrate for NO generation is the amino acid L-arginine. In CKD, urea competes with L-arginine for uptake into endothelial cells creating a relative L-arginine deficiency.[56] In addition, asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) concentrations are elevated in CKD, partly due to diminished degradation pathways (such as DDAH which metabolizes ADMA) and partly through decreased excretion through the urine. ADMA competes with NOS inhibiting the generation of NO, and SDMA inhibits endothelial NO production by limiting the availability of its main substrate L-arginine, as well as stimulating proinflammatory mediators such as IL-6 and TNF-alpha, which participate in increasing BP through inflammatory pathways that damage vessels.[57]

Vascular endothelial dysfunction is common in CKD.[56] One of the most important vascular endothelial functions is the ability to produce local vasodilator NO. Several pathways have been proposed to explain the endothelial dysfunction linked with the impaired NO production, including oxidative stress, L-arginine deficiency, and formation of ADMA and N-monomethylarginine.

Oxidative stress is a particularly potent means to impair endothelial function and potentiate hypertension. Cellular oxidation generates several species that are important signaling molecules. One potent stimulus to reactive oxygen species generation is angiotensin II. This is particularly evident when angiotensin II is infused in an animal model that is deficient in antioxidants. There is an increase in BP and urinary protein excretion, and kidney function declines substantially, more so than in other models, such as the DOCA-salt form of hypertension.[58] Other sources of oxidant stress include xanthine oxidase and NADPH oxidase. Testimony to the importance of xanthine oxidase is the reduction in the rate of kidney function loss when allopurinol is given to patients with CKD,[59] and the reduction in BP that occurs when adolescents with hyperuricemia are treated with allopurinol.[60]

Several other systems are also active to a pathologic degree in some patients with CKD. Among those amenable to potential drug treatment are endothelin[61] and aldosterone.[62] Endothelin levels are elevated in many CKD patients with uncontrolled BP, which may respond to an endothelin antagonist,[61,63] though this class of drugs is technically only FDA-approved for pulmonary hypertension.

DRUGS AND OTHER EXPOSURES

The anemia accompanying CKD is often treated by erythropoiesis-stimulating agents, which are known to increase BP. In addition, lead, nonsteroidal antiinflammatory drugs (NSAIDs), calcineurin inhibitors, and the use of illicit compounds such as cocaine are also potential contributors to increases in BP in CKD and ESRD patients.[64]

There is some progress on the role of genetic factors in BP regulation. There are several infrequent genotypes in which the link between the kidneys and hypertension has been described, mostly in the realm of sodium absorption, shedding light on important intrarenal BP regulation pathways.[65] Aside from diagnostic value, little new antihypertensive drug development has resulted from the pursuit of genetic studies.

NOVEL/NONTRADITIONAL MECHANISMS

Inflammation and the Immune System

Inflammation and immunity are gaining greater recognition as factors in the increased BP noted in several situations, including CKD. The role of T-regulatory cells in hypertension, and in CKD-associated hypertension, remains an active area of investigation. The various cells involved in the immune system generate reactive oxygen species, such as superoxides and hydrogen peroxides, which although intended to kill pathogens may lead to endothelial dysfunction through oxidant stress. Persistent inflammation results in a decrease in available NO, which results in impaired vascular relaxation. Both effector T cells, which participate in innate immunity, and regulatory T lymphocytes, which participate in adaptive immunity, contribute to vasoconstriction in hypertension through their participation in inflammation.[66] This is mediated in part through cytokine generation, adding another dimension to the impairment of endothelial function.[67]

Gut Microbiota

A growing body of evidence links metabolites and small peptides derived from gut microorganisms (bacterial, fungal, and viral) to changes in BP and uremic symptoms in CKD. Although the effects of the gut microbiome on BP, and uremic symptoms, appear to be mediated through pathways linked to metabolism, and pathways that intersect with immunity/inflammation, little is understood about specific mechanisms involved in BP effects from the microbiome.[68]

Arterial Stiffness

Several large cohorts have shown that, in addition to BP itself, arterial stiffness and increased pulse wave reflection are prominent in CKD and ESRD and are independent risks for death, CKD progression, and cardiovascular endpoints in CKD.[69–73] In the longitudinal follow-up of arterial stiffness measurements in the CRIC Study, increasing aortic stiffness, as estimated by carotid-to-femoral pulse wave velocity, was independently associated with death and the development of ESRD.[74] Several longitudinal studies have observed that increased arterial stiffness precedes a diagnosis of essential hypertension.[75,76] Given the frequent comorbidities present with a diagnosis of CKD, it is likely that underlying arterial stiffness plays an independent role in the increased BP noted with CKD.

CONCLUSIONS

Hypertension is highly prevalent in CKD and increases progressively as kidney function declines. The pathogenesis of hypertension in CKD is complex and multifactorial. Sodium/fluid retention and salt sensitivity, sympathetic dysfunction, and abnormalities in endothelial function are prominent features which contribute to hypertension, and which in turn potentiate the hypertensive effects of other factors.

There remain unanswered questions in the pathogenesis of hypertension in CKD. Large genetic studies may add more light on precise patient-related factors related to the development of hypertension, especially in CKD.[77] Immunity/inflammation, the microbiome, and arterial stiffness are newer areas of investigation to develop further our understanding of the pathogenesis of hypertension in the complex milieu of CKD.

References

1. Coresh J, et al. Prevalence of chronic kidney disease in the United States. *J Am Med Assoc* 2007;**298**(17):2038–47.
2. Hsu RK, Powe NR. Recent trends in the prevalence of chronic kidney disease: not the same old song. *Curr Opin Nephrol Hypertens* 2017;**26**(3):187–96.
3. Coresh J, et al. Prevalence of high blood pressure and elevated serum creatinine level in the United States: findings from the third National Health and Nutrition Examination Survey (1988-1994). *Arch Intern Med* 2001;**161**(9):1207–16.
4. Muntner P, et al. Low medication adherence and hypertension control among adults with CKD: data from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study. *Am J Kidney Dis* 2010;**56**(3):447–57.
5. Whelton PK, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018;**71**(6):e13–115.
6. Hsu CY, et al. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. *Arch Intern Med* 2005;**165**(8):923–8.
7. Muntner P, et al. Hypertension awareness, treatment, and control in adults with chronic kidney disease: results from the chronic renal insufficiency cohort (CRIC) study. *Am J Kidney Dis* 2009;**55**(3):441–51.
8. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. *J Am Med Assoc* 2010;**303**(20):2043–50.
9. Snyder JJ, Collins AJ. KDOQI hypertension, dyslipidemia, and diabetes care guidelines and current care patterns in the United States CKD population: National Health and Nutrition Examination Survey 1999-2004. *Am J Nephrol* 2009;**30**(1):44–54.
10. Sarafidis PA, et al. Hypertension awareness, treatment, and control in chronic kidney disease. *Am J Med* 2008;**121**(4):332–40.
11. Cohen DL, Huan Y, Townsend RR. Ambulatory blood pressure monitoring in chronic kidney disease. *Curr Hypertens Rep* 2013;**15**(3):160–6.
12. Drawz PE, et al. Masked hypertension and elevated nighttime blood pressure in CKD: prevalence and association with target organ damage. *Clin J Am Soc Nephrol* 2016;**11**(4):642–52.
13. Pogue V, et al. Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. *Hypertension* 2009;**53**(1):20–7.
14. Appel LJ, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010;**363**(10):918–29.
15. Brown MA, Whitworth JA. Hypertension in human renal disease. *J Hypertens* 1992;**10**(8):701–12.
16. Ridao N, et al. Prevalence of hypertension in renal disease. *Nephrol Dial Transplant* 2001;**16**(Suppl. 1):70–3.
17. Klag MJ, et al. End-stage renal disease in African-American and white men. 16-year MRFIT findings. *J Am Med Assoc* 1997;**277**(16):1293–8.
18. Gillum RF. The epidemiology of cardiovascular disease in black Americans. *N Engl J Med* 1996;**335**(21):1597–9.
19. Clark LT, Emerole O. Coronary heart disease in African Americans: primary and secondary prevention. *Clevel Clin J Med* 1995;**62**(5):285–92.
20. Friedman DJ, et al. Population-based risk assessment of APOL1 on renal disease. *J Am Soc Nephrol* 2011;**22**(11):2098–105.
21. Lipkowitz MS, et al. Apolipoprotein L1 gene variants associate with hypertension-attributed nephropathy and the rate of kidney function decline in African Americans. *Kidney Int* 2013;**83**(1):114–20.
22. Tedla FM, et al. Hypertension in chronic kidney disease: navigating the evidence. *Int J Hypertens* 2011;**2011**:132405.
23. Agarwal R, Lewis RR. Prediction of hypertension in chronic hemodialysis patients. *Kidney Int* 2001;**60**(5):1982–9.

24. Agarwal R, et al. Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. *Am J Med* 2003;**115**(4):291–7.
25. Cocchi R, et al. Prevalence of hypertension in patients on peritoneal dialysis: results of an Italian multicentre study. *Nephrol Dial Transplant* 1999;**14**(6):1536–40.
26. Tedla F, et al. Hypertension after renal transplant. *J Clin Hypertens* 2007;**9**(7):538–45.
27. Frequent Hemodialysis Network Group, et al. In-center hemodialysis six times per week versus three times per week. *N Engl J Med* 2010;**363**(24):2287–300.
28. Opelz G, Dohler B, Collaborative Transplant S. Improved long-term outcomes after renal transplantation associated with blood pressure control. *Am J Transplant* 2005;**5**(11):2725–31.
29. Kasiske BL, et al. Hypertension after kidney transplantation. *Am J Kidney Dis* 2004;**43**(6):1071–81.
30. Guyton AC, et al. The pathogenic role of the kidney. *J Cardiovasc Pharmacol* 1984;**6**(Suppl. 1):S151–61.
31. Koomans HA, et al. Salt sensitivity of blood pressure in chronic renal failure. Evidence for renal control of body fluid distribution in man. *Hypertension* 1982;**4**(2):190–7.
32. Sanders PW. Effect of salt intake on progression of chronic kidney disease. *Curr Opin Nephrol Hypertens* 2006;**15**(1):54–60.
33. Schalekamp MA, et al. Interrelationships between blood pressure, renin, renin substrate and blood volume in terminal renal failure. *Clin Sci Mol Med* 1973;**45**(4):417–28.
34. Ito Y, et al. Norepinephrine responsiveness in patients with borderline hypertension under three different sodium balances. *Clin Exp Hypertens* 1989;**11**(Suppl. 1):363–70.
35. Kobori H, et al. The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. *Pharmacol Rev* 2007;**59**(3):251–87.
36. Struthers AD, MacDonald TM. Review of aldosterone- and angiotensin II-induced target organ damage and prevention. *Cardiovasc Res* 2004;**61**(4):663–70.
37. Mehta PK, Griendling KK. Angiotensin II cell signaling: physiological and pathological effects in the cardiovascular system. *Am J Physiol Cell Physiol* 2007;**292**(1):C82–97.
38. Greene EL, Kren S, Hostetter TH. Role of aldosterone in the remnant kidney model in the rat. *J Clin Investig* 1996;**98**(4):1063–8.
39. Rozansky DJ, et al. Aldosterone mediates activation of the thiazide-sensitive Na-Cl cotransporter through an SGK1 and WNK4 signaling pathway. *J Clin Investig* 2009;**119**(9):2601–12.
40. Rubin MF, Townsend RR. Aldosterone blockade in diabetic nephropathy: relative risks and potential promise. *J Am Soc Nephrol* 2009;**20**(12):2487–9.
41. DiBona GF, Kopp UC. Neural control of renal function. *Physiol Rev* 1997;**77**(1):75–197.
42. Klein IH, et al. Sympathetic nerve activity is inappropriately increased in chronic renal disease. *J Am Soc Nephrol* 2003;**14**(12):3239–44.
43. Campese VM, Mitra N, Sandee D. Hypertension in renal parenchymal disease: why is it so resistant to treatment? *Kidney Int* 2006;**69**(6):967–73.
44. Krum H, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009;**373**(9671):1275–81.
45. Esler MD, et al. Renal sympathetic denervation for treatment of drug-resistant hypertension: one-year results from the symplicity HTN-2 randomized, controlled trial. *Circulation* 2012;**126**(25):2976–82.
46. Symplicity HTN-1 Investigators, et al. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* 2011;**57**(5):911–7.
47. Symplicity HTN-2 Investigatros, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010;**376**(9756):1903–9.
48. Hering D, et al. Renal denervation in moderate to severe CKD. *J Am Soc Nephrol* 2012;**23**(7):1250–7.
49. Schlaich MP, et al. Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with end-stage renal disease. *Int J Cardiol* 2013;**168**(3):2214–20.
50. Converse Jr RL, et al. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992;**327**(27):1912–8.
51. Desir GV, Wang L, Peixoto AJ. Human renalase: a review of its biology, function, and implications for hypertension. *J Am Soc Hypertens* 2012;**6**(6):417–26.
52. Kohno M, et al. Therapeutic benefits and safety of carvedilol in the treatment of renal hypertension. An open, short term study. Carvedilol Renal Hypertension Study Group in Japan. *Drugs* 1988;**36**(Suppl. 6):129–35.
53. Wright Jr JT, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *J Am Med Assoc* 2002;**288**(19):2421–31.
54. Messerli FH. Doxazosin and congestive heart failure. *J Am Coll Cardiol* 2001;**38**(5):1295–6.
55. Aucella F, et al. Methylarginines and mortality in patients with end stage renal disease: a prospective cohort study. *Atherosclerosis* 2009;**207**(2):541–5.
56. Martens CR, Edwards DG. Peripheral vascular dysfunction in chronic kidney disease. *Cardiol Res Pract* 2011;**2011**:267257.
57. Schepers E, et al. Symmetric dimethylarginine as a proinflammatory agent in chronic kidney disease. *Clin J Am Soc Nephrol* 2011;**6**(10):2374–83.
58. Haugen EN, Croatt AJ, Nath KA. Angiotensin II induces renal oxidant stress in vivo and heme oxygenase-1 in vivo and in vitro. *Kidney Int* 2000;**58**(1):144–52.
59. Goicoechea M, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *Clin J Am Soc Nephrol* 2010;**5**(8):1388–93.
60. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *J Am Med Assoc* 2008;**300**(8):924–32.
61. Dhaun N, Goddard J, Webb DJ. The endothelin system and its antagonism in chronic kidney disease. *J Am Soc Nephrol* 2006;**17**(4):943–55.
62. Del Vecchio L, et al. Mechanisms of disease: the role of aldosterone in kidney damage and clinical benefits of its blockade. *Nat Clin Pract Nephrol* 2007;**3**(1):42–9.
63. Richter CM. Role of endothelin in chronic renal failure–developments in renal involvement. *Rheumatology (Oxford)* 2006;**45**(Suppl. 3):iii36–8.
64. Agarwal R. Hypertension in chronic kidney disease and dialysis: pathophysiology and management. *Cardiol Clin* 2005;**23**(3):237–48.
65. Lifton RP. Genetic dissection of human blood pressure variation: common pathways from rare phenotypes. *Harvey Lect* 2004;**100**:71–101.
66. Harrison DG, et al. Inflammation, immunity, and hypertension. *Hypertension* 2011;**57**(2):132–40.

67. Agita A, Alsagaff MT. Inflammation, immunity, and hypertension. *Acta Med Indones* 2017;**49**(2):158–65.
68. Yang T, et al. The gut microbiota and the brain-gut-kidney axis in hypertension and chronic kidney disease. *Nat Rev Nephrol* 2018; **14**(7):442–56.
69. Townsend RR, et al. Aortic PWV in chronic kidney disease: a CRIC ancillary study. *Am J Hypertens* 2010;**23**(3):282–9.
70. Townsend RR, et al. Central pulse pressure in chronic kidney disease. A chronic renal Insufficiency cohort ancillary study. *Hypertension* 2010;**56**(3):518–24.
71. Briet M, et al. Arterial stiffness and pulse pressure in CKD and ESRD. *Kidney Int* 2012;**82**(4):388–400.
72. Vlachopoulos C, et al. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *Eur Heart J* 2010;**31**(15):1819–22.
73. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; **55**(13):1318–27.
74. Townsend RR, et al. Association of pulse wave velocity with chronic kidney disease progression and mortality: findings from the CRIC study (chronic renal insufficiency cohort). *Hypertension* 2018;**71**(6):1101–7.
75. Najjar SS, et al. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. *J Am Coll Cardiol* 2008;**51**(14):1377–83.
76. Kaess BM, et al. Aortic stiffness, blood pressure progression, and incident hypertension. *J Am Med Assoc* 2012;**308**(9):875–81.
77. Evangelou E, et al. Publisher correction: genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat Genet* 2018;**50**(12):1755.

QUESTIONS AND ANSWERS

Question 1

Hypertension in patients with underlying CKD is more likely to be associated with all of the following except?

A. More severe hypertension than matched controls without CKD
B. Difficulty in control
C. Requirement for more BP medications to achieve control of hypertension
D. Poorer compliance with BP medications than matched controls without CKD
E. Increased risk of cardiovascular disease

Answer: D

Hypertension in CKD is more severe, more difficult to control, requires more medications, and is associated with increased CVD than patients with hypertension without preexisting CKD. Although most CKD patients require multiple antihypertensive agents to control BP, nonadherence does not appear to be more common in CKD patients compared with the general population.

Question 2

A 55-year-old man with stage 3 CKD, hypertension, and gout presents for a routine office visit. He says when he checks his BP at home, it is usually around 150/90−95 mm Hg. He has no other complaints. He takes lisinopril 20 mg daily, amlodipine 5 mg daily, and hydrochlorothiazide 25 mg daily. On examination, his BP is 132/84 mm Hg and 136/82 mm Hg in the office. The rest of his physical examination is benign. His laboratory examination is stable, S[Cr] is 1.6 mg/dL. The next step in his management would be?

A. Increase lisinopril to 40 mg daily
B. No change to his management
C. Schedule a 24-hour ambulatory BP monitor
D. Increase amlodipine to 10 mg daily
E. Add a fourth BP agent to his current regimen

Answer: C

Masked hypertension is defined as patients who have normal office BP readings but elevated BP readings on ABPM or home BP. Masked hypertension is more common in CKD and has been shown to be present in studies using ABPM in this population. It is important to identify masked hypertension so the physician can appropriately treat BP to the desired goal. In the AASK Disease Cohort Study, of the 61% of participants with controlled clinic BP, 70% had masked hypertension. This is thought to be the reason why these patients had progressive CKD despite good office BP control.

Question 3

All of the following dugs contribute to increased hypertension in CKD except?

A. Erythropoietin and other erythropoietic agents
B. NSAIDs
C. Use of illicit substances such as cocaine
D. Acetaminophen-containing agents
E. Calcineurin inhibitors

Answer: D

Many drugs contribute to worsening hypertension in CKD patients, including erythropoietin-stimulating agents, NSAIDS, calcineurin inhibitors, and cold preparations containing pseudoephedrine type substances. Some migraine preparations and use of illicit drugs such as cocaine also may contribute to or exacerbate hypertension. Acetaminophen does not worsen hypertension.

Question 4

A 54-year-old woman has an ambulatory BP monitor performed for suspected white coat hypertension. Which of the following is not typically associated with CKD?

A. Masked hypertension
B. White coat hypertension
C. Night time dipping of 10%
D. Reverse dipping pattern
E. Altered circadian rhythm

Answer: C

Patients with CKD may have an abnormal circadian rhythm associated with nondipping, reverse dipping, and frequency masked hypertension. White coat hypertension is also frequently seen and may lead to overdiagnosis of hypertension in CKD.

Question 5

Which of the following is not typically associated with the pathophysiology of hypertension in CKD?

A. Hyperactivation of the RAAS
B. Low renin
C. Hyperactivation of the sympathetic nervous system
D. Salt sensitivity
E. Disordered endothelial cell dysfunction

Answer: B

Hypertension in CKD is associated with hyperactivation of the RAAS and sympathetic nervous systems and disordered endothelial dysfunction. CKD patients often do not have normal suppression of plasma renin activity given their usual state of sodium retention and volume expansion; therefore, renin activity is inappropriately

high. CKD patients are also salt sensitive, with increasing salt sensitivity as GFR declines.

Question 6

A 44-year-old man with stage 4 CKD and S[Cr] 2.8 mg/dL due to focal segmental glomerulosclerosis presents to the renal clinic for ongoing routine care. He does not check his BP at home regularly. He has no specific complaints. His antihypertensive regimen currently is losartan 100 mg daily, clonidine 0.2 mg t.i.d., amlodipine 10 mg daily, and metoprolol XR 50 mg daily. His BP is 165/98 mm Hg. His heart rate is 65 beats/minute. Trace pedal edema is present. 100 mg of proteinuria per 24 hours is present. The rest of the physical examination is benign.

What adjustment would be appropriate to improve BP control?

A. Add lisinopril 20 mg daily
B. Change to catapres patch #3
C. Increase metoprolol to 100 mg daily
D. Add torsemide 20 mg daily
E. Add minoxidil 5 mg daily

Answer: D

All of the above medication changes could be implemented, but the most critical would be to add a diuretic. Resistant hypertension is defined as BP greater than 140/90 mm Hg in a patient on maximal doses of at least three antihypertensive agents, one of which must be a diuretic. Addition of furosemide to this patient's regimen should result in lowering of BP and improved control. Use of minoxidil causes fluid retention, and this should not be used without concomitant use of furosemide.

CHAPTER

22

Chronic Kidney Disease and the Vascular Endothelium

Michael S. Goligorsky

Departments of Medicine, Pharmacology and Physiology, Renal Research Institute, New York Medical College, Valhalla, NY, United States

Abstract

Although historically the contribution of the endothelium to chronic kidney disease (CKD) had been neglected, recent investigations provide conclusive evidence of its role in maintaining tissue homeostasis, supporting tissue regeneration, and, when dysfunctional, instigating development and progression of tissue fibrosis. These findings are of critical importance for understanding the development of nephrosclerosis and the progression of CKD. Three endothelial pathways involved in the progression of CKD include stress-induced premature senescence of endothelial cells, the endothelial–mesenchymal transition, and the loss of the endothelial surface layer. These abnormalities are involved in the pathogenesis of proteinuria, a pro-inflammatory microenvironment, microvascular rarefaction, a profibrotic state, and failure of regeneration. Therapeutic strategies to overcome endothelial cell dysfunction and its renal consequences are discussed.

Weighing 1 kg and covering a surface area of 7000 m^2, the human vascular endothelium constitutes a large monolayer organ penetrating almost all compartments of the body. The main functions of this organ include regulation of vasomotion through production of endothelium-derived vasoactive substances, fine tuning of vascular permeability; and exchange of solutes, gaseous molecules, and macromolecules between the blood and the interstitium, regulation of coagulation and fibrinolysis, control of the trafficking of circulating immune-competent cells, and a recently discovered angiocrine-mediated regulation of tissue regeneration. Some or all of these functions may become compromised in CKD, leading to far-reaching consequences, such as predisposition to cardiovascular morbidity and progression of CKD. This chapter will (a) illustrate the role of the vascular endothelium in the induction and maintenance of CKD, (b) discuss established and potential mechanisms whereby the endothelium can affect CKD progression, (c) outline pathways that explain the role of endothelial stem and progenitor cells in regenerative processes, and (d) propose strategies to alleviate endothelial dysfunction and, by doing so, slow the progression of CKD.

DEVELOPMENT AND LIFE-SPAN OF THE VASCULAR ENDOTHELIUM

During early embryonic development, mesodermal cells migrate toward the extraembryonic yolk sac and create "blood islands." The outer luminal layer of blood islands contains endothelial precursors, and the inner mass consists of hematopoietic precursors. The aorto-gonado-mesonephric region (AGM), which harbors endothelial progenitor cells (EPC), becomes the first hematopoietic organ due to the ability of EPC to give rise to hematopoietic stem cells (HSC) and mesenchymal stem cells (MSC).[1,2] This ability is conserved in mammals throughout adulthood, long after the disappearance of the AGM. The process of embryonic endothelial–hematopoietic transition in zebrafish occurs through a unique Runx1-dependent mechanism of endothelial cell bending and escaping the aortic ventral wall in the direction of the subaortic space.[3] This process bears some similarities to the transition of adult endothelial cells (EC) into pericytes, as described in adipose tissue.[4,5] EC insert or "dive" into the basement membrane, in the process transitioning to the pericyte, which later acquires the properties of MSC and preadipocytes. It is not known whether similar processes take place in the renal microcirculation.

EPC and endothelial stem cells are represented in all vascular beds and play a role in vasculogenesis and

https://doi.org/10.1016/B978-0-12-815876-0.00022-X

angiogenesis.[6] Solitary cells or small clusters of EPC are present in all three layers: adventitial, medial, and intimal. These c-Kit+/VEGFR2+/CD45 cells are clonogenic and can differentiate toward EC, smooth muscle cells (SMC), and fibroblasts.[7] A small number of c-Kit-expressing EC (lin−CD31+ CD105+ Sca1+ CD117/c-Kit+) reside in the adult blood vessel endothelium. This subpopulation can undergo clonal expansion *in vivo* and *in vitro*, whereas other EC have a very limited proliferative capacity.[8,9] These c-Kit+ adult vascular endothelial stem cells (VESCs) comprise only 0.4% of all adult vessel wall lin-CD31+ CD105+ ECs. Transplantation of isolated VESCs confirmed that a single c-kit+ VESC can generate *in vivo* functional blood vessels that connect to the host circulation. By performing repeated rounds of cell isolation and *in vivo* serial transplantation, it has been demonstrated that VESCs also display long-term self-renewal capacity.

Yoder and coworkers[10] determined that the expression of neuropilin-1 (NP-1) in human pluripotent stem cells confers on them commitment toward endothelial lineage, which results in formation of NP-1+CD31+ cells highly resembling those obtained from the cord blood. Future studies are required to compare lin− CD31+CD105+ Sca1+CD117/c-Kit+ with NP-1+CD31+ cells to elucidate whether these are overlapping populations or distinct ones.

Endothelium-dependent vasorelaxation and angiogenic competence are reduced in aging compared to young animals.[11] A similar defect occurs in prematurely senescent Klotho mice.[12] Caloric restriction rescues angiogenic competence.[13]

One of the downstream targets of caloric restriction, sirtuin-1, is robustly expressed in EPC and EC. Sirtuin-1 expression declines with age and following application of cardiovascular stressors.[14] The mechanism of sirtuin-1 deficiency leading to premature senescence of EPC and EC is demonstrated by the stress-induced loss of integrity of lysosomal membranes and leakage of cathepsins, which are capable of directly degrading this deacetylase, as shown in *in vitro* studies.[14] EPC isolated from the bone marrow of mice genetically engineered to lack endothelial sirtuin-1 exhibit higher rates of premature senescence and apoptosis even at young ages.[14]

Endothelial cell turnover is very slow under physiological conditions. In different vascular beds it has been estimated to vary from 2 months to 3 years.[15] The disposal of damaged EC occurs as a result of the patrolling function of a noninvading subset of $Ly6C^{low}$ monocytes. Intravital microscopy studies demonstrated that these monocytes crawl on the luminal surface of glomerular and peritubular capillaries and scavenge microparticles.[16] In response to nucleic acid "danger" signaling, $Ly6C^{low}$ monocytes exhibit prolonged dwell times in glomerular and peritubular capillaries, more complex patrolling routes, attachment to damaged EC, and recruitment of neutrophils, which induce focal necrosis and disposal of cellular debris. Cells that escape this *in situ* disposal mechanism detach from their basement membranes and appear in the circulation.

STRUCTURAL COMPONENTS OF RENAL MICROVASCULATURE

EC are heterogeneous. They have specialized functions in every organ. In addition to nutrient delivery, gas exchange, and removal of waste products, they produce diverse paracrine-trophic, angiocrine factors necessary for differentiation and regeneration of tissues as dissimilar as pancreatic acini, neurons, hematopoietic precursors, hepatocytes, or alveolar epithelia.[17] Angiocrine factors relevant to the kidney are yet to be characterized.

Glomerular and peritubular capillary endothelium is fenestrated. Fenestrae, most probably, lack diaphragms. Instead, EC are coated with an endothelial surface layer (ESL), consisting of an electron-dense, fluffy glycocalyx composed of covalently membrane-bound proteoglycans and the inner, luminal cell coat layer composed of charge-interacting proteoglycans, glycosaminoglycans, glycoproteins, and plasma proteins.[18] Of note, these layers, in addition to the basement membrane and slit diaphragms in podocytes, are in part responsible for glomerular permselectivity, as demonstrated by enzymatic degradation or high-salt elution of glycosaminoglycans resulting in proteinuria, with other structures of the glomerular filtration barrier remaining intact. These structures remain similarly intact in transgenic mice overexpressing angiopoietin-2 in podocytes, characterized by apoptosis of glomerular EC and development of proteinuria.[19] Salmon et al.[20] demonstrated that old Munich-Wistar-Fromter rats exhibit a widespread loss of ESL, not only in fenestrated glomerular EC but in continuous mesenteric microvessels as well, and develop increased microvascular permeability and proteinuria.

Glomerular EC and podocytes together with the basement membrane form a functional filtration and permselectivity unit. The endothelium maintains podocytes through secretion of platelet-derived growth factor (PDGF), while podocytes maintain the endothelium through release of VEGF to the glomerular basement membrane. Furthermore, increased production of endothelin-1 by stressed EC triggers shedding of the key component of slit diaphragms, nephrin, from podocytes.[21] Therefore, any damage to each of the members

of this functional unit results in a defective performance of the other.

PRIMARY ENDOTHELIAL DYSFUNCTION LEADING TO KIDNEY DISEASE

The cooperative behavior of EC and pericytes or podocytes plays a key role in the development of kidney disease induced by activation of and damage to the vascular endothelium. This is best illustrated by cases of development of kidney disease in preeclampsia, HUS, TTP, and complications of anti-VEGF treatments.

In preeclampsia, which complicates 3–5% of pregnancies, the immune- and/or cytotrophoblast-mediated activation of EC results in the imbalance of prostacyclin/thromboxane production, elevated production of asymmetric dimethylarginine (ADMA), reduced generation of annexin-V,[22] increased shedding of the VEGF receptor-1 (soluble VEGFR1, sFlt-1), and endoglin.[23] All these factors conspire to compromise the viability of EC, induce thrombophilia, impair vasomotion, and eventually affect the renal microcirculation exemplified by the appearance of proteinuria and hypertension. A similar mechanism may contribute to endothelial dysfunction in CKD. Di Marco et al.[24] demonstrated that in patients with CKD plasma levels of sFlt-1 were elevated compared to healthy controls. Levels of sFlt-1 were found exclusively to be associated with renal function and degree of endothelial dysfunction, and they may predict cardiovascular risk.

In TTP, exocytosis of Weibel–Palade bodies and release of multimeric von Willebrand factor (vWF) are impaired, due to the defect in the metalloprotease ADAMTS13 (either due to genetic abnormalities as in Upshaw–Schulman syndrome, or due to autoimmune production of anti-ADAMTS13 antibodies), which normally cleaves ultralarge multimers of vWF. Defective cleavage results in formation of vWF multimeric "strings" on the surface of EC and in the circulation, leading to platelet aggregation and disseminated thrombophilia,[25] followed by the development of proteinuria and renal insufficiency. Damage to the endothelium in HUS is mediated by members of the Shiga toxin family, which bind to their specific receptor globotriaosylceramide on the surface of EC. After receptor-mediated endocytosis, they inactivate 28S ribosomal RNA and inhibit protein synthesis.[26–28] Despite these differences, there is growing realization that both syndromes have common roots, as Shiga toxin was found to induce release of vWF from EC and impair its cleavage *in vitro* and *in vivo*, producing a TTP-like syndrome in mice lacking ADAMTS13.[29] In both cases endothelial dysfunction plays a paramount role. Both disorders only rarely result in CKD. Perhaps this can be explained by the fact that the acutely developing endothelial dysfunction is reversible on removal of the causative agent, while persistent activation of the endothelium may lead to the development of chronic disease.

Therapeutic use of anti-VEGF antibodies in cancer patients revealed development of proteinuria as their on-target side effect.[30] Analogous functional and morphologic perturbations are observed in genetically engineered mice lacking VEGF production by podocytes. These findings reinforce the role of VEGF in the maintenance of glomerular endothelial architecture and the existing cross talk between the endothelium and the neighboring podocytes.

ANGIOGENIC INCOMPETENCE IN CKD

Studies by Bohle et al. demonstrated microvascular rarefaction at the sites of tubulointerstitial fibrosis.[31,32] These observations were confirmed and mechanistically expanded in a series of studies by Johnson's group,[33] giving rise to the idea that microvascular rarefaction and tubulointerstitial fibrosis are causally linked. Such a link has been also established in glomerulosclerosis. In a rat renal ablation model, injury and activation of EC was associated with a biphasic response, characterized by an early hypertrophic phase, followed in 3 weeks by increased expression of fibronectin, laminin B1, angiotensinogen, and TGF-β1 RNA transcripts, all becoming widespread among endothelial and mesangial cells in sclerotic areas 2.5 months after ablation.[34] This scenario is typical of the angiogenic wound-healing response to injury, which is triggered by proinflammatory mediators, causing local release of VEGF by platelets and ischemic parenchyma, followed by increased microvascular permeability with the leakage of matrix proteins (some of which have antiangiogenic properties) and culminating in vascular drop-out and tissue scarring. This process is partially recapitulated in rat models of focal segmental glomerulosclerosis and other human glomerulopathies. Kriz et al.[35] described the development of synechia between glomerular capillaries and Bowman's capsule. Because synechia contain perfused glomerular capillaries, this leads to filtration of plasma proteins into the paraglomerular and peritubular spaces, proliferation of interstitial fibroblasts, and eventual remodeling toward glomerulosclerosis, tubulointerstitial fibrosis, and formation of atubular glomeruli. The biphasic response of the renal microvascular endothelium to injury, namely, the initial proliferative, angiogenic phase and the later antiangiogenic microenvironment predisposing to obliteration of vascular beds explains the divergent results of several

therapeutic strategies. For instance, in the early proliferative stages of diabetic nephropathy, anti-VEGF treatments may be beneficial, whereas stimulation of angiogenesis may become preferable during fibrotic remodeling in CKD. In most cases the second phase predominates, as is the case with anti-GBM nephritis, where within 3–8 weeks after induction of injury, peritubular capillaries are found to be rarefied, EC undergo apoptotic cell death, and fibrosis ensues.[36] The loss of the glomerular capillary endothelium occurs within a similar time course. These findings are consistent with the conclusion that glomerular capillary regression due to the injury and angiogenic incompetence lead to glomerular sclerosis.[37] Similar observations were made in other models of renal disease, as well as in the aging kidney, where the loss of endothelial nitric oxide synthase and peritubular capillaries is associated with the development of tubulointerstitial fibrosis.[38] Severe acute renal ischemia leads to the gradual loss of peritubular capillaries in the inner stripe of the outer medulla even before the development of manifest tubulointerstitial disease.[39] In humans with different types of chronic tubulointerstitial disease, rarefaction of peritubular capillaries occurs in association with a variable pattern of VEGF expression. Increased VEGF expression in morphologically intact areas and decline in sclerotic glomeruli have been described.[40] Persistent, cyclosporine A-resistant rejection of transplanted kidneys differs from the treatment-responsive cases in that the former exhibits the loss of peritubular capillaries and proliferation of myofibroblasts, leading to progressive interstitial fibrosis.[41]

The main process responsible for ablation of the microvasculature involves the following steps. Damaged EC precipitate cessation of normal blood flow and perturb the flow-dependent shear stress–induced activation of eNOS, leading to further cell damage and apoptosis. These damaged and apoptotic EC induce local platelet adhesion and attract macrophages, which in turn recruit other leukocytes, eventually disposing of cell debris.[15] That leaves behind a decellularized basement membrane, referred to as a string vessel or empty basement membrane tube. The remaining scaffold of the basement membrane is rich in endothelial and pericyte growth factors, such as VEGF, basic fibroblast growth factor, and PDGF. These growth factors guide repopulation of string vessels with EC, leading to the deposition of a new layer of basement membrane material, potentially restoring blood flow to the area. Restoration of the endothelial lining of string vessels occurs by proliferation of EC and is assisted by EPC.[42] Sequential rounds of recellularization of string vessels result in the appearance of thickened basement membranes, a frequent morphologic companion of renal disease.

Why does the rarified microvasculature in CKD not undergo self-repair *via* angiogenic or vasculogenic processes? Sprouting angiogenesis is initiated by the gradient in VEGF-A and Notch receptor, which guides the pathfinder "tip" EC to navigate within the interstitium and direct the "stalk" EC to the growing vessel branch.[2] Endothelial SIRT1 exerts an inhibitory effect on signaling by the Notch intracellular domain, which is usually expressed in stalk cells of sprouting angiogenic vessels, thus resulting in enhanced angiogenesis. Reduced NAD abundance in aging cells leads to reduced SIRT1 activity. This can be reversed by supplementation with an NAD precursor, nicotineamide mononucleotide.[43] Other guidance cues, such as class 3 semaphorins, netrins, and SLIT proteins assist in orchestrating this process. Forming sprouts undergo lumenization and mature by recruiting mural cells, pericytes and SMC, to stabilize and maintain their structure. Bone marrow-derived EPC were proposed to contribute to angiogenesis, but their direct contribution through engraftment of growing vessels has recently been questioned. This multistep angiogenic process can be disrupted at multiple, but as of yet not precisely identified, stages. Endothelial dysfunction is the main contributor to the insufficiency of angiogenesis to meet metabolic requirements. EC exposed to diverse cardiovascular risk factors exhibit impaired ability to form angiogenic sprouts even in the presence of VEGF-A.[44,45] Angiopoietin-1 deficiency further contributes to microvascular rarefaction.[46] This imbalance between the demand and supply leads to the observed microvascular rarefaction, patchy tissue hypoxia, and fibrosis (Figure 22.1).

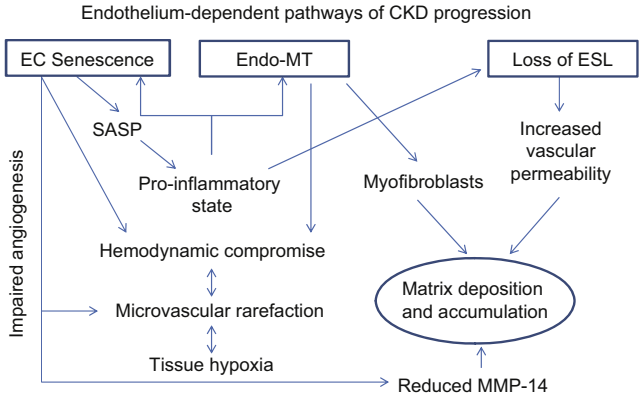


FIGURE 22.1 **Endothelium-dependent pathways of chronic kidney disease progression.** *Endo-MT,* endothelial–mesenchymal transition; *ESL*, endothelial surface layer; *SASP*, senescence-associated secretory products.

ENDOTHELIAL CELL DYSFUNCTION IN CKD—TRANSCRIPTOMIC AND METABOLIC ANALYSES

Multiple lines of evidence indicate that endothelial cell dysfunction (ECD) develops in CKD. Flow-dependent relaxation of conduit vessels, a function of endothelium-derived relaxing factors, mainly NO production, is suppressed in patients and animals with CKD. Different modifications of testing endothelium-dependent vasorelaxation have become the standard for diagnosing ECD, together with other surrogate biomarkers such as markers of oxidative stress (8-iso-PGF2α and oxidized LDL), markers of inflammation (high-sensitivity CRP, lipoprotein-associated PLA2, soluble ICAM-1, IL-6, von Willebrand factor), the inhibitor of eNOS ADMA, circulating procoagulants, and others.[47] Diverse traditional and nontraditional risk factors for cardiovascular disease (CVD), such as ADMA, advanced glycation end products, and prooxidants, all accumulating in CKD, conspire to induce ECD by eNOS uncoupling (Figure 22.2). Cardiovascular microarray gene screens of EC with inhibited or uncoupled eNOS revealed that this condition is associated with upregulation of the receptor for oxidized LDL (LOX-1),[48] induction of 3-hydroxy-3-methylglutaryl coenzyme A reductase leading to endothelial lipidosis,[49] upregulation and redistribution of a gap-junctional protein connexin-43, resulting in perturbed transmission of endothelium-derived hyperpolarizing factor to vascular SMC,[50] increased synthesis of collagen XVIII[51], and accumulation of its antiangiogenic fragment, endostatin, which actuates endothelial−mesenchymal transition (Endo-MT).[52] Transcriptomic analyses of iliac arteries from renal transplant recipients and renal arteries from healthy living kidney donors revealed 15 differentially expressed gene transcripts with upregulation of mRNAs associated with apoptosis, NF-kB signaling, smooth muscle contractility, HIF-3α, and vimentin, among others.[53]

ECD is associated with profound metabolic abnormalities. Such abnormalities can not only initiate but also tend to aggravate preexisting ECD. Screening renal microvascular isolates obtained from mice with inhibited eNOS revealed (using 2-D electrophoresis, in-gel digestion and mass-spectrometry analyses) at

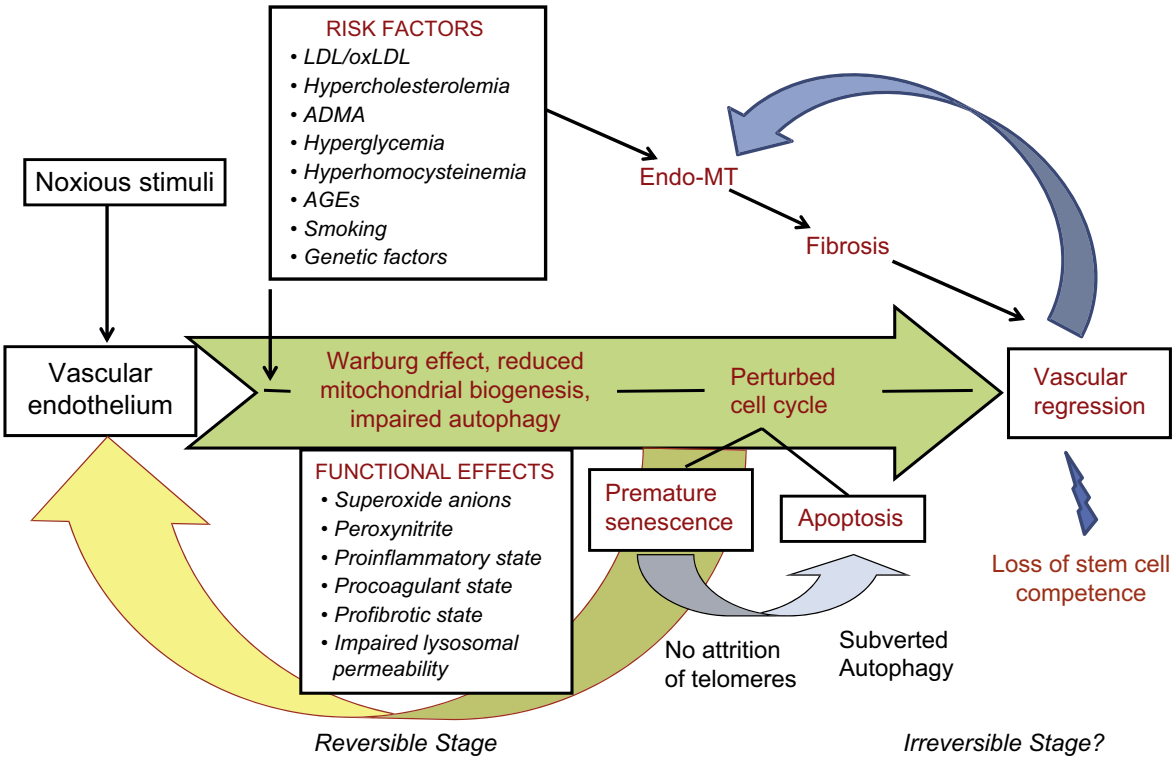


FIGURE 22.2 Mechanisms of endothelial dysfunction, premature senescence and microvascular rarefaction. A long list of traditional and nontraditional risk factors illustrates the vulnerability of endothelial cells, which respond to these stressors by evoking a cascade of reactions summarized under the rubric "Functional Effects." These result in impaired intermediary metabolism with a switch toward a Warburg-like normoxic glycolysis, reduced mitochondrial biogenesis, and subverted autophagy, a result of lysosomal dysfunction. Cell cycle arrest and development of premature senescence of endothelial cells follows. Notably, this type of senescence is not associated with attrition of telomeres and, if the effects of noxious stimuli and risk factors are eradicated, the cells have the potential to reverse to a normal state. The point-of-no-return is not well-defined, but perhaps is determined by the persistence of noxious stimuli, loss of stem cell competence, endothelial−mesenchymal transition, and progressive microvascular drop-out. The details of this sequence of events are provided in the text. *Endo-MT*, endothelial−mesenchymal transition.

least 13 nonredundant differentially expressed proteins with high level of confidence. Five of those are specific for mitochondria, and two downregulated proteins, aconitase-2 and enoyl-coA-hydratase-1, are components of the Krebs cycle.[54] This deficiency of key enzymes is associated with reduced mitochondrial mass, mitochondrial oxidative stress, and a switch to normoxic glycolysis (Warburg type of metabolic hypoxia seen in chronic uncoupling of eNOS) to support energy metabolism. Moreover, by supplying cultured cells with the metabolic intermediate downstream of the deficient aconitase-2—α-ketoglutarate (which enters the Krebs cycle bypassing the enzymatic bottleneck)—it becomes possible to restore energy metabolism and prevent cell death or premature senescence. These findings raise the question whether it could be possible to restore EC metabolism in ECD by supplementing animals with glutamine. This question has been addressed in follow-up metabolomic studies of isolated renal microvasculature and plasma of mice chronically receiving an eNOS uncoupler with and without glutamine supplementation. This treatment ameliorated vasculopathy (as judged by restored endothelium-dependent vasorelaxation) and decreased proteinuria.[55] In addition, metabolomic studies conducted using liquid chromatography−mass spectrometry analyses disclosed multiple metabolite abnormalities developing in ECD and restored by glutamine supplementation. Among those were elevated lysophospholipids and hippuric acid, and reduced levels of glutamine/glutamate, which were normalized after glutamine supplementation.[55] Hence, metabolic abnormalities affect EC functions. Correcting these abnormalities leads to amelioration of ECD and vasculopathy, both of which contribute to the progression of CKD.

Another metabolic aberration typical of CKD consists of the activation of glycocalyx-degrading enzymes such as heparanases, hyaluronidases, and ADAM17, which leads to structural and functional damage to the endothelial glycocalyx, the structure that is normally responsible for the mechanotransduction of flow parameters to eNOS, regulation of permeability, deterrence of leukocytes, protection from oxidative stress, and harboring growth/survival factors.[56–58]

PREMATURE ENDOTHELIAL CELL SENESCENCE IN CKD

A role of telomere attrition and cell senescence in aging and diseased kidneys has been initially promoted by Halloran's group.[59] It has become clear from studies by Chen et al.[60] that stress-induced premature senescence (SIPS) of EC occurs even in the presence of relatively unaffected telomeres. A diverse group of stress signals, such as prooxidants, ADMA, and nonenzymatically glycation-modified proteins induce cell cycle arrest, SIPS, and eventual apoptosis in low-passage cultured cells and in young mice. A flow-chart depicting the role of SIPS in microvascular drop-out is shown in Figure 22.2. It emphasizes the fact that SIPS can be reversed after the withdrawal of the offending stressor. If the stressor persists, SIPS becomes irreversible, and EC may undergo apoptosis, which culminates in microvascular rarefaction.

Senescent EC not only disrupt the function of the endothelial lining of the vessels but also affect the neighboring cells by their secretome, collectively designated as senescence-associated secretory products (SASP). SASP contain TGF-alpha, galectin-3, IGFBP-3, -4, and -6, and MIC-1.[61] Dysfunctional senescent EC also release collagen XVIII and its C-terminal antiangiogenic fragment, endostatin.[52] High-resolution mass spectrometric analysis of the secretome of EPC disclosed 133 proteins, some known as membrane-bound, others as secreted.[62] Specifically, soluble forms of VEGF receptors, adhesion molecules, semaphorin 3F and TGF-β, CD109, members of the roundabout (robo) family, and endothelial markers were detected. Mass spectrometry screen of the secretome of colony-forming units, precursors of mature EC, identified 272 nonredundant proteins, of which 124 were also found in cultured EPC.[63] Secretory products included MMP-9, IL-8, MIF, various cathepsins and protease inhibitors, S100 proteins A11, A8 and A4, PAI-2 and apolipoprotein E, as well as a proangiogenic and prosurvival factor, thymidine phosporylase. These investigations explain the observed incipient shift from "cell-based therapy" to "cell-free therapy". Several successful and on-going clinical trials, conducted mostly in patients with CVD, are underway.

Regeneration of the microvasculature is further impaired by the production of antiangiogenic substances, such as endostatin, and developing incompetence of EPC. EST has been described as an interactive partner of another profibrogenic factor, transglutaminase 2 (TG2), an enzyme cross-linking extracellular matrix proteins, rendering them resistant to proteolytic degradation, which is elevated in kidney disease and aging.[64] Individually EST and TG2 suppress angiogenesis. Transgenic mice overexpressing EST show renal interstitial fibrosis at a young age. Injection of TG2 in the intact kidney produces increased cross-linking within 24 hours, and increased matrix accumulation was detected after two weeks. Subcapsular injection of TG2 or EST in kidneys of young mice not only induced fibrosis but also increased the proportion of prematurely senescent cells. In addition, obliteration of the microvasculature occurs *via* Endo-MT.

ENDOTHELIAL-MESENCHYMAL TRANSITION

Endo-MT is a physiological developmental stage occurring during embryonic formation of heart valves and septa. In adulthood, Endo-MT is implicated in pulmonary hypertension, vein graft failure, atherosclerosis, and metastatic spread of malignant cells. Endo-MT is a major contributor to vascular drop-out and development of tubulointerstitial fibrosis, as detected in three different models of renal disease—unilateral ureteral obstruction, streptozotocin-induced diabetic nephropathy, and a mouse model of Alport syndrome.[65,66] About 30–50% of interstitial fibroblasts were found to originate from the endothelium. TGF-β is a major mediator of Endo-MT, and BMP-7 is a factor counteracting Endo-MT, as demonstrated using an endothelial cell fate-tracing technique. Actions of TGF-β are mediated *via* activin receptor-like kinases 1 and 5 (Alk1 and Alk5). Activation of Alk1, selectively expressed on EC, results in cell migration, proliferation, and angiogenesis, while stimulation of Alk5 induces (*via* Smads 2/3 phosphorylation) the transcription of SM22α, fibronectin, and PAI-1, which mediate differentiation along the smooth muscle/mesenchymal phenotype, leading to formation of myofibroblasts. The balance between activation of these two Alk pathways is regulated by endoglin, another specific endothelial TGF coreceptor. Prolonged activation with TGF-β results in the escape of Alk1 signaling and predominant signaling *via* Alk 5, thus promoting Endo-MT.[67] A recent study of Endo-MT showed that energy-supplying mitochondrial β-oxidation of long-chain fatty acids (FAO) in EC is inhibited by TGF-β signaling.[68] Reduced activity of FAO results in a fall of acetyl-CoA levels and impaired acetylation of SMAD7, leading to the liberation of SMAD2.

Endo-MT is also a contributing factor in the acute-to-chronic kidney disease continuum and the development of chronic graft dysfunction.[69,70] The role of endothelial dysfunction in kidney transplantation is further emphasized by a recent study on enhancing protection of EC using a Corline Heparin Conjugate (CHC™), which improved early outcomes in preclinical investigations.[71]

Gene microarray analysis of cultured EC treated with an inhibitor of nitric oxide synthase revealed upregulation of collagen XVIII and its antiangiogenic fragment endostatin, a finding confirmed *in vivo* in mice chronically treated with an NOS inhibitor.[52] Enhanced generation of endostatin in these animals leads to the development of Endo-MT and eventual rarefaction of renal microvasculature, thus further compounding vascular and parenchymal pathology. EC exposed to diverse stressors respond with lysosomal dysfunction, leakage of cathepsins, and degradation of SIRT1. SIRT1 depletion, in turn, leads to downregulation of MMP-14 and accumulation of ECM.

While the secretory products of intact EC contribute to the maintenance of the surrounding parenchyma, the dysfunctional endothelium secretes a host of profibrogenic factors that activate resident fibroblasts, as well as further worsening endothelial dysfunction, Endo-MT, and microvascular rarefaction.[72]

LYMPHATIC ENDOTHELIUM

Lymphatic EC originate as sprouts from the embryonic veins and, perhaps, the adjacent mesenchyme, then sprout, branch and proliferate to form the lymphatic network, which drains into lymph nodes and eventually into the venous circulation at subclavian veins. The first podoplanin-positive lymphatic EC appear in the hilus of a developing kidney. From there they form tubular structures that branch and invade renal parenchyma. Terminal lympatics, blind-ended capillaries, collect and evacuate protein-enriched fluid, lymphocytes and antigen-presenting dendritic cells from the interstitium, thus participating in tissue homeostasis and immune surveillance.[2] VEGF-C, and to a lesser extent VEGF-D, fibroblast growth factor, hepatocyte growth factor, PDGF, and insulin-like growth factors are necessary for sprouting and maintenance of the lymphatic architecture. Lymphatic capillaries lack pericyte coverage and have a discontinuous basement membrane and discontinuous button-like cell–cell junctions, allowing the entry of fluid, lymphocytes, and dendritic cells.[73] In chronic inflammation, infiltrating macrophages produce VEGF-C that induces lymphangiogenesis, which in turn provides an outlet for the resolution of inflammatory infiltrates and the reduction of edema. In the rat remnant kidney model, fibrotic interstitial areas are characterized by a massive proliferation of lymphatic vessels. If specific markers of lymphatic endothelium such as podoplanin are not used for characterization, these cells could be readily mistaken for vascular endothelium.[74] In the setting of renal transplantation, CCL21 produced by host lymphatic vessels serves as a guidance cue for CCR-7–expressing dendritic cells.[75] These cells elicit antigen recognition and immune response. Therefore, strategies designed to curtail lymphangiogenesis may be beneficial for graft survival.

The emerging understanding of the role of lymphatics in cardiovascular homeostasis is attributed to the fact that these vessels are present in the adventitia of arteries where they accompany vasa vasorum. During progression of atherosclerosis, plaque areas develop dysfunctional lymphatic vessels, which by interfering with the normal processes of eliminating inflammatory cells and lipids contribute to their expansion.[76]

The lymphatic endothelium has been linked to the maintenance of blood pressure, with the failure of lymphangiogenesis resulting in development of hypertension in animals with high-salt consumption.[77] Salt load results in the elevation of osmotic pressure of the skin interstitium, attracting macrophages that produce VEGF-C and stimulate lymphangiogenesis. This in turn restores tissue homeostasis and helps maintain the blood pressure. Disruption of this adaptive lymphangiogenic mechanism leads to the development of salt-sensitive hypertension, even though the expression of eNOS is elevated. These seminal studies establish the macrophage–lymphatics axis as an extrarenal regulator of extracellular volume and blood pressure homeostasis.

The relationship between the lymphatic microvasculature and CKD remains to be fully explored, and it awaits investigation into the role of this system in maintaining interstitial pressure and renal function in health and disease.

MICROVASCULAR AND TISSUE REGENERATION: ROLE OF STEM AND PROGENITOR CELLS

The identification of EPC[78] and their potential to regenerate blood vessels resulted in a body of experimental evidence confirming their role in diverse diseases. Specifically, adoptive transfer of EPC has been shown to improve the course of several cardiovascular and renal diseases. Recent studies, however, have questioned the direct involvement of stem cells in general and EPC in particular in regenerative processes. Using genetic fate tracing technology, it has been documented that bone marrow-derived or circulating cells do not contribute to regeneration of a distal phalanx in an adult mouse. The germ layer and lineage-restricted stem/progenitor cells are responsible for the regeneration.[79] It has been concluded that endothelial stem/progenitor cells involved in adult angiogenesis must be local, nonhematopoietic, and noncirculating, tissue resident cells. Furthermore, it has been demonstrated[7] that c-Kit+ adult VESCs reside in the vascular wall. The importance of the vascular endothelium for tissue regenerative processes has been amply illustrated in a study by Rafii's group,[80] which provides evidence for angiocrine signals generated during vascular regeneration through production of EGF-like laminin fragments. The latter foster growth of the pulmonary epithelia. Whether analogous processes takes place in the kidney remains unknown, although the recently discovered product of EC and platelets, SCUBE1 protein containing several EGF-like repeats, has been shown to be upregulated after the injury and to promote regeneration of tubular epithelial cells.[81]

THERAPEUTIC STRATEGIES TO AMELIORATE ENDOTHELIAL DYSFUNCTION

Sir William Osler opined "The physics of a man's circulation are the physics of the waterworks of the town in which he lives, but once out of gear, you cannot apply the same rules for the repair of the one as of the other." Indeed, this calls for an in-depth understanding of the metabolic abnormalities associated with the affected endothelium, a field of knowledge that still remains in its infancy. Although the functional abnormalities have been elucidated, the molecular basis for developing endothelial dysfunction in CKD still remains obscure. The first glimpses on proteomic and metabolomic disparities between normal and dysfunctional endothelium, as detailed above, constitute the backbone for the rational design of therapeutic strategies. Some well-established, traditional therapeutic interventions are considered.[82]

Inhibitors of Angiotensin-2 Action

One of the mainstay therapies directed to slow the progression of CKD, ACEIs and ARBs, exert their action through inhibition of NADPH oxidase, preservation of eNOS function and bradykinin levels, thus improving EC dysfunction.

HMG-CoA Reductase Inhibitors

Statins elicit their effect on EC by reducing oxidative stress and improving eNOS function, independent of their lipid-lowering effects.[82,92]

PPAR-α Agonists

Fibrates improve endothelial cell function *via* reduction of oxidative stress and NF-kB activation.[93]

Antioxidants

Tempol and ebselen protect the endothelium by preventing eNOS uncoupling, thus restoring endothelial functions. A synthetic triterpenoid, bardoxolone methyl, an activator of the antioxidant Keap1-Nrf2 pathway, has been advocated as a potential therapeutic agent restoring endothelial dysfunction[83] and improving renal function in CKD patients with type 2 diabetes.[84] Yet, the study of more than 2000 patients with type 2 diabetes and stage 4 CKD showed no benefit of bardoxolone methyl therapy over placebo.[85] A possible therapeutic role of an endogenous antioxidant, lipoic acid, in vascular and renal protection against elevated levels of

angiotensin II-induced injury has been demonstrated in transgenic rats harboring human renin and angiotensinogen genes.[86]

Several well-rationalized experimental strategies for vascular protection have emerged. These are briefly noted below.

mTOR Inhibitor

Rapamycin may improve endothelial dysfunction by preventing SIPS of EC.[94]

Activators of Sirtuins

Resveratrol and newly developed analogues should have a place in the prevention of endothelial cell senescence and the restoration of metabolic abnormalities. Based on earlier studies of sirtuin 1 activation by resveratrol, a number of small-molecule SIRT1 activators have been synthesized and are being currently tested.[87] Sirtuin-activating compounds (STACs) exert their effect by allosteric activation of this deacetylase. Three generations of STACs include, in addition to resveratrol, quercetin and butein (first generation), SRT 1720, 1460, and 2183 (second generation), and STAC-5, -9, and -10 (third generation), all extending lifespan and/or health-span in preclinical settings. These compounds are presently undergoing clinical trials. Dietary restriction, which induces SIRT1, acts *via* mTOR signaling and nicotine amide dinucleotide (NAD)−dependent pathways accompanied by a shift toward oxidative metabolism,[88] both representing novel modes of rejuvenation therapy.

NAD+ is a cofactor for activation of several sirtuins. NAD+ bioavailability is reduced in disease states and aging.[89] A precursor of NAD+, nicotinamide, is being evaluated as a therapy to correct NAD+ deficiency and improve sirtuin activity.

Glutamine Supplementation

Glutamine supplementation remains in experimental stages.[54]

Suppression of the JNK Pathway

Suppression of the JNK pathway, which prevents vascular dysfunction, can be achieved through activation of adenosine monophosphate kinase by chronic pretreatment with 5-aminoimidazole-4-carboxamide 1-β-D-ribofuranoside, acadesine, N^1-(β-D-Ribofuranosyl)-5-aminoimidazole-4-carboxamide (ICAR) or metformin.[90] Their effect is mediated *via* activation of PGC-1α and improved mitochondrial biogenesis and cytoprotection, leading to attenuation of oxidative stress−induced endothelial injury.

Activation of Endothelin Type B Receptors

Endothelin type B receptors, expressed predominantly by EC, mediate activation of endothelial nitric oxide synthase. Intrarenal infusion of these receptors in sarafotoxin 6c insulinopenic streptozotocin-injected rats improved renal hemodynamics.[91]

SUMMARY

Endothelium-dependent pathways of fibrogenesis play critical roles in the maintenance and progression of CKD. The mechanics of the process involve microvascular rarefaction, which itself is a result of the confluence of a multitude of pathogenic factors, such as Endo-MT, SIPS and associated abnormal secretory profiles, impaired angiogenesis and curtailed regeneration of obliterated microvascular beds, an aberrant secretome of dysfunctional EC, and enhanced degradation of endothelial glycocalyx. Strategies to alleviate endothelial dysfunction and improve the renal microcirculation must be tested in animal studies and clinical trials. Although the accumulated knowledge leaves no doubt regarding the participation of the endothelium in the pathogenesis of CKD, there remains a long translational journey to use these findings to improve outcomes in patients.

References

1. Zovein A, Hofmann J, Lynch M, et al. Fate tracing reveals the endothelial origin of hematopoietic stem cells. *Cell Stem Cell* 2008;**3**:625−36.
2. Adams R, Alitalo K. Molecular regulation of angiogenesis and lymphangiogenesis. *Nat Rev Mol Cell Biol* 2007;**8**:464−78.
3. Kissa K, Herbomel P. Blood stem cells emerge from aortic endothelium by a novel type of cell transition. *Nature* 2010;**464**:112−6.
4. Gupta R, Mepani R, Kleiner S, et al. Zfp423 expression identifies committed preadipocytes and localizes to adipose endothelial and perivascular cells. *Cell Metabol* 2012;**15**:230−9.
5. Tran K-V, Gealekman O, Frontini A, et al. The vascular endothelium of the adipose tissue gives rise to both white and brown fat cells. *Cell Metabol* 2012;**15**:222−9.
6. Goligorsky MS, Salven P. Endothelial stem and progenitor cells and their habitats. *Stem Cell Translational Med* 2013;**2**(7):499−504.
7. Bearzi C, Leri A, Lo Monaco F, et al. Identification of coronary vascular progenitor cell in the human heart. *Proc Natl Acad Sci USA* 2009;**106**:15885−90.
8. Fang S, Wei J, Pentinmikko N, Leinonen H, Salven P. Generation of functional blood vessels from a single c-kit+ adult vascular endothelial stem cell. *PLoS Biol* 2012;**10**:1001407.
9. Sedwick C. On the hunt for vascular endothelial stem cells. *PLoS Biol* 2012;**10**(10):e1001408.
10. Prasain N, Lee M, Vemula S, Meador JL, Yoshimoto M, Ferkowicz MJ, Fett A, et al. Differentiation of human pluripotent

stem cells to cells similar to cord-blood endothelial colony-forming cells. *Nat Biotechnol* 2014;**32**:1151–7.
11. Reed M, Karres N, Eyman D, et al. Culture of murine aortic explants in 3-dimensional matrix: a novel, miniaturized assay of angiogenesis in vitro. *Microvasc Res* 2007;**73**:248–52.
12. Shimada T, Takeshita T, Murohara T, et al. Angiogenesis and vasculogenesis are impaired in the precocious-aging klotho mouse. *Circulation* 2004;**110**:1148–55.
13. Facchetti F, Monzani E, Cavallini G, et al. Effect of caloric restriction regimen on the angiogenic capacity of aorta and on the expression of endothelin-1 during aging. *Exp Gerontol* 2007; **42**:662–7.
14. Chen J, Xavier S, Moskowitz-Kassai E, et al. Cathepsin cleavage of sirtuin 1 in endothelial progenitor cells mediates stress-induced premature senescence. *Am J Pathol* 2012;**180**:973–83.
15. Brown W. A review of string vessels or collapsed, empty basement membrane tubes. *J Alzheimer's Dis* 2010;**21**:725–39.
16. Carlin L, Stamatiades E, Auffray C, et al. Nr4a1-dependent $Ly6C^{low}$ monocytes monitor endothelial cells and orchestrate their disposal. *Cell* 2013;**153**:362–75.
17. Butler J, Kobayashi H, Rafii S. Instructive role of the vascular niche in promoting tumor growth and tissue repair by angiocrine factors. *Nat Rev Canc* 2010;**10**:138–46.
18. Haraldsson B, Nystrom J. The glomerualr endothelium: new insights on function and structure. *Curr Opin Nephrol Hypertens* 2012;**21**:258–63.
19. Davis B, Dei Cas A, Long D, et al. Podocyte-specific expression of angiopoietin-2 causes proteinuria and apoptosis of glomerular endothelia. *J Am Soc Nephrol* 2007;**18**:2320–9.
20. Salmon A, Ferguson J, Burford J, et al. Loss of the endothelial glycocalyx links albuminuria and vascular dysfunction. *J Am Soc Nephrol* 2013;**23**:1339–50.
21. Hauser P, Collino F, Bussolati B, Camussi G. Nephrin and endothelial injury. *Curr Opin Nephrol Hypertens* 2009;**18**:3–8.
22. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. *Lancet* 2005;**365**: 785–99.
23. Levine R, Lam C, Qian C, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *N Engl J Med* 2006; **355**:992–1005.
24. Di Marco G, Reuter S, Hillebrand U, et al. The soluble VEGF receptor sFlt1 contributes to endothelial dysfunction in CKD. *J Am Soc Nephrol* 2009;**20**:2235–45.
25. Tsai H. The molecular biology of thrombotic microangiopathy. *Kidney Int* 2006;**70**:16–23.
26. Norris M, Remuzzi G. Hemolytic uremic syndrome. *J Am Soc Nephrol* 2005;**16**:1035–50.
27. Desch K, Motto D. Is there a shared pathophysiology for thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome? *J Am Soc Nephrol* 2007;**18**:2457–60.
28. Zoja C, Buelli S, Morigi M. Shiga toxin-associated hemolytic uremic syndrome: pathophysiology of endothelial dysfunction. *Pediatr Nephrol* 2010;**25**:2231–40.
29. Motto D, Chauhan A, Zhu G, et al. Shigatoxin triggers thrombotic thrombocytopenic purpura in genetically susceptible ADAMTS13-deficient mice. *J Clin Investig* 2005;**115**:2752–61.
30. Eremina V, Jefferson A, Kowalewska J, et al. VEGF inhibition and renal thrombotic microangiopathy. *N Engl J Med* 2008;**358**:1129–36.
31. Bohle A, Herfarth C. Zur Frage eines intercapillaren Bindegewebes im Glomerulum der Niere des Menschen. *Virchows Arch Pathol Anat* 1958;**331**:573–90.
32. Bohle A, Mackensen-Haen S, von Gise H. Significance of tubulointerstitial changes in the renal cortex for the excretory function and concentration ability of the kidney: a morphometric contribution. *Am J Nephrol* 1987;**7**:421–33.
33. Nakagawa T, Kang D-H, Ohashi R, Suga S, Herrera-Acosta J, Rodriguez-Iturbe B, Johnson R. Tubulointerstitial disease: role of ischemia and microvascular disease. *Curr Opin Nephrol Hypertens* 2003;**12**:233–41.
34. Lee L, Meyer T, Pollock A, Lovett D. Endothelial cell injury initiates glomerular sclerosis in the rat remnant kidney. *J Clin Investig* 1995; **96**:953–64.
35. Kriz W, Hosser H, Hahnel B, Gretz N, Provoost A. From segmental glomerulosclerosis to total nephron degeneration and interstitial fibrosis: a histopathological study in rat models and human glomerulopathies. *Nephrol Dial Transplant* 1998;**13**:2781–98.
36. Ohashi R, Kitamura H, Yamanaka N. Peritublar capillary injury during the progression of experimental glomerulonephritis in rats. *J Am Soc Nephrol* 2000;**11**:47–56.
37. Shimizu A, Kitamura H, Masuda Y, Ishizaki M, Sugisaki Y, Yamanaka N. Rare glomerular capillary regeneration and subsequent capillary regression with endothelial cell apoptosis in progressive glomerulonephritis. *Am J Pathol* 1997;**151**:1231–9.
38. Thomas S, Anderson S, Gordon K, Oyama T, Shankland S, Johnson R. Tubulointerstitial disease in aging: evidence for underlying peritubular capillary damage, a potential role for renal ischemia. *J Am Soc Nephrol* 1998;**9**:231–42.
39. Basile D, Donohoe D, Roethe K, Osborn J. Renal ischemic injury results in permanent damage to peritubular capillaries and influences long-term function. *Am J Physiol* 2001;**281**:F887–99.
40. Choi Y-J, Chakraborty S, Nguyen V, Nguyen C, Kim B, Shim S, Suki W, Truong L. Peritubular capillary loss is associated with chronic tubulointerstitial injury in human kidney: altered expression of vascular endothelial growth factor. *Hum Pathol* 2000;**31**: 1491–7.
41. Shimizu A, Yamada K, Sachs D, Colvin R. Persistent rejection of peritubular capillaries and tubules is associated with progressive interstitial fibrosis. *Kidney Int* 2002;**61**:1867–79.
42. Otani A, Kinder K, Ewalt K, Otero F, Schimmel P, Friedlander M. Bone marrow-derived stem cells target retinal astrocytes and can promote or inhibit retinal angiogenesis. *Nat Med* 2002;**8**:1004–10.
43. Das A, Huang G, Bonkowski M, Longchamp A, Li C, et al. Impairment of an endothelial NAD+-H2S signaling network is a reversible cause of vascular aging. *Cell* 2018;**173**:74–89. 2-18.
44. Kim BS, Chen J, Weinstein T, Noiri E, Goligorsky MS. VEGF expression in hypoxia and hyperglycemia: reciprocal effect on branching angiogenesis in epithelial-endothelial co-cultures. *J Am Soc Nephrol* 2002;**13**:2027–36.
45. Gealekman O, Brodsky SV, Zhang F, Chander PN, Friedli C, Nasjletti A, Goligorsky MS. Endothelial dysfunction as a modifier of angiogenic response in Zucker diabetic fat rat: amelioration with Ebselen. *Kidney Int* 2004;**66**:2337–47.
46. Loganathan K, Salem S, Winterrowd E, et al. Angiopoietin-1 deficiency increases renal capillary rarefaction and tubulointerstitial fibrosis. *PLoS One* 2018;**13**:e0189433.
47. Goligorsky MS. Clinical assessment of endothelial dysfunction: combine and rule. *Curr Opin Nephrol Hypertens* 2006;**15**:617–24.
48. Smirnova I, et al. Up-regulation of lectin-like oxidized LDL receptor-1 in endothelial cells by nitric oxide deficiency. *Am J Physiol Renal* 2004;**287**:F25–32.
49. Li H, Lewis A, Brodsky S, Rieger R, Iden C, Goligorsky MS. Homocysteine induces 3-hydroxy-3-methylglutaryl coenzyme a reductase in vascular endothelial cells: a mechanism for development of atherosclerosis? *Circulation* 2002;**105**(9):1037–43.
50. Li H, Brodsky S, Kumari S, Valiunas V, Brink P, Kaide J, Nasjletti A, Goligorsky MS. Paradoxical overexpression and translocation of connexin-43 in homocysteine-treated endothelial cells. *Am J Physiol Heart* 2002;**282**:H2124–33.
51. Goligorsky MS. Endothelial cell dysfunction: can't live with it, how to live without it. *Am J Physiol Renal* 2005;**288**:F871–80.
52. O'Riordan E, Mendelev N, Patschan S, Chander P, Goligorsky MS. Chronic NOS inhibition actuates endothelial-mesenchymal transformation. *Am J Physiol* 2007;**292**:H285–94.

53. Stubbe J, Skov V, Thiesson H, et al. Identification of differential gene expression patterns in human arteries from patients with chronic kidney disease. *Am J Physiol Renal* 2018;**314**(6):F1117−28.
54. Addabbo F, et al. The Krebs cycle and mitochondrial mass are early victims of endothelial dysfunction. *Am J Pathol* 2009;**174**:34−43.
55. Addabbo F, Chen Q, Patel D, et al. Glutamine supplementation alleviates vasculopathy and alters plasma metabolome in an in vivo model of endothelial cell dysfunction. *PLoS One* 2013;**8**(6):e65458.
56. Padberg J-S, Wiesinger A, di Marco GS, Reuter S, et al. Damage of the endothelial glycocalyx in chronic kidney disease. *Atherosclerosis* 2014;**234**:335−43.
57. Reitsma S, Slaaf D, Vink H, et al. The endothelial glycocalyx: composition, functions, and visualization. *Pflügers Archiv* 2007; **454**:345−59.
58. Zhang F, Sun D, Song J, et al. Endothelial cell dysfunction and glycocalyx − a vicious circle. *Matrix Biol* 2018;**71**−**72**:421−31.
59. Melk A, Halloran P. Cell senescence and its implications for Nephrology. *J Am Soc Nephrol* 2001;**12**:385−93.
60. Chen J, Brodsky SV, Goligorsky MS, et al. Glycated collagen I induces premature senescence-like phenotypic changes in endothelial cells. *Circ Res* 2002;**90**:1290−8.
61. Suzuki M, Boothman D. Stress-induced premature senescence (SIPS) − influence of SIPS on radiotherapy. *J Radiat Res* 2008;**49**: 105−12.
62. Hemmen K, Reinl T, Buttler K, et al. High-resolution mass spectrometric analysis of the secretome from mouse lung endothelial progenitor cells. *Angiogenesis* 2011;**14**:163−72.
63. Pula G, Mayr U, Evans C, et al. Proteomics identifies thymidine phosphorylase as a key regulator of the angiogenic potential of colony-forming units and endothelial progenitor cell cultures. *Circ Res* 2009;**104**:32−40.
64. Lin S, Chen J, Zhang Z, et al. Endostatin and transglutaminase 2are involved in fibrosis of the aging kidney. *Kidney Int* 2016;**89**:1281−92.
65. Zeisberg E, Potenta S, Sugimoto H, Zeisberg M, Kalluri R. Fibroblasts in kidney fibrosis emerge via endothelial-to-mesenchymal transition. *J Am Soc Nephrol* 2008;**19**:2282−7.
66. Li J, Qu X, Bertram J. Endothelial-myofibroblast transition contributes to the early development of diabetic renal interstitial fibrosis in streptozotocin-induced diabetic mice. *Am J Pathol* 2009;**175**: 1380−8.
67. Gaengel K, Genove G, Armulik A, Betsholtz C. Endothelial-mural cell signaling in vascular development and angiogenesis. *Arterioscler Thromb Vasc Biol* 2009;**29**:630−8.
68. Xiong J, Kawagishi H, Yan Y, Liu J, Wells Q, et al. A metabolic basis for endothelial-to-mesenchymal transition. *Mol Cell* 2018;**69**: 689−98.
69. Situmorang G, Sheerin N. Ischemia reperfusion injury: mechanisms of progression to chronic graft dysfunction. *Pediatr Nephrol* 2019;**34**(6):951−63.
70. Basile D, Yoder M. Renal endothelial dysfunction in acute kidney ischemia reperfusion injury. *Cardiovasc Haematol Disord - Drug Targets* 2014;**14**:3−14.
71. Nordling S, Brannstrom J, Carlsson F, Lu B, et al. Enhanced protection of the renal vascular endothelium improves early outcome in kidney transplantation: preclinical investigation in pig and mouse. *Sci Rep* 2018;**8**:5220.
72. Lipphardt M, Song JW, Matsumoto K, Dadafarin S, Dihazi H, Müller G. Goligorsky MS the third path of tubulointerstitial fibrosis: aberrant endothelial secretome. *Kidney Int* 2017;**92**(3):558−68.
73. Alitalo K. The lymphatic vasculature in disease. *Nat Med* 2011;**17**: 1371−9.
74. Matsui K, Nagy-Bojarsky K, Laakkonen P, Krieger S, Mechtler K, Geleff S, Kang D, Johnson R, Kerjaschki D. Lymphatic microvessels in the rat remnant kidney model of renal fibrosis: aminopeptidase p and podoplanin are discriminatory markers for endothelial cells of blood and lymphatic vessels. *J Am Soc Nephrol* 2003;**14**: 1981−9.
75. Kerjaschki D, et al. Lymphatic endothelial progenitor cells contribute to de novo lymphangiogenesis in human renal transplants. *Nat Med* 2006;**12**:230−4.
76. Lim H, Rutkowski JM, Helft J, et al. Hypercholesterolemic mice exhibit lymphatic vessel dysfunction and degeneration. *Am J Pathol* 2009;**175**:1328−37.
77. Machnik A, Neuhofer W, Jantsch J, et al. Macrophages regulate salt-dependent volume and blood pressure by a VEGF-C-dependent buffering mechanism. *Nat Med* 2009;**15**:545−52.
78. Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. *Science* 1997;**275**:964−7.
79. Rinkevich Y, Lindau P, Ueno H, Longaker MT, Weissman IL. Germ-layer and lineage-restricted stem/progenitors regenerate the mouse digit tip. *Nature* 2011;**476**:409−13.
80. Ding B-S, Nolan D, Guo P, et al. Endothelial-derived angiocrine signals induce and sustain regenerative lung alveolarization. *Cell* 2011;**147**:539−53.
81. Zhuang J, Deane J, Yang R-B, Li J, Ricardo S. SCUBE1, a novel developmental gene involved in renal regeneration and repair. *Nephrol Dial Transplant* 2010;**25**:1421−8.
82. Turner J, Bauer C, Abramowitz M, Melamed M, Hostetter T. Treatment of chronic kidney disease. *Kidney Int* 2012;**81**:351−62.
83. Miyata T, Suzuki N, van Ypersele de Strihou C. Diabetic nephropathy: are there new and potentially promising therapies targeting oxygen biology? *Kidney Int* 2013;**84**(4):693−702.
84. Pergola P, Rasin P, Toto R, Meyer C, Huff J, Grossman E, Krauth M, Ruiz S, Audhya P, Christ-Schmidt H, Wittes J, Warnock D. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. *N Engl J Med* 2011;**365**:327−36.
85. deZeeuw D, Akizawa T, Audhya P, , et alfor the BEACON Trial Inveswtigators. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *NEJM* 2013;**369**:2492−503.
86. Mervaala E, Finckenberg P, Lapatto R, et al. Lipoic acid supplementation prevents angiotensin II-induced renal injury. *Kidney Int* 2003;**64**:501−8.
87. Hubbard B, Sinclair D. Small molecule SIRT1 activators for the treatment of aging and age-related diseases. *Trends Pharmacol Sci* 2014;**35**:146−54.
88. Moroz N, Carmona J, Anderson E, Hart A, Sinclair D, Blackwell T. Dietary restriction involves NAD-dependent mechanisms and a shift toward oxidative metabolism. *Aging Cell* 2014;**13**:1075−85.
89. Verdin E. NAD+ in aging, metabolism, and neurodegeneration. *Science* 2015;**350**:1208−13.
90. Schultz E, Dopheide J, Schuhmacher S, et al. Suppression of the JNK pathway by induction of a metabolic stress response prevents vascular injury and dysfunction. *Circulation* 2008;**118**:1347−57.
91. Franzen S, Pihl L, Fasching A, Palm F. Intrarenal activation of endothelin type B receptors improves kidney oxygenation in type 1 diabetic rats. *Am J Physiol Renal* 2018;**314**:F439−44.
92. Kuldo J, Ogawara K, Werner N, Asgeirsdottir S, Kamps J, Kok R, et al. Molecular pathways of endothelial cell activation for (targeted) pharmacological intervention of chronic inflammatory diseases. *Curr Vasc Pharmacol* 2005;**3**(1):11−39.
93. Dragomir E, Tircol M, Manduteanu I, Voinea M, Simionescu M. Aspirin and PPAR-alpha activators inhibit monocyte chemoattractant protein-1 expression induced by high glucose concentration in human endothelial cells. *Vasc Pharmacol* 2006;**44**(6): 440−9.
94. Johnson SC, Rabinovitch PS, Kaeberlein M. mTOR is a key modulator of ageing and age-related disease. *Nature* 2013;**493**(7432): 338−45.

QUESTIONS AND ANSWERS

Question 1

A 25-year-old prima para is followed in the outpatient clinic. Until the present visit all physiological and laboratory data were within the normal range. She is in the third trimester of pregnancy. Her blood pressure is found to be elevated at 158/95 mm Hg. Dipstick of her urine shows 2+ protein. Her BUN and S[Cr] are in the upper normal range, as is her uric acid level. She denies any recent intercurrent infections. You strongly suspect development of preeclampsia. Being aware of the role played by vascular endothelium in this syndrome, you ask yourself: What are the mediators of preeclampsia?

A. Increased serum concentration of the soluble Flt-1
B. Increased serum concentration of VEGF
C. Decreased serum concentration of ADMA
D. All of the above

Answer: A

Choices B and C are incorrect because the opposite occurs in preeclampsia: decreased levels of VEGF and increased levels of ADMA. Therefore, Choice D is automatically eliminated. The only correct choice is A, as the cleavage of Flt-1 receptor on EC and elevated levels of its soluble fragment are characteristic findings in preeclampsia, as well as other chronic kidney diseases.

Question 2

A 59-year-old truck driver is seen by you in the outpatient clinic. He has been referred by his family physician, who on a routine check-up found elevated blood pressure and proteinuria. During your examination and analysis of the laboratory data you come across S[Cr] of 5.3 mg/dL. You immediately perform a renal ultrasound and find that both kidneys are shrunken to 7.9 cm in length. Since you are well aware of the endothelial contribution to nephrosclerosis, you ask yourself: What are the known endothelium-dependent mediator(s) of fibrosis?

A. Activation of matrix metalloproteinases
B. Inhibition of tissue inhibitor of matrix metalloproteinase-1 (TIMP-1)
C. Epithelial−mesenchymal transition (EMT)
D. Endo-MT

Answer: D

Choices A and B are incorrect because neither activation of MMPs nor inhibition of TIMP-1, which also results in the activation of MMPs, could be considered mechanisms of fibrosis. EMT has been proposed as a mechanism of fibrosis; however, this choice is incorrect because it is not an endothelium-dependent mediator of fibrosis. Hence, the only correct choice is D—Endo-MT.

Question 3

Considering lymphatic EC, which of the following statements is correct?

A. Terminal lymphatic capillaries are blind-ended
B. VEGF-C is the main growth factor for lymphatic endothelium
C. Dysfunctional lymphatic EC in the vascular wall contribute to progression of atherosclerosis
D. All of the above

Answer: D

Although our knowledge of lymphatic endothelial cells in general and renal lymphatics in particular is rather scanty, all three statements are correct. The answer is D.

Question 4

A 63-year-old woman with CKD and eGFR of 45 mL/min/1.73 m^2 is admitted to the hospital with chest pain and T-wave inversions on ECG. Having controlled her chest pain and while you are waiting for the results of biomarker tests, you search through your memory for established relations between CKD and cardiovascular disease (CVD). Which of the following statements is correct?

A. Endothelial cell dysfunction is in part responsible not only for the progression of CKD but also for the increased cardiovascular morbidity and mortality in CKD patients compared to the general population without kidney disease
B. The main therapies for endothelial cell dysfunction include statins, ACEIs, ARBs, and PPAR-alpha agonists
C. Exercise and calorie restriction regimens may improve endothelial function
D. All of the above

Answer: D

You are aware of the fact that stage 3 CKD is associated with a dramatic increase in cardiovascular death. Endothelial cell dysfunction is a nearly constant companion of CKD. This makes choice A a correct one. Indeed, the therapeutic modalities mentioned in choice B are correct and new modalities are on the way. This shows choice B is also correct. There is a plethora of data obtained in humans with endothelial cell dysfunction, as diagnosed using impaired endothelium-dependent vasorelaxation, elevation in levels of markers

of chronic inflammation and oxidative stress, which demonstrate beneficial effects of exercise and caloric restriction on dysfunctional endothelium. Hence, your choice of C is also correct. Having correctly answered all three choices, you have logically selected as the best answer choice D—all of the above.

Question 5

Which of these statements correctly characterize renal glomerular EC?

A. They are fenestrated
B. They are coated with glycocalyx, removal of which can lead to albuminuria
C. EC and podocytes form a functional unit
D. All of the above

Answer: D

EC of glomeruli and peritubular capillaries are fenestrated, as are EC in endocrine glands or sinusoidal cells in the liver. Therefore, Answer A is correct. Indeed, EC are coated with glycocalyx, and its removal from glomerular EC leads to albuminuria. This makes Answer B correct. Glomerular EC and podocytes, together with the glomerular basement membrane, represent a glomerular filtration unit. Damage to any portion of this unit leads to dysfunction of the other components. For this reason Answer C is also correct. Having correctly answered all three choices, you have necessarily selected as the best answer choice D—all of the above.

CHAPTER

23

Cardiovascular Disease and Chronic Kidney Disease

Janani Rangaswami[a,b], *Peter A. McCullough*[c,d,e]

[a]Einstein Medical Center, Philadelphia, PA, United States; [b]Sidney Kimmel College of Thomas Jefferson University, Philadelphia, PA, United States; [c]Baylor University Medical Center, Dallas, TX, United States; [d]Baylor Heart and Vascular Institute, Dallas, TX, United States; [e]Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, TX, United States

Abstract

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with chronic kidney disease (CKD). The various phenotypes of cardiovascular disease including heart failure, ischemic heart disease, valvopathies, and arrhythmias are all represented with high disease burden in patients with CKD. Several traditional and nontraditional vascular risk factors are operational in the pathogenesis of cardiovascular disease in this population. Despite the well-known risk of cardiovascular disease, patients with CKD tend to be excluded from major cardiovascular outcome trials. Therefore there is less-robust available evidence on how to deliver optimal medical and procedural therapies for CVD in the CKD population. CKD patients also present with atypical symptom profiles and receive less aggressive goal–directed medical therapies for CVD compared to patients without CKD. Therapeutic effects of medical therapies as well as procedural interventions tend to be associated with higher complication rates related to the brittle bleeding–clotting paradigm in CKD, altered pharmacotherapeutics of drugs, and high vascular calcific burden. There is an urgent need to prioritize the inclusion of patients with CKD in cardiovascular trials, as well as to implement efforts to deliver cohesive care *via* multidisciplinary cardio-renal team models to achieve optimal long-term outcomes and CVD reduction in this vulnerable patient population.

INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem with increasing disease burden, poor outcomes, and higher costs in the US and worldwide.[1] According to the US Renal Data System, the overall prevalence of CKD in the US was 14.8% in 2011–2014 with high rates of diabetes, hypertension, and self-reported cardiovascular disease (CVD) in this population.[1] The classification of CKD as outlined in the clinical practice guidelines of the National Kidney Foundation in 2002 with the subsequent update from the Kidney Disease: Improving Global Outcomes (KDIGO) in 2012 stratifies the severity of CKD by estimated glomerular filtration rate (eGFR) and the degree of microalbuminuria. CKD (as defined by a eGFR <60 mL/min/1.73 m^2 for at least 3 months, or presence of markers of kidney damage such as a spot albumin:creatinine ratio $\geq$30 mg/g or structural abnormalities) is a well-recognized independent risk factor for the development of CVD.[2] The risk of CVD mirrors the degree of decline in eGFR, as well as the degree of albuminuria.[3] The 1998 National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Kidney Disease as well as the KDIGO Clinical Practice Guideline on CKD in 2012 emphasized that patients with underlying CKD should be considered in the "highest risk group" and at "increased risk" for CVD, respectively.[4,5] The elevated risk of CVD in CKD represents the interplay of several "traditional" risk factors such as those in the Framingham Heart Study as well as "nontraditional" risk factors such uremia, oxidative stress, abnormalities in bone mineral metabolism, and chronic inflammation that are hallmarks of the CKD milieu.[2] The elevated risk of CVD extends across the spectrum of nondialytic CKD, maintenance dialysis as well as after kidney transplantation, with the risk of developing a major adverse cardiovascular event (MACE) in patients with CKD exceeding the likelihood of needing renal replacement therapy (RRT).[6] This chapter will focus on the pathophysiology, diagnosis, and management of CVD in patients with

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00023-1

CKD (not treated with dialysis or transplantation) considering the following major phenotypes: heart failure (HF), atherosclerotic cardiovascular disease (ASCVD), valvular heart disease, and arrhythmias.

HEART FAILURE IN CKD

Pathophysiology and Diagnosis of Heart Failure in Chronic Kidney Disease

As early as in 1836, Richard Bright described cardiac structural alterations in patients with kidney disease, establishing the concept of a "cardio-renal" axis, reminiscent of the type 4 cardio-renal syndrome (CRS) phenotype defined by the Acute Dialysis Quality Initiative in a more contemporary context.[7] (Table 23.1). Left ventricular hypertrophy (LVH) is the principal myocardial structural perturbation in CKD. A cross-sectional echocardiographic study of 3487 patients in the Chronic Renal Insufficiency Cohort reported prevalence rates of LVH of 32%, 48%, 57%, and 75% for eGFR categories >60, 45−59, 30−44, and <30 mL/min/1.73 m^2, respectively.[8] There is strong evidence that abnormalities of LV structure, function, and the development of myocardial fibrosis are present in early stages of CKD, prompting the term CKD-associated cardiomyopathy instead of "uremic cardiomyopathy".[9] The increase in myocardial fibrotic tissue impairs LV contractility in three ways: increase in the collagen type I: III ratio enhances ventricular stiffness; changes in collagen alignment relative to cardiomyocytes impairs diastolic relaxation, leading to exercise intolerance, and ultimately to HF and arrhythmias; and with increasing thickness, there is a reduced capillary density and impaired oxygen delivery, particularly in regions distant from the epicardium and endocardium.[9] The burden of LVH and concomitant myocardial fibrosis through the various stages of CKD form the common basis for the development of HF, in conjunction with preexisting vascular risk factors and the neuro-humoral-inflammatory pathways activated in CKD/type 4 CRS.

TABLE 23.1 Description of the Clinical Phenotypes of the Cardio-Renal Syndromes as Outlined by the Acute Dialysis Quality Initiative (ADQI)

Phenotype	Nomenclature	Description	Clinical Examples
Type 1 CRS	Acute cardio-renal syndrome *Worsening kidney function in the setting of high dose loop diuretics in acute heart failure	Heart failure resulting in AKI *May represent a functional elevation of kidney biomarkers such as S[Cr] or Cystatin C, and not true acute kidney injury	ACS resulting in cardiogenic shock and AKI, AHF resulting in AKI *Appropriately decongested patients with Type 1 CRS with an asymptomatic elevation of S[Cr], which meets criteria for AKI, with negative renal tubular injury biomarkers.
Type 2 CRS	Chronic cardio-renal syndrome **Worsening kidney function in the setting of use of goal directed therapies in heart failure	Chronic heart failure resulting in CKD **May represent appropriate reduction in GFR from effective reduction of FF without affecting RBF	Chronic heart failure **Asymptomatic elevation in S[Cr] seen in stable and compensated chronic heart failure with the use of RAASi
Type 3 CRS	Acute reno-cardiac syndrome	AKI resulting in acute heart failure	Heart failure in the setting of AKI from volume overload, inflammatory surge, and metabolic disturbances in uremia.
Type 4 CRS	Chronic reno-cardiac syndrome	CKD resulting in chronic heart failure	LVH and heart failure from CKD associated cardiomyopathy
Type 5 CRS	Secondary cardio-renal syndrome	Acute or chronic systemic process resulting in concomitant heart and kidney failure	Sepsis, cirrhosis, preeclampsia, Fabry's disease

ACS, acute coronary syndrome; *AHF*, acute heart failure; *AKI*, acute kidney injury; *CKD*, chronic kidney disease; *CRS*, cardio-renal syndrome; *FF*, filtration fraction; *GFR*, glomerular filtration rate; *LVH*, left ventricular hypertrophy; *RBF*, renal blood flow.

** Refers to "pseudo" AKI or "functional" changes in S[Cr] or serum Cystatin C in the setting of high dose loop diuretics in acute heart failure that may not represent "true renal tubular injury despite meeting accepted definitions of AKI.(Not included in original ADQI classification of CRS). Furthur reading: Ahmad T, Jackson K, Rao VS, et al. Worsening renal function in acute heart failure patients undergoing aggressive diuresis is not associated with tubular injury.* Circulation *2018.*

*** Not included in original ADQI classification but represents a common phenotype of functional kidney injury by AKI definition/criteria when using goal directed medical therapies in heart failure.*

The risk factors associated with LVH and myocardial fibrosis in patients with CKD-associated cardiomyopathy are divided into three categories: preload-dependent factors (volume overload), afterload-dependent factors (pressure overload), and nonhemodynamic factors associated with CKD (cardiomyopathy).[10] Preload-related factors involve expansion of intravascular volume, anemia, and high-flow arteriovenous fistulae created for vascular access for hemodialysis. Afterload-related factors include systemic arterial resistance (systolic and diastolic hypertension) and decreased large-vessel compliance (vascular calcification), resulting in myocardial cell thickening and concentric LV remodeling. Activation of the intracardiac renin–angiotensin aldosterone system (RAAS) seems to be critically involved in this pathway, but angiotensin II and aldosterone can also be involved in myocardial cell hypertrophy and fibrosis, independent of afterload.

Nonhemodynamic factors involved in the pathophysiology of LVH and myocardial fibrosis in CKD include persistent activation of the RAAS, elevated parathyroid hormone levels, activation of the mammalian target of rapamycin pathway, and the fibroblast growth factor (FGF) family.[11] The FGFs are a family of peptides with broad biologic functions that include the regulation of growth and differentiation of cardiac myocytes. In contrast to other members of the FGF family, FGF-23 has unique paracrine functions in the kidney, which facilitate phosphate excretion by blocking the synthesis of vitamin D_3 and inhibition of phosphate reabsorption in the proximal nephron. The independent association between elevated FGF-23 levels and LVH in a racially diverse CKD cohort, as well as the *klotho* independent causal role of FGF-23 in LVH in rat cardiomyocytes was demonstrated elegantly by Faul et al. in the FGF receptor-dependent activation of the calcineurin–NFAT signaling pathway.[12] Galectin-3 (a member of the β-galactoside–binding lectin family that is synthesized by macrophages) can also bind directly to cardiac fibroblasts and reduces LV function through an increase in collagen production.[13] Finally, there are emerging data on the cross talk between cardiac and kidney dendritic cells that play a central role in innate and adaptive immune responses in the context of chronic CRS.[14] The pathophysiological aspects of cardio-renal cross talk in patients with type 4 CRS are illustrated in Figure 23.1.[15]

The diagnosis of HF requires the presence of clinical signs and symptoms along with evidence of a structural or functional cardiac abnormality, several of which can pose diagnostic dilemmas in the setting of CKD. Given the frequent coexistence of renal impairment along with HF, it is important to distinguish long-term decline in eGFR from CKD progression (type 4 CRS) from short-term fluctuations in renal function in the context of decompensated type 1 CRS and/or its targeted therapies. Similarly, making the clinical distinction between type 2 CRS and type 4 CRS can be challenging as patients will inevitably "switch" from a subacute to a chronic CRS phenotype with progression of kidney disease. The use of renal and cardiac biomarkers, noninvasive imaging modalities, and a careful temporal assessment of evidence of cardiac and kidney end organ involvement will help establish the diagnosis of HF in CKD.

The 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure reiterated the existing 1A recommendation for the use of BNP and its inactive cleavage protein N terminal pro B type natriuretic peptide (pro BNP) in the diagnosis/exclusion of HF, as well as establishing prognosis and quantifying severity in acute and chronic HF.[16] Patients with CKD have higher baseline BNP levels compared to matched patients with normal renal function, due to impaired renal clearance (more notably with NT-pro BNP) as well as chronic pressure/volume overload and CKD-associated cardiomyopathy.[17] Other biomarkers such as suppressor of tumorigenicity 2 (ST2) (a decoy protein produced by the endothelial cells lining the left ventricle and aortic outflow tract in response to biomechanical strain) and galectin-3 may offer incremental value to natriuretic peptides levels in predicting HF-related deaths and hospitalizations.[18]

Uremic cardiomyopathy evolves through the course of progression of CKD, with subtle alterations in cardiac structure occurring even before clinically significant decline in renal function occurs.[9] Speckle echocardiography with strain analysis allows a more detailed evaluation of myocardial systolic function in the setting of normal left ventricular ejection fraction (LVEF) and may have additive value over echocardiographic assessment of LVEF in uremic cardiomyopathy (type 4 CRS)[19] (Figure 23.2). In a study of 40 controls and 90 patients with CKD across a range of eGFR, LV longitudinal systolic strain, early, and late diastolic strain rates were significantly reduced in CKD patients ($-16.9 \pm 3.8\%$, $1.6 \pm 0.5\%$, and $1.3 \pm 0.4\%$ in CKD vs. $-22.5 \pm 0.6\%$, $2.3 \pm 0.2\%$, and $1.9 \pm 0.1\%$ in controls, $p < 0.001$ for all), despite over-all preservation of ejection fraction.[20] Early attempts to characterize and quantify myocardial fibrosis in end-stage renal-disease (ESRD) using gadolinium enhanced cardiac MRI described a high prevalence of "late gadolinium enhancement" characteristic of coronary artery disease (CAD), but also described a noninfarct pattern typical of more diffuse fibrosis.[9] The limitations to the use of gadolinium in advanced CKD (due to the risk of nephrogenic systemic fibrosis) were overcome in two recent studies that described prolonged native T1 relaxation time and abnormal global

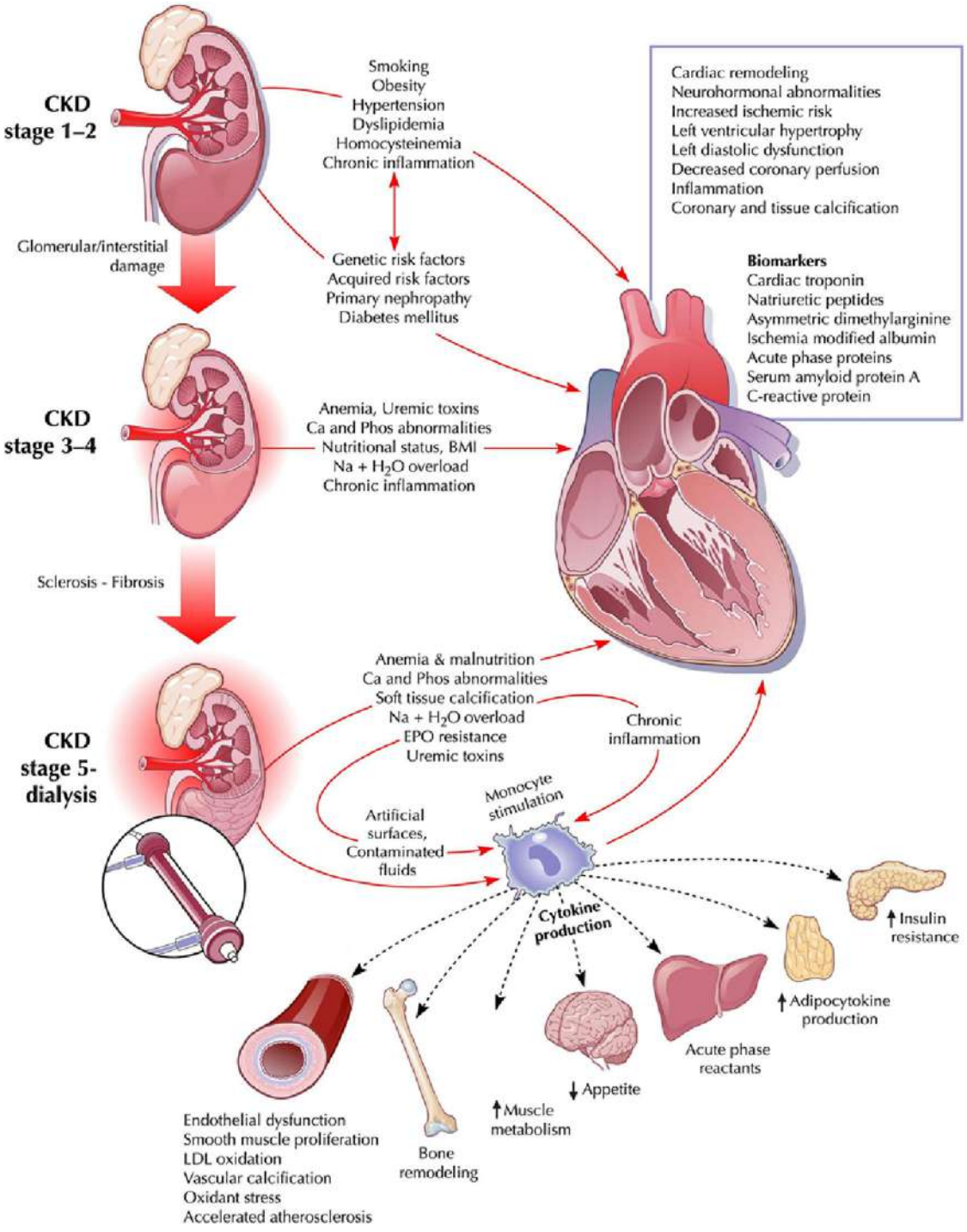


FIGURE 23.1 Pathophysiological interactions between heart and kidney in type 4 cardio-renal syndrome (CRS) or "chronic reno-cardiac syndrome" (for example, chronic glomerular disease contributing to decreased cardiac function, cardiac hypertrophy, or increased risk of adverse cardiovascular events). *BMI*, body mass index; *EPO*, erythropoietin; *LDL*, low-density lipoprotein. *Figure reproduced with permission from reference 15.*

longitudinal strain in prevalent hemodialysis patients with preserved EF compared to controls.[21,22] These advances will help further our understanding of the nuances of CKD-associated cardiomyopathy and its progression in future studies.

Management Strategies in Patients with Heart Failure with Chronic Kidney Disease

Despite the significant burden of HF in CKD, high-quality data from randomized controlled trials (RCTs)

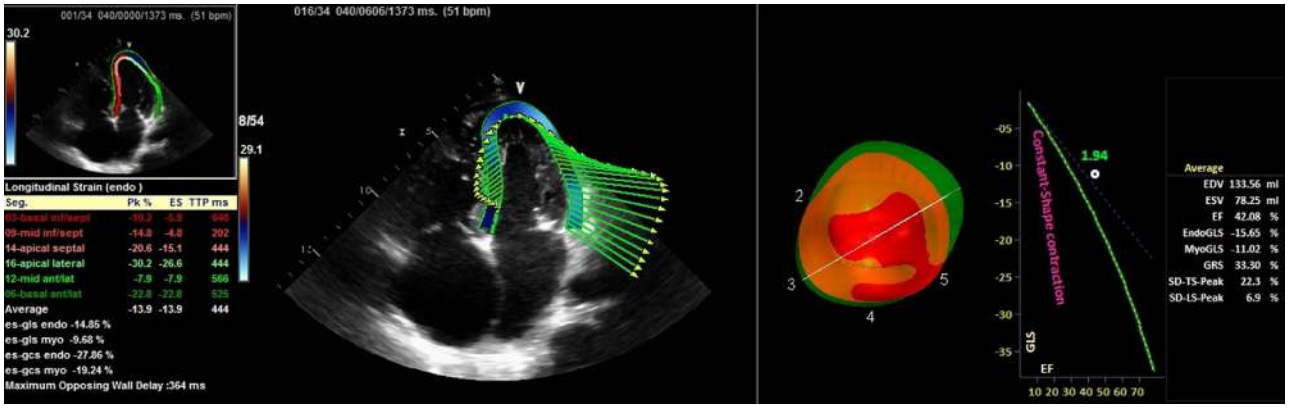


FIGURE 23.2 The panel shows a 2D speckle tracking echocardiographic measurement of global longitudinal strain in apical 4-chamber view in a patient with heart failure with preserved ejection fraction with CKD with eGFR of 40 mL/min/1.73 m^2. On the left is a segmental strain distribution with the mid- to basal inferior septal segments with reduced strain (−14.8% and −10.2%). The mid anterolateral area also exhibited reduced strain (−7.9%). The image on the far right shows the average global longitudinal strain from three views (4 chamber, 2 chamber, and 3 chamber) which is reduced (−15.65%) compared to the normal value that is equal to or more negative than −18%.

evaluating delivering goal directed medical therapies for HF are notably lacking in patients with CKD. Patients with advanced CKD and HF are less likely to receive certain therapies that are used in the general HF population.[23] The cornerstones of HF therapies including preload and afterload reduction, treatment of myocardial ischemia and related structural causes of worsening HF, inhibition of the sympathetic nervous system, and RAAS modification apply to patients with CKD as well as HF. The use of sodium restriction and diuretics to maintain volume control, despite being central to the management of HF with CKD, has not been confirmed in RCT settings with hard cardiovascular endpoint benefits in CKD patients. Diuretic therapy in patients with HF and CKD is characterized by the need for higher drug doses to achieve intended targets. Loop diuretics are more effective with advanced CKD (eGFR <30 cc/min/1.73 m^2) compared to thiazide-type diuretics. Diuretic resistance, defined as the attenuation of the maximal diuretic effect that ultimately limits sodium and chloride excretion, is encountered more frequently in HF with CKD. CKD patients with diuretic resistance have increased risk of worsening renal function, rehospitalizations for HF, and mortality.[24] Diminished nephron mass, acute and chronic diuretic "braking," distal tubular hypertrophy from chronic diuretic use, and persistent RAAS activation are some of the factors underlying diuretic resistance in patients with HF and CKD.[25] Frequent and escalated diuretic dosing, consistent with CKD stage, use of longer acting loop diuretics such as torsemide, reduction of neurohumoral activation by avoidance of chloride depletion, and optimizing RAAS hyperactivity may help circumvent some of these factors in HF with CKD.[26,27] Whether the concept of diuretic synergy (use of a distal diuretic to augment furosemide-mediated sodium excretion) can be used effectively in patients with HF and CKD is uncertain. A large-scale randomized clinical trial of thiazide-type diuretics as an adjunct to furosemide in HF/CRS/CKD is lacking; however, the ATHENA-HF trial (Efficacy and Safety of Spironolactone in Acute Heart Failure) tested spironolactone, a potassium sparing diuretic that targets another hypertrophied downstream nephron segment, against placebo. Investigators did not demonstrate significant clinical benefit.[28] Finally, novel drug delivery routes, such as subcutaneous administration of furosemide, are being developed and may offer promise in reducing the burden of HF-related hospitalizations.[29] Their impact on HF with CKD at this time is, however, unknown.

Goal directed medical therapeutic drug classes in HF include beta adrenergic receptor blockers (BB), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists, vasodilator therapies hydralazine/isosorbide dinitrate), ivabradine, digitalis glycosides, and cardiac resynchronization therapy/implantable defibrillator therapy (CRT/ICD). Data are also evolving from major cardiovascular outcomes trials on the role of the novel antidiabetic agents such as sodium glucose cotransporter 2 inhibitors (SGLT2i) and glucagon like receptor 1 agonists (GLP1-RA) with respect to reduction in cardiovascular deaths and HF-related hospitalizations, including in patients with mild to moderate CKD. Relevant information on graded evidence levels in HF are available in the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure,[16] and outlines of pharmacotherapies and their risk/benefit profiles with respect to HF and CKD are summarized by Covic and Damman et al.[30,31] Figure 23.3 **(Panels A and B)** depicts relative strengths of evidence for these goal directed

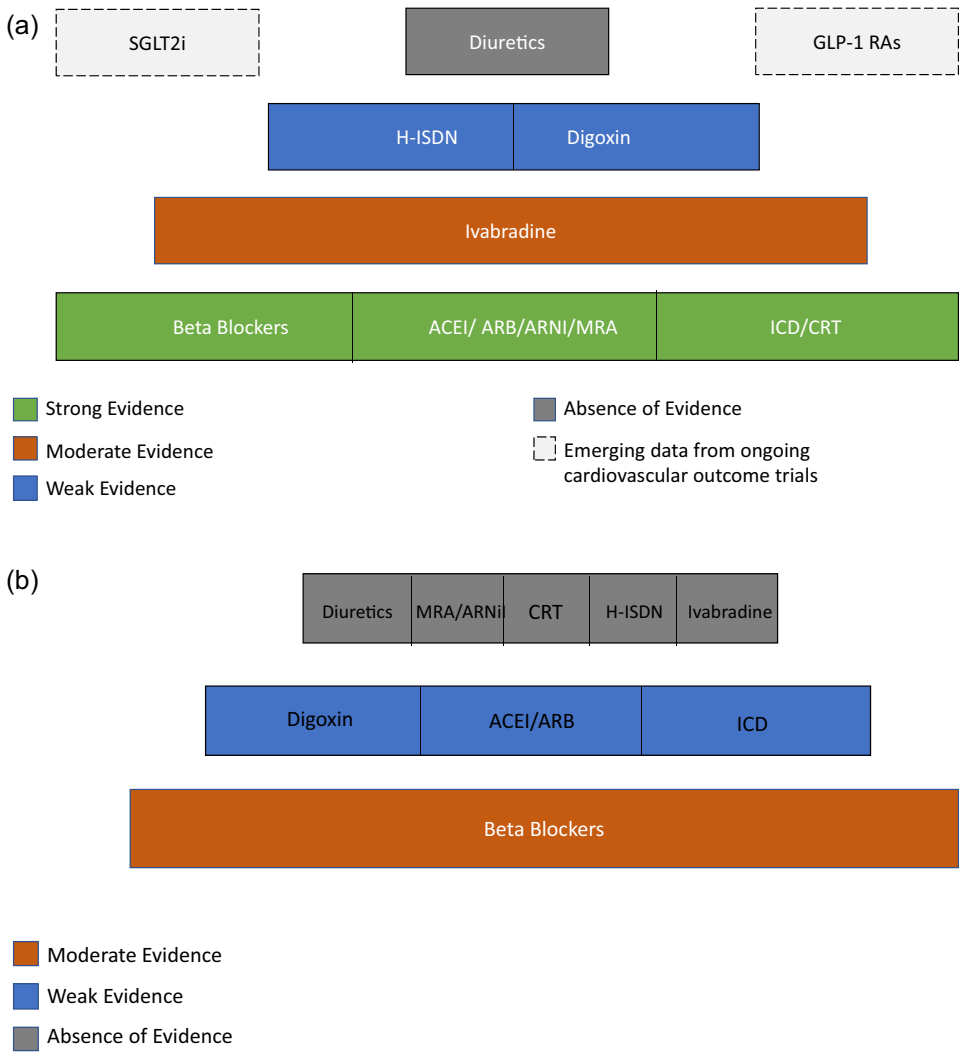


FIGURE 23.3 **Panel A** shows the relative strengths of evidence (ungraded) for goal directed medical therapies for heart failure in patients with underlying stage 1–3 CKD. **Panel B** shows the relative strengths of evidence (ungraded) for goal directed medical therapies for heart failure in patients with stage 4–5 CKD. Both panels exclude data in patients treated with dialysis and kidney transplant recipients. *ACEi*, angiotensin converting enzyme inhibitors; *ARB*, angiotensin receptor blockers; *ARNi*, angiotensin receptor blocker/neprilysin inhibitors; *CRT*, cardiac resynchronization therapy; *GLP 1 RA*, glucagon-like peptide 1 receptor agonist; *H-ISDN*, hydralazine-isosorbide dinitrate; *ICD*, implantable cardiac defibrillators; *MRA*, mineralocorticoid receptor antagonists; *SGLT2i*, sodium glucose cotransporter 2 inhibitors.

therapies in HF with respect to the different stages of CKD (excluding dialysis and transplantation).

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN CHRONIC KIDNEY DISEASE

Pathophysiology and Risk Factors

Patients with CKD exhibit high disease burden from ASCVD, including CAD as well as peripheral arterial disease. Atheromatous plaques, the *sine qua non* of this phenotype of CVD, are quantitatively similar to those found in patients without CKD as shown in autopsy studies.[32] However, the plaques are more calcified with abundance of hydroxyapatite, i.e. calcium phosphate) with significant intimal and medial calcification in CKD compared to those without CKD.[33] The presence of CKD, independent of other CVD risk factors, appears to accelerate the atherosclerotic process including the recruitment of monocytes, upregulation of adhesion molecules, ingress of monocytes and conversion to macrophages and foam cells, mobilization of vascular smooth muscle cells, breakdown of the elastic lamina, and development of an atheroma, which expands both toward the lumen and outward toward the adventitium.[34] In addition, CKD has a significant influence on calcification in atherosclerosis. The majority of anatomic and visible calcium by imaging in atherosclerosis is the result of osteoblastic conversion of smooth muscle cells,

and the deposition of calcium hydroxyapatite crystals in the extracellular matrix.[35] Phosphate appears to be an important stimulator of the vascular smooth muscle cells to both undergo osteoblastic deposition and deposit calcium, and it may represent a major influence on the development of the disproportionately calcified lesions seen in CKD.[35,36] Finally, angiographic evidence of CAD in CKD (eGFR <60 cc/min/1.73 m^2) has demonstrated higher rates of triple vessel disease or left main disease as reported in the CKD subset of the Clinical Outcomes Utilizing Revascularization and Drug Evaluation (COURAGE) trial as well as in other databases.[37,38] Although these studies do not report the etiology of CKD or degree of albuminuria, the strong correlation between decreased eGFR and clinicopathological evidence of ASCVD reinforces the designation of CKD as an ASCVD equivalent.

Stable Ischemic Artery Disease and Acute Coronary Syndromes: Diagnostic Strategies

Currently available tools for the diagnosis of ASCVD including clinical symptoms, electrocardiogram, and cardiac stress testing are overall less reliable in the CKD population.[39] In a study evaluating the occurrence of chest pain or related symptoms (arm or jaw pain) during total balloon occlusion of an epicardial coronary artery with plaque, 48% and 50% of patients with eGFR 30–59 mL/min/1.73 m^2 and <30 mL/min/1.73 m^2, respectively, experienced no pain on occlusion, compared with 20.6% and 28.2% of patients with eGFR >90 mL/min/1.73 m^2 and 60–89 mL/min/1.73 m^2, respectively (χ^2 test for trend $p = 0.004$).[40] Coronary calcification seen on computed tomographic studies is a proxy for a greater burden of atherosclerosis, reduced vascular compliance, and more mature and stable plaques and not a passive process of calcification such as Mönckeberg's sclerosis. When the coronary calcium score (either volumetric or Agatston) is >400 units, then the probability of at least one significant ($>70\%$) lesion resulting in reduced myocardial blood flow with stress is $>80\%$. Thus, if a calcium score is known at the time of evaluation and the score is >400, further functional testing is reasonable.[41]

Despite the higher burden of CAD risk factors in CKD, the overall performance of cardiac stress testing in this population is suboptimal. A meta-analysis of cardiac stress testing performance (primarily dobutamine stress echocardiography and myocardial perfusion scintigraphy) identified a median sensitivity of 69% and specificity of 80% for myocardial perfusion scintigraphy, and median sensitivity of 80% and specificity of 89% for dobutamine stress echocardiography.[42] This translates to a higher proportion of both false-positive stress tests as well as false-negative stress tests. LVH, balanced ischemia due to multivessel disease, increased baseline coronary flow reserve, and baseline ECG abnormalities resulting in high interobserver variability are some of the factors that contribute to the lower accuracy of stress testing in CKD.[43] An overview of the utility of select diagnostic tests for CVD in CKD with emphasis on CAD is presented in Table 23.2.[41] There is no clear cut indication to evaluate asymptomatic patients with screening stress tests or other imaging modalities. The exception to this situation is the preoperative cardiac workup of the kidney transplant recipient (which is beyond the scope of this chapter). Such approaches are outlined in detail in the ACCF/AHA Scientific Statement on the preoperative workup of the potential kidney and liver transplant recipient.[44]

As CKD stage worsens, patients are more likely to present with acute coronary syndrome (ACS) than stable ischemic heart disease (SIHD).[45] McCullough et al. demonstrated that patients with CKD presenting to the emergency room with chest pain had a 40% risk of MI, HF, or death.[46] Patients with CKD presenting with ACS tend to have more extensive CAD, higher risk for reinfarction, HF, and death. Paradoxically the presentation tends to be more atypical with delayed initial presentation, with a lesser likelihood of receiving evidence-based therapies for ACS compared to patients without CKD.[47] The severity of CKD correlates with both short-term and long-term outcomes with ACS.[48] In addition to symptoms of ACS, physical findings, and electrocardiographic evaluation, cardiac biomarkers of injury play a critical role in the diagnostic algorithm for ACS as well as for prognostication. In CKD, baseline elevations in cardiac troponins can reflect myocardial damage, decreased renal clearance, skeletal muscle expression of cardiac specific isotopes, and metabolic abnormalities. Thus, in a patient with CKD and suspected ACS, baseline cardiac troponin levels of >99 percentile values for the general population are a common finding. The characteristic rise and fall of these biomarkers must be accompanied by at least one other piece of supportive evidence, including new ST–T wave changes or left bundle branch block, signs and symptoms consistent with ischemia, new myocardial wall motion abnormalities, the presence of thrombus on coronary angiography, or supportive autopsy findings to make a diagnosis.[49]

Management Strategies for Stable Ischemic Heart Disease in Chronic Kidney Disease

The evidence-based approach to the medical management of SIHD and ACS in patients with CKD is limited by the underrepresentation of this population in major

TABLE 23.2 Overview of Select Diagnostic Tests for Cardiovascular Disease in CKD

Test	Comment
12-lead electrocardiogram	Should be done yearly, evaluates baseline rhythm, presence of Q-waves, chamber enlargements, left ventricular hypertrophy
Functional imaging Exercise stress echocardiography Exercise stress nuclear scintigraphy (Tc-99 sestamibi or Tl-201) Pharmacologic stress imaging (regadenoson, dobutamine, adenosine, dipyridamole)	Evaluates exercise-related functional status with >10 metabolic equivalents of work being excellent prognosis; imaging identifies fixed and reversible ischemia; large zones of reversible ischemia call for anti-ischemic therapy and additional evaluation usually with angiography; stress echocardiography gives all the baseline information of resting echocardiography in addition to the evaluation of reversible ischemia
Cardiac computed tomographic angiography	Appropriate for the evaluation of chest pain with an uninterpretable stress test; not appropriate for patients with established CAD or ESRD; generates calcium score, can evaluate degree of lumen stenosis if calcification is not severe; normal result has excellent negative predictive value for cardiac events; calcium score >400 usually indicates severe disease on invasive angiography, while score of 0 portends excellent prognosis
Coronary angiography Left ventriculography	Definitive diagnosis of coronary luminal obstruction, left ventricular function, and opportunity for *ad hoc* PCI
Resting echocardiography	Test of choice to evaluate diastolic and systolic function, valve disease
24-hour Holter monitor	Records all beats over 24 hours, calculates mean atrial and premature beats per hour (>10 abnormal), identifies ST segment shifts, identifies asymptomatic arrhythmias
Cardiac event monitor	Worn for prolonged periods, patient activates device to record symptomatic arrhythmias
Insertable loop recorder	Subcutaneous, pectoral placement of device that records patient and device-detected arrhythmias for approximately 2 years

CAD, coronary artery disease; *ESRD*, end-stage renal disease; *PCI*, percutaneous coronary intervention; *Tc*, technetium; *Tl*, thallium.
Reproduced with permission from reference 41.

cardiovascular outcome trials (CVOTs), despite the higher baseline risk for CAD in CKD. Charytan et al. analyzed 86 large cardiovascular trials on 5 different types of therapies for CAD.[50] 75% of these trials excluded patients with CKD, and over 80% excluded subjects on dialysis. Baseline renal function was reported only in 7% of study participants. This key factor may contribute to the "therapeutic nihilism" seen in the management of CAD in CKD, in addition to the fear of causing harm (such as with antiplatelet agents or RAAS inhibitors) and the inaccurate extrapolation of data in the non-CKD patients to those with CKD.

Blood Pressure Targets

Blood pressure (BP) optimization in subjects with CKD at elevated CVD risk or with established CVD has been a moving target, with potentially conflicting data in different subpopulations (diabetic vs. nondiabetics). The Systolic Hypertension Intervention Trial (SPRINT) demonstrated benefits with intensive BP control (SBP <120 mm Hg) in nondiabetic hypertensives at high cardiovascular risk, including in its CKD subset (about 28% of participants).[51] However, the trial also reported higher rates of hypoperfusion-related serious adverse outcomes, such as AKI, syncope, and hypotension, and was limited in long-term follow-up due to premature termination of the trial after analyses of the primary outcome exceeded the monitoring boundary at two consecutive time points. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (with less representation of CKD), in contrast, showed no benefits with a similar intensive BP reduction target in diabetics with established or high risk for CVD.[52] Beddhu et al. reported on a comparative analysis of incident CKD in the SPRINT and ACCORD trials, which showed the intensive BP target group in ACCORD experienced the highest rates of incident CKD.[53] These observations may be explained in the context of the known effects of intensive BP lowering with impaired renal blood flow autoregulation in subjects with preexisting hypertension and CKD, thus increasing the potential risk of renal hypoperfusion–related AKI, which may serve as a springboard for future CKD.[54] Finally, Malhotra et al. demonstrated an overall reduction in all-cause mortality in a meta-analysis of 18 trials looking at standard vs. intensive BP control, in subjects with stages 3–5 CKD.[55] The 2017 ACCF/AHA guidelines for management of hypertension target a SBP >130 mm Hg for treatment in CKD with ACEI/ARB being the drugs of choice in patients with albuminuria.

Statin Therapy

3-Hydroxy-3 methyl-glutaryl-coenzyme A reductase inhibitors (statins) have been studied in the CKD population in three high-quality RCTs: the Die Deutsche Diabetes Dialysis (4D) trial,[56] An Assessment of Survival and Cardiovascular Events (AURORA) trial,[57] and the Study of Heart and Renal Protection (SHARP) trial.[58] The use of statins in patients with end-stage renal disease accrued no benefits toward primary or secondary prevention of the composite cardiovascular outcomes. In the SHARP trial, the combination of simvastatin and ezetimibe in patients with CKD (including those treated with dialysis) reduced major atherosclerotic events by 17% but did not reduce overall mortality. A meta-analysis of 38 trials comparing statins vs. placebo or no treatment suggested benefits in patients with moderate CKD not requiring dialysis.[59] Given the reduction in nonfatal cardiovascular events and the lack of significant harm from statins in these trials, the KDIGO lipid guidelines recommend therapy in all patients with CKD >50 years and with high ASCVD risk in the age group of 18–49 years.[60]

Antiplatelet Agents

Patients with CKD represent both extremes of the bleeding-clotting paradigm. Baseline higher levels of platelet reactivity in patients with reduced GFR has been demonstrated,[61] as well as less robust reduction in platelet reactivity in response to P2Y12 inhibitors, such as clopidogrel in patients with CKD or proteinuria.[62] This may be a contributory factor to in-stent thrombosis, which is a bigger concern in patients with CKD than in those without CKD. The role of aspirin is limited to prevention of MI in patients with CKD, with no effect on mortality.[63,64] At this time, there are limited data on the efficacy of the newer P2Y12 inhibitors in CKD and ESRD.

Myocardial Revascularization for Stable Ischemic Heart Disease in CKD Patients

The only true randomized trial comparing medical therapy vs. revascularization of SIHD in CKD was performed by Manske et al. in 1992, which was stopped after enrollment of 26 subjects due to excessive rates of the primary outcome (unstable angina, MI, or cardiac death) in the medically managed group. This must be interpreted in the context of "optimal medical therapy" for CAD being limited to aspirin and calcium channel blockers at that time. After this, no prospective RCTs have addressed this question with the current therapeutic armamentarium available for the medical management of CAD in patients with CKD. A *post hoc* analyses of 320 subjects from COURAGE with eGFR<60 cc/min/1.73 m^2 demonstrated no differences in rates of death and MI between the medically managed group and the revascularization group. The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) showed that an initial revascularization strategy with percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG) vs. medical management in SIHD was not superior regarding reduction in all-cause mortality or MI. However, S[Cr] >2 mg/dL was an exclusion criteria for this trial, and no formal results are available on comparative strategies and outcomes from BARI 2D in CKD. Thus, at this time, robust evidence in favor of revascularization for SIHD in CKD does not exist, but other important conclusions can be made from available observational data, as well as from *post hoc* analyses of RCTs. Drug-eluting stents may offer superior outcomes compared to bare metal stents in patients with SIHD and CKD.[65] Patients with triple vessel disease or on maintenance dialysis may benefit from CABG, especially when complete revascularization cannot be achieved with PCI, regarding long-term outcomes.[66,67] Finally, "zero contrast" PCI techniques in patients with advanced CKD afford renoprotection and reduction of contrast-induced AKI rates even in patients with advanced predialysis CKD.[68,69]

Management of Acute Coronary Syndromes in Chronic Kidney Disease

Patients with CKD presenting with an ST elevation myocardial infarction (STEMI) should undergo primary PCI with stenting within 90 minutes (door to balloon time). Treatment patterns for STEMI in CKD are characterized by delayed therapy due to difficulty with recognition of the condition and confusion regarding the risks and benefits of treatment. Newsome et al. found that of 109,169 Medicare patients with MI, fewer patients with kidney disease received thrombolytic therapy, and those with the worst kidney disease (S[Cr] >1.6 mg/dL) waited the longest for therapy. There are no formal dose adjustment recommendations for the use of streptokinase, alteplase, reteplase, or tenecteplase in patients with CKD.[49] After reperfusion, medical management of STEMI is similar to that of patients with non-ST elevation myocardial infarction (NSTEMI). Once a patient with suspected unstable angina or NSTEMI is diagnosed, standard medical therapy should include aspirin, a beta adrenergic receptor blocker, anticoagulant therapy, possibly a glycoprotein IIb/IIIa antagonist, and a thienopyridine, unless a specific contraindication exists.[49]

Mild to moderate CKD is considered a risk for major complications in patients with unstable angina or

NSTEMI, and an early invasive strategy is preferred to conservative medical management. Although patients with predialysis CKD are less likely to be offered coronary angiography in the setting of ACS, they benefit from revascularization with improved long-term survival.[70] The Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) reported in 23,262 cases of NSTEMI that the utilization of coronary angiography and revascularization decreased with declining eGFR.[71] In SWEDEHEART, the benefits of an early invasive strategy on 1-year mortality confirmed in patients with mild and moderate CKD were not observed in patients on dialysis, likely due to several other competing factors in patients on dialysis that increase mortality risk. A detailed summary by Narala et al. highlights the benefits, hazards, drug dosing, and caveats with the management of SIHD and ACS in CKD to assist with clinical decision-making in this population.[49]

Valvular Heart Disease in Chronic Kidney Disease

The two most common forms of cardiac valvular disease in CKD are aortic valve calcification and sclerosis, and mitral annular calcification (MAC). In CKD, there is a graded relationship between progressive decline in eGFR and the prevalence of calcification, hospitalizations, cardiovascular events, and death[72] (Figure 23.4). Complications associated with valvular calcification include thromboembolic phenomenon, arrhythmias, and stenosis-related symptoms. Patients with CKD and aortic stenosis (AS) are considered "rapid progressors" with annual reduction in aortic valve area being around $0.23\ cm^2$/year compared to the typical $0.05–0.1\ cm^2$/year in patients without CKD.[73] Valve replacement is the only therapy shown to have survival benefit in AS regardless of underlying CKD. The two main treatment options for aortic valve replacement are surgical (SAVR) vs. transcatheter aortic valve replacement (TAVR). CKD is a risk factor for increased 30-day mortality and a greater than 50% increase in median post SAVR mortality long term.[74] Higher complication rates with SAVR in CKD result from the technical challenges associated with high valvular and vascular calcific burden and bleeding risk, resulting in increased hospital length of stay as well as ICU duration.[75] The less-invasive TAVR is an available therapeutic option in patients with high surgical risk and CKD. However, underlying CKD is associated with higher incidence of MACEs (composite of death, myocardial infarction, or stroke), net adverse cardiovascular events (composite of MACEs, major bleeding, or vascular complications), and pacemaker implantation, compared with patients without CKD.[76] In another analysis, in additional to higher mortality rates, the risk of AKI and needing dialysis were higher in subjects with underlying CKD.[77] Finally, a recent meta-analysis of TAVR outcomes in CKD reported an increased short-term and long-term mortality risk in high-risk surgical patients undergoing TAVR with underlying CKD. This association was not seen in low/intermediate-risk patients with CKD undergoing TAVRs.[78] Given the high-risk patient profile and

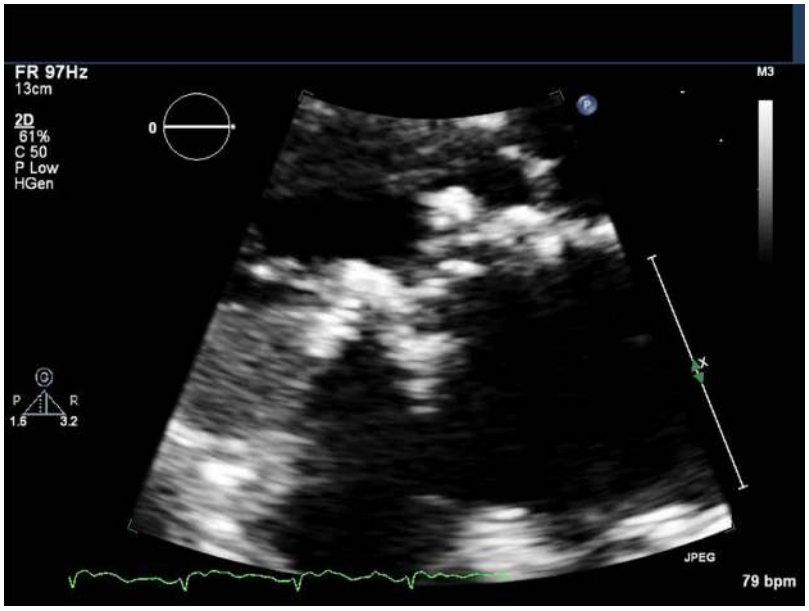


FIGURE 23.4 Parasternal long-axis view on 2-D echocardiography of a patient with stage 5 CKD (not on dialysis) with a severely calcified bioprosthetic mitral valve 6 months after valve replacement.

complexity of planned valvular procedures in patients with CKD, clinical decision-making on valve replacement choice/techniques must be conducted with a multidisciplinary heart–kidney team to achieve optimal outcomes.

Mitral stenosis and/or regurgitation can occur secondary to MAC and may require surgical or percutaneous (Mitra Clip or transcatheter mitral valve replacement) interventions. Patients with CKD undergoing Mitra Clip (placement of a stitch between the anterior and posterior leaflet, producing a double orifice valve and reducing the effective orifice area) are more likely to be male, older, and have higher preprocedural STS and EuroScores.[79] Also, patients with CKD, especially with eGFR <30 mL/min/1.73 m^2, require a higher number of postprocedure blood transfusions or experience major bleeding. Irrespective of underlying CKD status, effective reduction of mitral regurgitation can lead to improvement in renal function, with documented reductions in diuretic use and improvements in LA and LV volumes and LV dimensions in patients with CKD at 1 year follow-up.[79] This is likely from the favorable impact of reduction of valvular leak on myocardial mechanics and hemodynamic/neurohumoral changes with decompensated CRS. Further research needs to be done to enhance clinical utility.

Arrhythmias and Chronic Kidney Disease

Patients with CKD are predisposed to heart rhythm disorders, including atrial fibrillation (AF)/atrial flutter, supraventricular tachycardias, ventricular arrhythmias, and sudden cardiac death (SCD). Although treatment options including drugs, devices, and procedural therapies are available, their use in the setting of CKD is limited by paucity of high-quality data. AF is the most common sustained arrhythmia and has a high prevalence in CKD. Consequences of AF in CKD include elevated stroke risk, increased risk of progressive CKD/ESRD, and death.[80–82] Among stroke prediction risk scores, the CHA_2DS_2-VASc score remains the most commonly recommended score for risk stratification. Observational data show a treatment threshold of CHA_2DS_2-VASc ≥ 2 is associated with benefit from oral anticoagulation therapy, including in CKD.[83]

Large RCTs have demonstrated that novel oral anticoagulants (NOACs) are noninferior to warfarin among patients with estimated creatinine clearance (eCrCl) of 30–50 mL/min, with significant reductions in the risk of intracranial hemorrhage.[84] However, the lack of head to head comparisons of these drugs in CKD precludes any recommendations of an individual drug. Among patients with creatinine clearance between 25 and 50 mL/min, treatment with apixaban and edoxaban resulted in significantly fewer major bleeding events compared with warfarin.[85] In patients with eGFR<30 cc/min/1.73 m^2 and in patients treated with dialysis, there is insufficient high-quality evidence on the safety and efficacy of anticoagulation for stroke prevention in AF, with conflicting results reported from large observational cohort studies.[86,87] Anticoagulation-related nephropathy may cause episodes of intraglomerular hemorrhage and accelerate decline in renal function and dialysis dependence.[88] The US Food and Drug Administration recently approved the use of apixaban 5 mg twice daily, rivaroxaban 15 mg daily in CKD 5 and ESRD and dabigatran 75 mg orally twice daily for CrCl 15–30 mL/min based on single/limited dose pharmacokinetic and pharmacodynamic data. The recent KDIGO controversies conference on CKD and arrhythmias suggested consideration of the lower dose of apixaban 2.5 mg orally twice daily in CKD 5 and ESRD patients to reduce bleeding risk until clinical safety data are available, an approach supported by a recent pharmacokinetic study comparing the two doses.[84] Ongoing and future randomized trials addressing the need and choice of drugs for safety and efficacy for stroke prevention in AF and CKD, will help determine best clinical practices to reduce stroke burden in this population.[89]

The burden of SCD is high in patients with CKD (fourfold increase with eGFR <60 cc/min/1.73 m^2) and increases further with transition to ESRD.[90] Although traditional risk factors such as reduced ejection fraction and atherosclerotic CAD are associated with SCD in CKD, they do not fully account for the high incidence of SCD seen in this population. Factors specific to the CKD milieu such as hyperkalemia and the malnutrition–inflammation complex may also contribute to this elevated risk.[91] Given the high prevalence of CKD in patients with HF and vice versa, implantable device therapy is part of the therapeutic armamentarium in this population. Although the benefits of placement of implantable cardioverter–defibrillators (ICDs) in patients with HF meeting select criteria are well established in the general population,[92] conflicting data exist regarding the benefits in patients with HF and CKD. Pun et al. reported on outcomes with ICDs for primary prevention in CKD in a meta-analysis of three primary prevention ICD RCTs that had data available on renal function: The Multicenter Automatic Defibrillator Implantation Trial I (MADIT-I), MADIT-II, and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).[93] ICDs were associated with survival benefit in patients with GFR >60 cc/min (adjusted HR, 0.49; 95% posterior credible interval, 0.24–0.95). This was not the case with patients with GFR <60 cc/min (aHR, 0.80; PCI, 0.40–1.53), wherein eGFR did not modify the association between ICDs and

rehospitalizations. In contrast, the DANISH trial (Danish study to assess the efficacy of ICDs in patients with non-ischemic systolic HF on mortality) showed that prophylactic ICD implantation in HFrEF not caused by CAD had no impact on mortality from any cause, including patients with CKD.[94] Subcutaneous defibrillators offer an attractive alternative to ICDs and pilot data on safety and efficacy exists in patients with ESRD.[95,96] Similarly, benefits from CRT are attenuated in the presence of underlying CKD.[97] However, improvements in EF, reduction in mitral regurgitation, and eGFR in mild to moderate CKD have been reported in *post hoc* analyses of The Multicenter InSync Randomized Clinical Evaluation study.[98] Given that patients with advanced CKD are routinely excluded from major cardiovascular therapy trials, and the lack of robust data on survival benefits, decisions to use device-based therapies for primary prevention in advanced CKD and ESRD must consider patient comorbidities, frailty, and quality of life to balance the risk–benefit profiles including higher infection rates, bleeding, central venous stenosis, and tricuspid regurgitation with specific devices.

CONCLUSIONS AND FUTURE DIRECTIONS

Patients with CKD experience unacceptably high rates of CVD, including all its phenotypes. Paradoxically, CKD remains an exclusion criterion for most major cardiovascular trials, thus leaving several key questions regarding the diagnosis and management of CVD in CKD unanswered. Ongoing major RCTs such as the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches–Chronic Kidney Disease trial (ISCHEMIA-CKD, NCT01985360) and the Trial to Evaluate Anticoagulation in Hemodialysis patients with Atrial Fibrillation (RENAL-AF, NCT02942407) will help shed light on key clinical questions pertaining to the cardiovascular care of the patient with CKD. The introduction of clinically meaningful composite cardio-renal outcomes such as Major Adverse Renal Cardiovascular Events (composite of myocardial infarction, need for RRT stroke, HF, hospitalizations for cardiac reasons, hospitalization for renal reasons, and death)[99] will allow the clinical consequences of CVD and CKD, and the effects of different interventions to be defined more accurately. There is an urgent need for dedicated "cardio-renal" interdisciplinary teams that will spearhead early identification of patients with complex CVD and CKD, and jointly manage appropriate clinical interventions across inpatient and outpatient settings (Figure 23.5). This collaboration would also oversee cross training among nephrology and cardiology fellows, and nursing and allied health care providers in both specialties, to foster a deeper understanding of the intricacies of cardio-renal cross talk.[100] These measures will help reduce the disease burden of CVD with CKD in a clinically effective and cost-favorable manner.

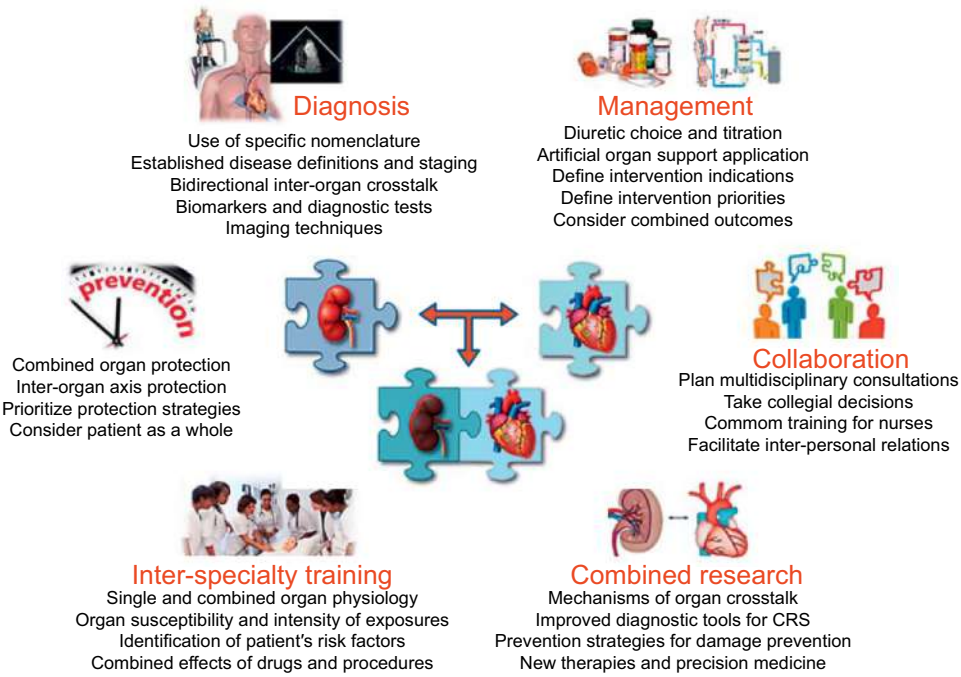


FIGURE 23.5 A model for a multidisciplinary cardio-renal team that would spearhead joint clinical decision-making, educational pathways, and research collaborative efforts in cardio-renal medicine. *Reproduced with permission from reference 100.*

References

1. United States Renal Data System. *USRDS annual data report: epidemiology of kidney disease in the United States*. National Institutes of Health NIDDK; 2017.
2. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension (Dallas)* 2003;**42**(5):1050−65.
3. van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2011; **79**(12):1341−52.
4. Levey AS, Beto JA, Coronado BE, et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kidney Dis* 1998;**32**(5):853−906.
5. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013; (Suppl. l):1−150.
6. Foley RN, Murray AM, Li S, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 2005;**16**(2):489−95.
7. McCullough PA, Kellum JA, Haase M, et al. Pathophysiology of the cardiorenal syndromes: executive summary from the eleventh consensus conference of the Acute Dialysis Quality Initiative (ADQI). *Contrib Nephrol* 2013;**182**:82−98.
8. Park M, Hsu CY, Li Y, et al. Associations between kidney function and subclinical cardiac abnormalities in CKD. *J Am Soc Nephrol* 2012;**23**(10):1725−34.
9. Edwards NC, Moody WE, Chue CD, Ferro CJ, Townend JN, Steeds RP. Defining the natural history of uremic cardiomyopathy in chronic kidney disease: the role of cardiovascular magnetic resonance. *JACC Cardiovasc Imag* 2014;**7**(7):703−14.
10. McCullough PA, Rios A, Smith B. Dialysis fistulas and heart failure. *Eur Heart J* 2017;**38**(24):1924−5.
11. Glassock RJ, Pecoits-Filho R, Barberato SH. Left ventricular mass in chronic kidney disease and ESRD. *Clin J Am Soc Nephrol* 2009; **4**(Suppl. 1):S79−91.
12. Faul C, Amaral AP, Oskouei B, et al. FGF23 induces left ventricular hypertrophy. *J Clin Investig* 2011;**121**(11):4393−408.
13. Sharma UC, Pokharel S, van Brakel TJ, et al. Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. *Circulation* 2004;**110**(19): 3121−8.
14. Virzi GM, Zhang J, Nalesso F, Ronco C, McCullough PA. The role of dendritic and endothelial cells in cardiorenal syndrome. *Cardiorenal Med* 2018;**8**(2):92−104.
15. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008;**52**(19):1527−39.
16. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017;**136**(6):e137−61.
17. Wu AH, Omland T, Wold Knudsen C, et al. Relationship of B-type natriuretic peptide and anemia in patients with and without heart failure: a substudy from the Breathing Not Properly (BNP) Multinational Study. *Am J Hematol* 2005;**80**(3):174−80.
18. Tumlin JA, Costanzo MR, Chawla LS, et al. Cardiorenal syndrome type 4: insights on clinical presentation and pathophysiology from the eleventh consensus conference of the Acute Dialysis Quality Initiative (ADQI). *Contrib Nephrol* 2013;**182**:158−73.
19. Kramann R, Erpenbeck J, Schneider RK, et al. Speckle tracking echocardiography detects uremic cardiomyopathy early and predicts cardiovascular mortality in ESRD. *J Am Soc Nephrol* 2014; **25**(10):2351−65.
20. Hassanin N, Alkemary A. Early detection of subclinical uremic cardiomyopathy using two-dimensional speckle tracking echocardiography. *Echocardiography (Mount Kisco, NY)* 2016; **33**(4):527−36.
21. Rutherford E, Talle MA, Mangion K, et al. Defining myocardial tissue abnormalities in end-stage renal failure with cardiac magnetic resonance imaging using native T1 mapping. *Kidney Int* 2016;**90**(4):845−52.
22. Graham-Brown MP, March DS, Churchward DR, et al. Novel cardiac nuclear magnetic resonance method for noninvasive assessment of myocardial fibrosis in hemodialysis patients. *Kidney Int* 2016;**90**(4):835−44.
23. Wang AY, Sanderson JE. Treatment of heart failure in long-term dialysis patients: a reappraisal. *Am J Kidney Dis* 2011;**57**(5):760−72.
24. Valente MA, Voors AA, Damman K, et al. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. *Eur Heart J* 2014;**35**(19):1284−93.
25. Ellison DH, Felker GM. Diuretic treatment in heart failure. *N Engl J Med* 2018;**378**(7):684−5.
26. Gehr TW, Rudy DW, Matzke GR, Kramer WG, Sica DA, Brater DC. The pharmacokinetics of intravenous and oral torsemide in patients with chronic renal insufficiency. *Clin Pharmacol Ther* 1994;**56**(1):31−8.
27. Hanberg JS, Rao V, Ter Maaten JM, et al. Hypochloremia and diuretic resistance in heart failure: mechanistic insights. *Circ Heart Fail* 2016;**9**(8).
28. Butler J, Anstrom KJ, Felker GM, et al. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. *JAMA Cardiol* 2017;**2**(9):950−8.
29. Rangaswami J, McCullough PA. Efficacy of subcutaneous versus intravenous administration of furosemide in patients with worsening heart failure: the devil is in the details. *JACC Heart Fail* 2018;**6**(3):266−7.
30. Segall L, Nistor I, Covic A. Heart failure in patients with chronic kidney disease: a systematic integrative review. *BioMed Res Int* 2014;**2014**:937398.
31. Damman K, Tang WH, Felker GM, et al. Current evidence on treatment of patients with chronic systolic heart failure and renal insufficiency: practical considerations from published data. *J Am Coll Cardiol* 2014;**63**(9):853−71.
32. Gross ML, Meyer HP, Ziebart H, et al. Calcification of coronary intima and media: immunohistochemistry, backscatter imaging, and x-ray analysis in renal and nonrenal patients. *Clin J Am Soc Nephrol* 2007;**2**(1):121−34.
33. Schwarz U, Buzello M, Ritz E, et al. Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. *Nephrol Dial Transplant* 2000;**15**(2):218−23.
34. McCullough PA, Li S, Jurkovitz CT, et al. Chronic kidney disease, prevalence of premature cardiovascular disease, and relationship to short-term mortality. *Am Heart J* 2008;**156**(2):277−83.
35. McCullough PA, Agrawal V, Danielewicz E, Abela GS. Accelerated atherosclerotic calcification and Monckeberg's sclerosis: a continuum of advanced vascular pathology in chronic kidney disease. *Clin J Am Soc Nephrol* 2008;**3**(6):1585−98.
36. McCullough PA. The impact of systemic calcified atherosclerosis in patients with chronic kidney disease. *Adv Chron Kidney Dis* 2008;**15**(4):335−7.

37. Sedlis SP, Jurkovitz CT, Hartigan PM, et al. Optimal medical therapy with or without percutaneous coronary intervention for patients with stable coronary artery disease and chronic kidney disease. *Am J Cardiol* 2009;**104**(12):1647–53.
38. Baber U, Mehran R, Kirtane AJ, et al. Prevalence and impact of high platelet reactivity in chronic kidney disease: results from the Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents registry. *Circ Cardiovasc Interv* 2015;**8**(6):e001683.
39. Sosnov J, Lessard D, Goldberg RJ, Yarzebski J, Gore JM. Differential symptoms of acute myocardial infarction in patients with kidney disease: a community-wide perspective. *Am J Kidney Dis* 2006; **47**(3):378–84.
40. Wetmore JB, Broce M, Malas A, Almehmi A. Painless myocardial ischemia is associated with mortality in patients with chronic kidney disease. *Nephron Clin Pract* 2012;**122**(1–2):9–16.
41. McCullough PA, Assad H. Diagnosis of cardiovascular disease in patients with chronic kidney disease. *Blood Purif* 2012;**33**(1–3): 112–8.
42. Wang LW, Fahim MA, Hayen A, et al. Cardiac testing for coronary artery disease in potential kidney transplant recipients: a systematic review of test accuracy studies. *Am J Kidney Dis* 2011;**57**(3): 476–87.
43. Bangalore S. Stress testing in patients with chronic kidney disease: the need for ancillary markers for effective risk stratification and prognosis. *J Nucl Cardiol* 2016;**23**(3):570–4.
44. Lentine KL, Costa SP, Weir MR, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation: endorsed by the American Society of Transplant Surgeons, American Society of Transplantation, and National Kidney Foundation. *Circulation* 2012;**126**(5):617–63.
45. Go AS, Bansal N, Chandra M, et al. Chronic kidney disease and risk for presenting with acute myocardial infarction versus stable exertional angina in adults with coronary heart disease. *J Am Coll Cardiol* 2011;**58**(15):1600–7.
46. McCullough PA, Nowak RM, Foreback C, et al. Emergency evaluation of chest pain in patients with advanced kidney disease. *Arch Intern Med* 2002;**162**(21):2464–8.
47. El-Menyar A, Zubaid M, Sulaiman K, et al. In-hospital major clinical outcomes in patients with chronic renal insufficiency presenting with acute coronary syndrome: data from a Registry of 8176 patients. *Mayo Clin Proc* 2010;**85**(4):332–40.
48. McCullough PA, Soman SS, Shah SS, et al. Risks associated with renal dysfunction in patients in the coronary care unit. *J Am Coll Cardiol* 2000;**36**(3):679–84.
49. Narala KR, Hassan S, LaLonde TA, McCullough PA. Management of coronary atherosclerosis and acute coronary syndromes in patients with chronic kidney disease. *Curr Probl Cardiol* 2013;**38**(5): 165–206.
50. Charytan D, Kuntz RE. The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. *Kidney Int* 2006;**70**(11):2021–30.
51. Wright Jr JT, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**(22):2103–16.
52. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;**362**(17):1575–85.
53. Beddhu S, Greene T, Boucher R, et al. Intensive systolic blood pressure control and incident chronic kidney disease in people with and without diabetes mellitus: secondary analyses of two randomised controlled trials. *Lancet Diabetes Endocrinol* 2018;**6**(7): 555–63.
54. Venkatachalam MA, Griffin KA, Lan R, Geng H, Saikumar P, Bidani AK. Acute kidney injury: a springboard for progression in chronic kidney disease. *Am J Physiol Renal Physiol* 2010;**298**(5): F1078–1094.
55. Malhotra R, Nguyen HA, Benavente O, et al. Association between more intensive vs less intensive blood pressure lowering and risk of mortality in chronic kidney disease stages 3 to 5: a systematic review and meta-analysis. *JAMA Intern Med* 2017;**177**(10): 1498–505.
56. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;**353**(3):238–48.
57. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;**360**(14):1395–407.
58. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**(9784): 2181–92.
59. Palmer SC, Navaneethan SD, Craig JC, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev* 2014;(5):Cd007784.
60. Wanner C, Tonelli M. KDIGO Clinical Practice Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int* 2014;**85**(6):1303–9.
61. Gremmel T, Muller M, Steiner S, et al. Chronic kidney disease is associated with increased platelet activation and poor response to antiplatelet therapy. *Nephrol Dial Transplant* 2013;**28**(8):2116–22.
62. Davila CD, Vargas F, Huang KH, et al. Dipstick proteinuria is an independent predictor of high on treatment platelet reactivity in patients on clopidogrel, but not aspirin, admitted for major adverse cardiovascular events. *Platelets* 2015;**26**(7):651–6.
63. Kim AJ, Lim HJ, Ro H, et al. Low-dose aspirin for prevention of cardiovascular disease in patients with chronic kidney disease. *PLoS One* 2014;**9**(8):e104179.
64. Jardine MJ, Ninomiya T, Perkovic V, et al. Aspirin is beneficial in hypertensive patients with chronic kidney disease: a post-hoc subgroup analysis of a randomized controlled trial. *J Am Coll Cardiol* 2010;**56**(12):956–65.
65. Volodarskiy A, Kumar S, Pracon R, et al. Drug-eluting vs bare-metal stents in patients with chronic kidney disease and coronary artery disease: insights from a systematic review and meta-analysis. *J Invasive Cardiol* 2018;**30**(1):10–7.
66. Ashrith G, Lee VV, Elayda MA, Reul RM, Wilson JM. Short- and long-term outcomes of coronary artery bypass grafting or drug-eluting stent implantation for multivessel coronary artery disease in patients with chronic kidney disease. *Am J Cardiol* 2010;**106**(3): 348–53.
67. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Revascularization in patients with multivessel coronary artery disease and chronic kidney disease: everolimus-eluting stents versus coronary artery bypass graft Surgery. *J Am Coll Cardiol* 2015;**66**(11):1209–20.
68. Ali ZA, Karimi Galougahi K, Nazif T, et al. Imaging- and physiology-guided percutaneous coronary intervention without contrast administration in advanced renal failure: a feasibility, safety, and outcome study. *Eur Heart J* 2016;**37**(40):3090–5.
69. Brar SS, Aharonian V, Mansukhani P, et al. Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. *Lancet* 2014;**383**(9931):1814–23.
70. Keeley EC, Kadakia R, Soman S, Borzak S, McCullough PA. Analysis of long-term survival after revascularization in patients with chronic kidney disease presenting with acute coronary syndromes. *Am J Cardiol* 2003;**92**(5):509–14.
71. Szummer K, Lundman P, Jacobson SH, et al. Influence of renal function on the effects of early revascularization in non-ST-

elevation myocardial infarction: data from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). *Circulation* 2009;**120**(10):851–8.
72. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**(13):1296–305.
73. System USRD. *Am J Kidney Dis* 1998;**32**:S1–162.
74. Brennan JM, Edwards FH, Zhao Y, O'Brien SM, Douglas PS, Peterson ED. Long-term survival after aortic valve replacement among high-risk elderly patients in the United States: insights from the Society of Thoracic Surgeons Adult Cardiac Surgery Database, 1991 to 2007. *Circulation* 2012;**126**(13):1621–9.
75. Nguyen TC, Babaliaros VC, Razavi SA, et al. Impact of varying degrees of renal dysfunction on transcatheter and surgical aortic valve replacement. *J Thorac Cardiovasc Surg* 2013;**146**(6):1399–406. discussion 13406-13407.
76. Gupta T, Goel K, Kolte D, et al. Association of chronic kidney disease with in-hospital outcomes of transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2017;**10**(20):2050–60.
77. Ifedili IA, Bolorunduro O, Bob-Manuel T, et al. Impact of pre-existing kidney dysfunction on outcomes following transcatheter aortic valve replacement. *Curr Cardiol Rev* 2017;**13**(4):283–92.
78. Makki N, Lilly SM. Advanced chronic kidney disease: relationship to outcomes post-TAVR, a meta-analysis. *Clin Cardiol* 2018;**41**(8):1091–6. https://doi.org/10.1002/clc.22993. Epub 2018 July 18. Review. PubMed PMID:29896847.
79. Schueler R, Nickenig G, May AE, et al. Predictors for short-term outcomes of patients undergoing transcatheter mitral valve interventions: analysis of 778 prospective patients from the German TRAMI registry focusing on baseline renal function. *EuroIntervention* 2016;**12**(4):508–14.
80. Providencia R, Marijon E, Boveda S, et al. Meta-analysis of the influence of chronic kidney disease on the risk of thromboembolism among patients with nonvalvular atrial fibrillation. *Am J Cardiol* 2014;**114**(4):646–53.
81. Bansal N, Fan D, Hsu CY, Ordonez JD, Go AS. Incident atrial fibrillation and risk of death in adults with chronic kidney disease. *J Am Heart Assoc* 2014;**3**(5):e001303.
82. Bansal N, Fan D, Hsu CY, Ordonez JD, Marcus GM, Go AS. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. *Circulation* 2013;**127**(5):569–74.
83. Bonde AN, Lip GY, Kamper AL, et al. Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study. *J Am Coll Cardiol* 2014;**64**(23):2471–82.
84. Wanner C, Herzog CA, Turakhia MP. Conference Steering Committee. Chronic kidney disease and arrhythmias: highlights from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2018;**94**(2):231–4. https://doi.org/10.1016/j.kint.2018.05.005. Epub 2018 June 21. PubMed PMID:29935952.
85. Qamar A, Bhatt DL. Anticoagulation therapy: balancing the risks of stroke and bleeding in CKD. *Nat Rev Nephrol* 2015;**11**(4):200–2.
86. Tan J, Liu S, Segal JB, Alexander GC, McAdams-DeMarco M. Warfarin use and stroke, bleeding and mortality risk in patients with end stage renal disease and atrial fibrillation: a systematic review and meta-analysis. *BMC Nephrol* 2016;**17**(1):157.
87. Carrero JJ, Evans M, Szummer K, et al. Warfarin, kidney dysfunction, and outcomes following acute myocardial infarction in patients with atrial fibrillation. *J Am Med Assoc* 2014;**311**(9):919–28.
88. Wheeler DS, Giugliano RP, Rangaswami J. Anticoagulation-related nephropathy. *J Thromb Haemost* 2016;**14**(3):461–7.
89. Khouri Y, Stephens T, Ayuba G, AlAmeri H, Juratli N, McCullough PA. Understanding and managing atrial fibrillation in patients with kidney disease. *J Atr Fibrillation* 2015;**7**(6):1069.
90. Pun PH, Smarz TR, Honeycutt EF, Shaw LK, Al-Khatib SM, Middleton JP. Chronic kidney disease is associated with increased risk of sudden cardiac death among patients with coronary artery disease. *Kidney Int* 2009;**76**(6):652–8.
91. Pun PH, Middleton JP. Sudden cardiac death in hemodialysis patients: a comprehensive care approach to reduce risk. *Blood Purif* 2012;**33**(1–3):183–9.
92. Russo AM, Stainback RF, Bailey SR, et al. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation appropriate use criteria task force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *Heart Rhythm* 2013;**10**(4):e11–58.
93. Pun PH, Al-Khatib SM, Han JY, et al. Implantable cardioverter-defibrillators for primary prevention of sudden cardiac death in CKD: a meta-analysis of patient-level data from 3 randomized trials. *Am J Kidney Dis* 2014;**64**(1):32–9.
94. Kober L, Thune JJ, Nielsen JC, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**(13):1221–30.
95. Koman E, Gupta A, Subzposh F, Saltzman H, Kutalek SP. Outcomes of subcutaneous implantable cardioverter-defibrillator implantation in patients on hemodialysis. *J Interv Card Electrophysiol* 2016;**45**(2):219–23.
96. El-Chami MF, Levy M, Kelli HM, et al. Outcome of subcutaneous implantable cardioverter defibrillator implantation in patients with end-stage renal disease on dialysis. *J Cardiovasc Electrophysiol* 2015;**26**(8):900–4.
97. Bazoukis G, Letsas KP, Korantzopoulos P, et al. Impact of baseline renal function on all-cause mortality in patients who underwent cardiac resynchronization therapy: a systematic review and meta-analysis. *J Arrhythm* 2017;**33**(5):417–23.
98. Boerrigter G, Costello-Boerrigter LC, Abraham WT, et al. Cardiac resynchronization therapy improves renal function in human heart failure with reduced glomerular filtration rate. *J Card Fail* 2008;**14**(7):539–46.
99. Keuffel E, McCullough PA, Todoran TM, et al. The effect of major adverse renal cardiovascular event (MARCE) incidence, procedure volume, and unit cost on the hospital savings resulting from contrast media use in inpatient angioplasty. *J Med Econ* 2017:1–9.
100. Ronco C, Ronco F, McCullough PA. A call to action to develop integrated curricula in cardiorenal medicine. *Blood Purif* 2017;**44**(4):251–9.

QUESTIONS AND ANSWERS

Question 1

The spectrum of structural, neuro-hormonal, and biochemical cardiovascular changes seen in patients with chronic kidney disease represent the following phenotype of cardio-renal syndrome as described by the Acute Dialysis Quality Initiative:

A. Type 1 cardio-renal syndrome
B. Type 2 cardio-renal syndrome
C. Type 3 cardio-renal syndrome
D. Type 4 cardio-renal syndrome
E. Type 5 cardio-renal syndrome

Answer: D

Type 4 cardio-renal syndrome reflects the chronic structural changes seen in cardio-vascular disease in the backdrop of chronic kidney disease. This phenotype is also represented by the changes seen in neuro-hormonal modulators of the sympathetic nervous system, renin angiotensin aldosterone system, inflammatory markers, disorders of bone and mineral metabolism, iron deficiency, and anemia.

Question 2

The following classes of pharmacotherapies show evidence from high-quality randomized controlled trials in heart failure with/without kidney disease **except**:

A. Beta adrenergic receptor blockers
B. Angiotensin converting enzyme inhibitors/ angiotensin receptor blockers
C. Mineralocorticoid receptor antagonists
D. Diuretics
E. Ivabradine

Answer: D

Of all the above classes of pharmacotherapies that are part of goal directed medical therapy in heart failure with/without kidney disease, diuretics are the one class of drugs that are used for decongestion and heart failure–related symptom relief in the absence of a randomized controlled trial testing the benefits of this form of therapy toward hard clinical endpoints. Despite this, diuretics remain a cornerstone for therapy in heart failure, and novel approaches to management of diuretic efficiency and diuretic resistance are being tested in ongoing trials.

Question 3

The following are causes of diuretic resistance in heart failure **except**:

A. Distal tubular remodeling from chronic diuretic exposure
B. Activation of the sympathetic nervous system and renin angiotensin aldosterone axis
C. Chronic kidney disease
D. Impaired drug absorption
E. Diuretic "braking"

Answer: C

Of all the potential causes for diuretic resistance in a patient with heart failure, chronic kidney disease *per se* is not a cause, with the exception of very advanced predialytic kidney disease. The other causes listed factor into the phenomenon of diuretic resistance, and are potentially correctable based on the underlying etiology such as switching to intravenous loop diuretics (and more recently, subcutaneous loop diuretic administration), use of longer acting loop diuretics such as torsemide for more predictable therapeutic concentrations, combining loop diuretics with a distal diuretic such as the thiazide class of drugs, and more frequent dosing in subjects with kidney disease. Diuretic resistance in addition to impairing efforts at decongestion in acute heart failure is also independently associated with worse outcomes, including all cause mortality.

Question 4

The following would be considered true in patients with ACS with underlying chronic kidney disease:

A. Patients present with higher rates of chest pain and typical symptoms as they have higher cardiovascular disease burden because of their chronic kidney disease
B. Patients with chronic kidney disease receive delayed goal directed therapy for ACSs given their concomitant chronic kidney disease
C. The presence of advanced chronic kidney disease precludes prompt revascularization in ACS as the renal risks outweigh the benefits
D. A baseline elevation in cardiac troponins is diagnostic of ACS in chronic kidney disease
E. Major cardiovascular trials routinely include patients with advanced chronic kidney disease given the high-risk population they represent.

Answer: B

Despite the well-known elevated risk for cardiovascular disease in chronic kidney disease including ischemic heart disease, patients presenting with ACSs in this population are underdiagnosed and undertreated. Part of this may be related to the atypical symptoms of ischemia seen in patients with chronic kidney disease, concerns of "harm" by using standard goal directed therapies for ACSs in this population, and the lack of high-quality data specific to patients with chronic kidney disease on optimal medical and

revascularization therapies and their delivery in patients with kidney disease. Patients with chronic kidney disease benefit from prompt and appropriate revascularization and medical therapies for ACSs, and the presence of kidney disease should not preclude evidence-based best medical practice therapies.

Question 5

The sodium glucose cotransporter 2 inhibitors (SGLT2i) have been shown to have significant risk reduction for cardiovascular and renal endpoints in major cardiovascular outcomes trials. Which of the following statements about this class of drugs is **false**?

A. The separation of Kaplan Meier outcome curves between treatment and placebo groups in cardiovascular outcomes trials in diabetics occurred early (around 3 months) into the trials
B. These drugs are effective in advanced chronic kidney disease
C. No differences were noted in cardiovascular trials of SGLT2i for acute kidney injury rates between drug and placebo arms
D. BP control was noted to be better in patients on SGLT2i in randomized controlled trials
E. SGLT2i activates tubulo-glomerular feedback due to higher sodium delivery to the macula densa and thus reduces intraglomerular pressures.

Answer: B

The SGLT2i represent a major class of novel antidiabetic therapies that have shown major cardiovascular and renal risk reduction in CVOTs. Targeted effects from blocking SGLT2 cotransporter of the proximal tubule include natriuresis, activation of tubule-glomerular feedback, and reduction of hyperfiltration injury. Two major CVOTs: EMPAREG OUTCOME and the CANVAS programs demonstrated significant cardiovascular risk reduction with empagliflozin and canagliflozin, respectively. In addition, *post hoc* analyses of EMPAREG OUTCOME showed reduction in the prespecified renal composite secondary outcome, and the CANVAS program showed possible benefits with reduction in albuminuria and the trial's prespecified renal endpoint. Although these benefits have also been demonstrated in mild to moderate CKD, this class of drugs is less effective with advanced CKD based on its mechanism of action. The early separation of Kaplan Meier outcome curves in these trials alludes toward nonatherosclerotic mechanisms of cardiovascular benefits, including reduction in heart failure hospitalization and cardiovascular deaths. Ongoing CVOTs involving several drugs in this class will help delineate the cardiovascular and renal benefits of these drugs in a more precise fashion.

Question 6

The following is **true** about patients with cardiovascular and kidney disease:

A. These patients represent an undertreated and vulnerable group when compared to the general population
B. Cardio-renal care is usually a seamless transition across health care settings and health care providers
C. Palliation has a limited role in patients with cardio-renal disease
D. High-quality data from randomized trials are used to devise best clinical practices in patients with cardiovascular and kidney disease
E. Awareness of the dual burden of cardiovascular and kidney disease is high in the lay population

Answer: A

Patients with the dual burden of cardiovascular and kidney disease represent an underserved and vulnerable population. Outcomes related to cardiovascular disease phenotypes such as heart failure and ischemia tend to be worse with chronic kidney disease, and complications from medical and interventional therapies tend to be higher. The lack of high-quality evidence and the perception of potential "harm" in this population results in some degree of therapeutic nihilism when approaching cardiovascular disease in patients with kidney disease. Despite the complexity and overall poor quality of life in patients with advanced cardiovascular and kidney disease, palliative care is an under-utilized resource in this field. Awareness of the role of kidney disease as a cardiovascular equivalent and the dual disease burden of cardiovascular and kidney disease is overall low in the lay population. Future studies and trials in the cardio-renal sphere will help define best practices, goals, and educational pathways in this field.

CHAPTER

24

Inflammation in Chronic Kidney Disease

Dominic S. Raj[a], *Roberto Pecoits-Filho*[b], *Paul L. Kimmel*[a]

[a]Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States; [b]School of Medicine, Pontificia Universidade Catolica do Parana, Curitiba, Brazil

Abstract

Systemic low-grade inflammation is common in patients with chronic kidney disease (CKD). The prevalence of signs of inflammation are inversely related to the level of kidney function and positively associated with the magnitude of proteinuria. Cytokines and acute-phase proteins are key mediators as well as markers of inflammation. The etiology of inflammation in CKD is multifactorial. Comorbidities such as older age, minority race, and the presence of diabetes are independent predictors of inflammation in CKD patients. Endotoxin translocation across the gut and damage/danger-associated molecular patterns may contribute to excess inflammation in CKD. Dysregulated immune responses and the resultant inflammation are mediators and/or catalysts in the progression of renal disease, pathogenesis of cardiovascular disease, and the development of insulin resistance, protein energy wasting, anemia, and abnormal bone-mineral metabolism in patients with CKD. Progress in treatment of inflammation in patients with CKD is hampered by the complexity of the molecular pathways related to inflammation and the essential nature of some of these signaling mechanisms for cell/organism survival. However, a number of novel treatment strategies to attenuate inflammation in CKD are currently being explored.

INTRODUCTION

The word inflammation derives from the Latin term "inflammare," meaning to set on fire. Inflammation is part of the complex biological response of vascular tissue to injury, infection, ischemia, and autoimmune diseases.[1] Within physiological limits, the inflammatory response enables removal of the inciting agent and initiates healing. Inability to eliminate the insulting event and/or separate the inflammatory processes leads to a chronic inflammatory state with undesirable systemic consequences.[2] Persistent, low-grade systemic inflammation is common in chronic kidney disease (CKD) and is closely linked to adverse outcomes.[3,4]

SCOPE OF THE PROBLEM

Prevalence of Inflammation in CKD

The other face of immunity is inflammation, especially when the immune response is unregulated and misdirected. Kimmel et al. reported that adequate T-cell function is associated with improved survival in patients with end-stage renal disease (ESRD) and elevated levels of proinflammatory cytokines are associated with higher mortality.[4] Another study showed that there were no major differences in circulating cytokine levels between long-term dialysis patients and those not yet dialyzed, suggesting uremia *per se* contributes to the inflammatory state.[5] The Chronic Renal Insufficiency Cohort (CRIC) study showed that 86% of participants with CKD have some evidence of inflammation, as defined by increased circulating levels of inflammatory biomarkers.[3] However, only about 12% of the study population exhibited profound elevation in markers of inflammation, a finding not different from that reported by Kimmel et al. in ESRD patients[6] (Figure 24.1). Gupta et al. demonstrated that plasma levels of proinflammatory cytokines and positive acute-phase proteins were higher in subjects with lower levels of kidney function.[3] Furthermore, within each level of estimated glomerular filtration rate (eGFR), the magnitude of proteinuria was associated with a higher level of inflammatory biomarkers[3] (Figure 24.2).

Determinants of Inflammation

A number of demographic features such as older age, male gender, obesity, and low socioeconomic status

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00024-3

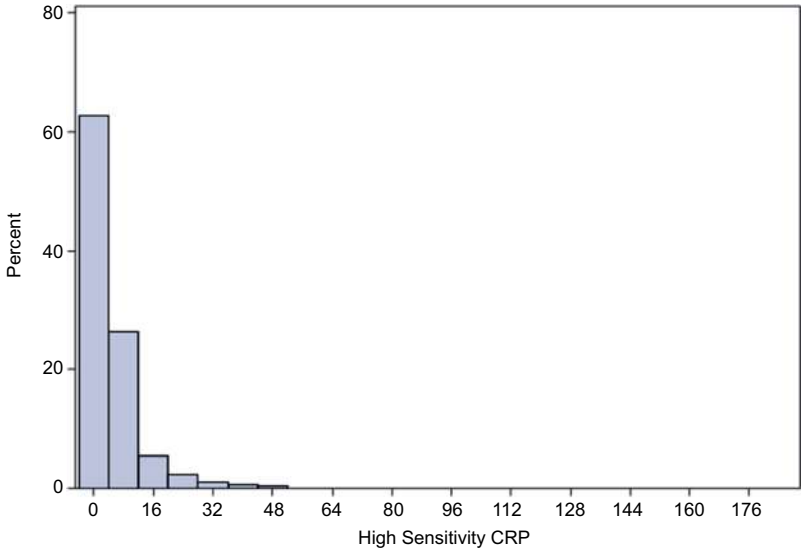


FIGURE 24.1 Distribution of high sensitivity C-reactive protein (CRP) levels in patients with chronic kidney disease. The concentration of CRP is within normal range in a significant proportion of subjects with chronic kidney disease. *Data from the Chronic Renal Insufficiency Cohort (CRIC) study.*

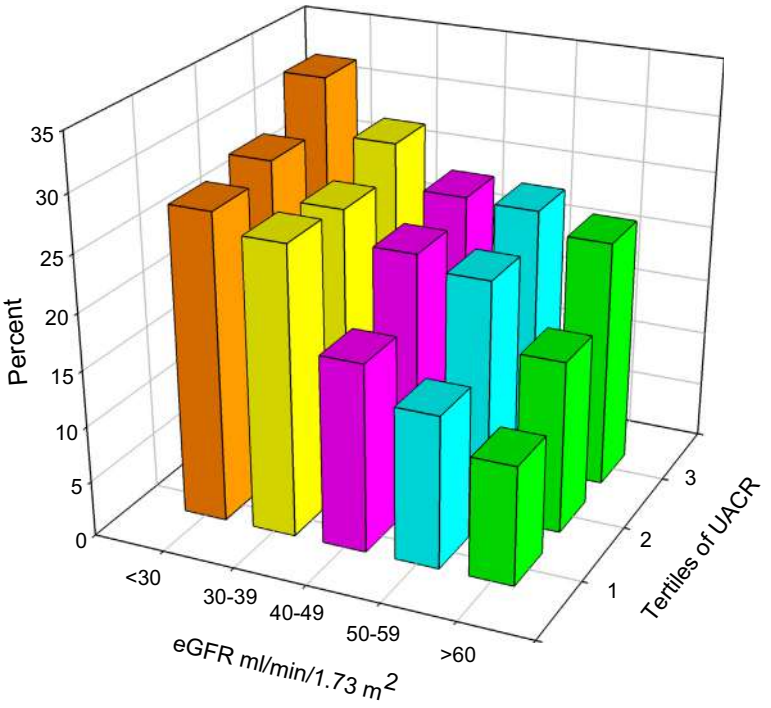


FIGURE 24.2 The percentage of subjects with evidence of inflammation increased across the quartiles of estimated glomerular filtration rate (eGFR) and tertiles of proteinuria (UACR).[3] *Data from the Chronic Renal Insufficiency Cohort (CRIC) study.*

were associated with higher level of inflammation in patients without CKD.[7] Chronic subclinical inflammation in the elderly population is attributed to an imbalance between inflammatory and antiinflammatory networks.[8] Patients with type 2 diabetes mellitus have elevation in Th17 and Th1 cellular subsets and a reduction in the Treg subset, explaining the inflammation noted in this patient population.[9] Furthermore, inflammation predicts incident diabetes as well as diabetes-related complications.[10] The CRIC study demonstrated increasing age, minority race, and presence of diabetes are associated with increased level of inflammation at each level of eGFR[3] (Figure 24.3).

Genetics of Inflammation

Stimulation of human blood samples with bacterial lipopolysaccharide (LPS) results in large interindividual variations in production of cytokines, suggesting a genetic component related to the inflammatory response. Thus, differences in inflammatory responses between populations may be due to variations in genes

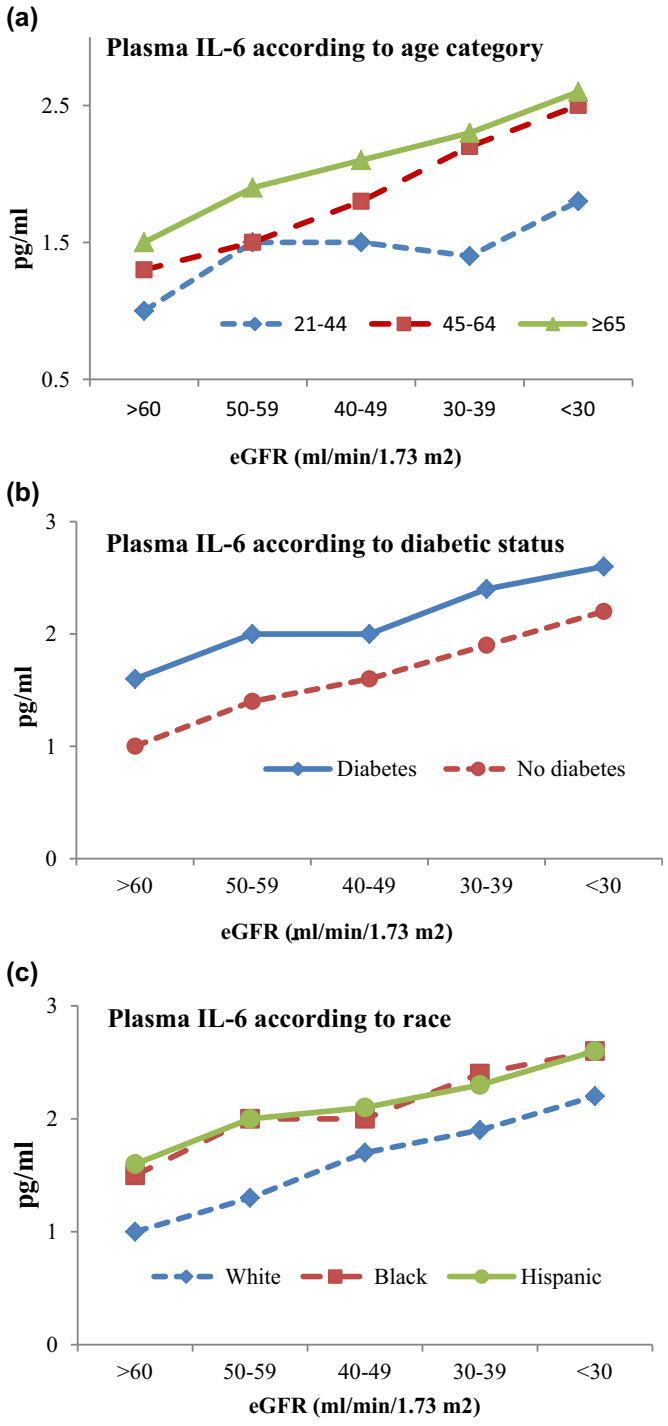


FIGURE 24.3 Association of inflammation with age, diabetes, and race in CKD. *Data from the Chronic Renal Insufficiency Cohort (CRIC) study.*

regulating inflammatory pathways. Using a relaxed linear separability model, Luttropp et al. showed the presence of inflammation in CKD patients, defined by circulating high sensitivity C-reactive protein (hsCRP), is linked to genetic variations.[11] Ness et al.[12] reported African Americans have an increased frequency of alleles related to increased production of proinflammatory cytokines, but this finding has not been confirmed by others.[13] Environmental factors and behavioral patterns may modify the inflammatory response.

Epigenetics refers to a heritable change in the pattern of gene expression mediated by mechanisms specifically not due to alterations in primary nucleotide sequences.[14] The epigenome is the interface of genetics and environment, where the plasticity of the epigenetic code modifies the rigid genetic code to determine final phenotypes. Epigenetic regulation of cytokines and transcription factors is important in directing lineage differentiation of Th1 and Th2, as well as Tregs, which play a role in determining the immune response.[15] Epigenetic effects seem to allow dividing immune cells to imprint, signaling events that allow immune cells to mount appropriate immune responses.

PATHOPHYSIOLOGY OF INFLAMMATION IN CKD

Mediators of Inflammation

The inflammatory state is generally characterized by activation of an array of soluble factors such as cytokines and chemokines.[2] Cytokines are secreted polypeptides that orchestrate the inflammatory response through autocrine, paracrine, and endocrine mechanisms. Chemokines are chemotactic cytokines, which control the attraction of leukocytes and mononuclear cells to sites of injury. These biomolecules may be broadly classified as pro- and antiinflammatory and also as ones involved in acute and chronic phases of inflammation. However, cytokines are pleiotropic in their actions, with considerable redundancy between their functions. Cytokines exhibit interactive cascades, in which they induce or repress their own synthesis, as well as that of other cytokines and cytokine receptors[2] (Figure 24.4). Circulating cytokine receptors may provide additional information regarding the state of inflammation because they generally have a longer half-life than the cytokines themselves and therefore exhibit more constant levels over time. The interleukin (IL)-1Ra binds to IL-1 receptors and blocks the activity of IL-1 and a soluble form of the p55 tumor necrosis factor (TNF) receptor (TNFsRp55) binds and neutralizes TNF.[2] Pereira et al. showed that plasma levels of IL-1Ra and TNF inhibitor TNFsRp55 are significantly higher in patients with CKD.[5] They also noted that hemodialysis patients with higher endotoxin-stimulated IL-1Ra synthesis had a higher rate of cardiovascular (CV) events.[16] Representative cytokines and their clinical significance are described in Table 24.1.

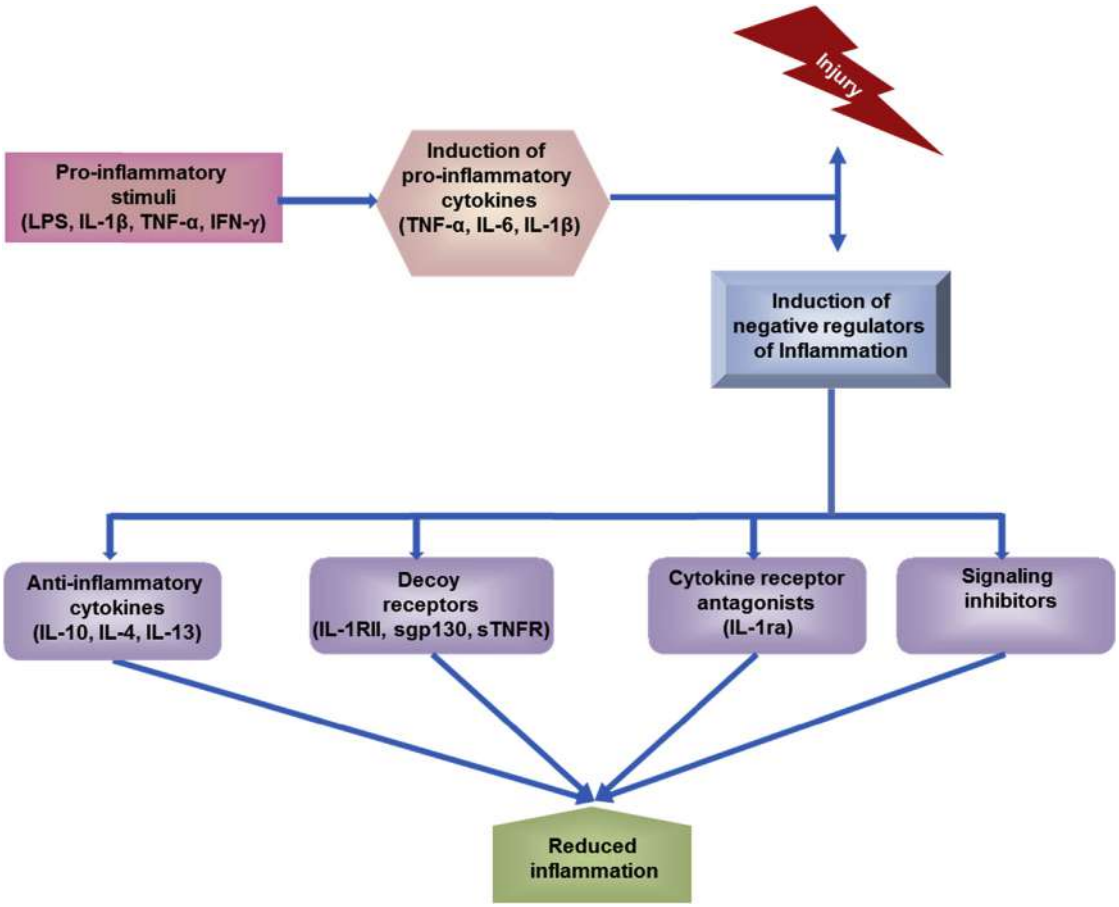


FIGURE 24.4 Cytokines are important modulators of immunoregulation, hematopoiesis, and the inflammatory cascade. These biomolecules act as a highly complex and coordinated network. There is considerable overlap and redundancy between the functions of individual cytokines. Cytokines induce or repress their own synthesis and that of other cytokines. The function of one cytokine is often modified or substituted by another's. The balance between pro- and antiinflammatory cytokines determines whether the intensity of inflammatory response is within physiological limits or in the pathologic range.

An important component of the inflammatory cascade is the acute-phase response, which is a nonspecific physiological response to diverse forms of systemic and local insults. Under the influence of cytokines, originating from the site of injury, the synthesis of positive acute-phase proteins is upregulated, and negative acute-phase proteins are downregulated, principally in hepatocytes.[17] Acute-phase proteins include complement components, antiproteases, and transport proteins, as well as proteins involved in coagulation and fibrinolytic systems. Many of the acute-phase proteins (such as CRP and ferritin) augment the inflammatory response, whereas others have an attenuating effect (e.g. albumin and hepcidin). The causes and mechanisms of downregulation of negative acute-phase protein synthesis are unknown, but this may be because resources need to be redirected toward synthesis of positive acute proteins that are required for survival in times of stress.

Etiology of Inflammation

The mechanisms underlying unprovoked inflammation in CKD are under intense investigation. Elevated plasma cytokine levels in CKD patients could be a consequence of decreased elimination and/or increased generation. Although most of the circulating cytokines are secreted from activated macrophages and lymphocytes, adipocytes and skeletal muscle are also possible sources.[18,19] It has been estimated that skeletal muscle contributes to about 12% and adipose tissue to about 10–35% of the circulating IL-6 level in patients with and without kidney disease.[20,21] Arteriovenous balance studies have shown that there is increased efflux of proinflammatory cytokines from the skeletal muscle of ESRD patients.[19,22] Preliminary findings from the CRIC study show that body fat mass as well as muscle mass are associated with circulating levels of several cytokines.[23] Myeloperoxidase (MPO) is secreted during

TABLE 24.1 Mediators and Markers of Inflammation in Chronic Kidney Disease (CKD)

Biomarker	Study Population	Remark
C-reactive protein (CRP)	CRP is a member of the pentraxin family of innate immune response proteins synthesized by the liver.	Extensively studied in patients with and without kidney disease. Associated with all cause and cardiovascular mortality, atherosclerosis, protein energy wasting, and erythropoietin resistance.
Fibrinogen	Soluble glycoprotein found in the plasma, synthesized by the liver.	Plays a vital role inflammation, atherogenesis, and thrombogenesis. Predictor of mortality in CKD.[154]
Serum amyloid A protein	Acute-phase protein synthesized by the liver.	Serves as an autocrine factor to influence vascular smooth muscle cells and platelet aggregation.[155]
IL-6	IL-6 acts *via* a receptor complex consisting of the cognate IL-6 receptor (IL-6R) and glycoprotein 130 (gp130 or IL6-ST). Signal activation necessitates association of IL-6 with gp130. The antiinflammatory activities of IL-6 are mediated by gp130, whereas its proinflammatory responses are mediated by trans-signaling through the soluble IL-6 receptor.[156,157]	Elevated IL-6 levels have been linked to malnutrition,[158] atherosclerosis,[159] and CV and all-cause mortality in patients with kidney disease.[4,160]
IL-1 family	The IL-1 family consists of two proinflammatory cytokines, IL-1α and IL-1β, and a naturally occurring antiinflammatory agent, the IL-1Ra.	Plasma IL-1 and IL-1Ra have been shown to predict cardiovascular outcomes and mortality in end-stage renal disease (ESRD) patients.[4,16,96,161]
IL-10	The principal function of IL-10 is to limit and ultimately terminate inflammatory signals.	The IL-10 low producer genotype (-1082 AA) is associated with increased CV mortality in ESRD patients,[162] and lower Karnofsky Index and nutritional indices.[163]
TNF-α	Produced primarily by macrophages and acts through two distinct cell surface receptors of 55 kDa (TNF-R1) and 75 kDa (TNF-R2). Activates NFkB and MAP kinase pathways and induces apoptosis.	Increased TNF-α levels are associated with metabolic syndrome, CVD, congestive heart failure, progression of CKD, and mortality.[4,164–166]
Soluble TNF-like weak inducer of apoptosis (sTWEAK)	Member of the TNF superfamily.	Elevated sTWEAK and IL-6 plasma concentrations are associated with mortality in HD patients.[167]
TGF-β	TGF-β has antiatherogenic, antiinflammatory, and profibrotic properties.[168,169]	Overproduction of TGF-β has been linked to hypertension, left ventricular hypertrophy, vascular remodeling, and renal fibrosis.
High mobility group box chromosomal protein-1(HMGB1)	HMGB1 is a nuclear protein that binds DNA, stabilizes nucleosomes, and facilitates gene transcription. It is a late-phase cytokine, which contributes to chronic inflammation.	HMGB1 levels correlate with GFR and markers of inflammation and malnutrition.[170]
Myeloperoxidase (MPO)	MPO is an enzyme stored in azurophilic granules of polymorphonuclear neutrophils and macrophages and released into extracellular fluid in the setting of inflammatory process.	Plasma MPO levels are elevated in patients with coronary artery disease, congestive heart failure, and are important predictors of cardiovascular events in the general population.[24,171,172] Associated with risk of death in ESRD patients.[25]
Endotoxin and soluble CD14	Endotoxin is a biologically active substance produced by bacteria, which consists of lipopolysaccharide. Endotoxin provokes an array of host responses by binding to the CD14 receptor.[173]	Abundant experimental and clinical evidence indicates that subclinical endotoxemia is involved in the pathogenesis of atherosclerosis.[174,175] Elevated soluble (s)CD14 level is associated with protein energy wasting and death in ESRD patients.[34,127]

activation of neutrophils, which plays an important role in the defense of the organism. Enhanced MPO generation is one of the major oxidative stress pathways in CKD, and a risk factor for vascular disease.[24,25]

Other potential causes of inflammation in CKD include chronic subclinical infections,[26] volume overload,[27] increased oxidative stress,[28] sympathetic overactivity,[29] poor nutrition, and vitamin D deficiency.[30] The gut microbial flora is quantitatively and qualitatively abnormal in patients with kidney disease compared with healthy subjects.[31–33] Endotoxin translocation across the gut could be one of the important causes of inflammation in CKD patients.[34] Uremic toxins cause dysfunction of both granulocytic and monocytic cell lines and should also be considered a major cause of inflammation. Among circulating monocytes, subpopulations with proinflammatory characteristics are expanded in patients with CKD. Several uremic toxins act as ligands in activation of Toll-like receptors, which are involved in the innate immune response and recognition of LPS.[35]

DAMPs and PAMPs

Accelerated cellular aging and augmented apoptosis are common in CKD. Damaged or dying cells release endogenous molecules called damage/danger-associated molecular patterns (DAMPs).[36] These molecules activate the immune system in a manner similar to pathogen-associated molecular patterns (PAMPs) molecules released by pathogenic bacteria or viruses (Figure 24.5). Many DAMPs released during renal injury are capable of activating inflammasomes, which are components of the innate immune system.[37] The inflammasome is a complex of proteins in the cytoplasm that is triggered by infectious or sterile injuries.[38] Proinflammatory mediators interact with innate danger-signaling platforms. NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) play a critical role in the pathophysiology of kidney diseases.[39] Thus, release of endogenous molecules from dying cells may lead to activation of innate immunity and downstream inflammation.

Resolution of Inflammation

Chronic, dysregulated inflammation is associated with several human diseases. The inflammatory response is counterbalanced by the release of "stop signals," which serve to attenuate an excess inflammatory response and to restore functional homeostasis.[40] During this highly regulated active process, synthesis of proinflammatory mediators is halted, preventing further leukocyte influx into tissue. Immune cells are cleared from tissue either by reentry into the systemic circulation or by apoptosis or necrosis. Recent evidence suggests that this process also promotes interaction between the innate and adaptive immune systems leading to immune tolerance.[41] The resolution of inflammation is governed by several factors which include chemical mediators (lipoxins, resolvins, protectins, and maresins), gases (hydrogen sulfide, nitric oxide, and low-dose carbon monoxide), and proteins (annexin A1 and galectin-1).[40,42,43] Kourtzelis et al. identified a new member of the group of proteins, developmental endothelial locus-1 (DEL-1), which governs the resolution response.[44] Endothelial cell–derived DEL-1 reduces neutrophil infiltration into tissues. Macrophage-derived DEL-1 facilitates efferocytosis through an α vβ 3-mediated response and

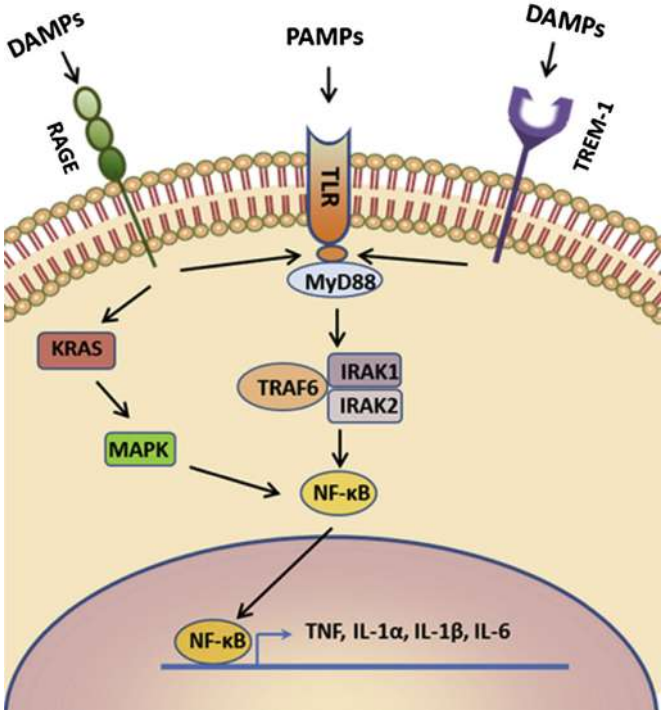


FIGURE 24.5 Mediation of pathogen-specific immune response by pathogen-associated molecular patterns (*PAMPs*) and pattern recognition receptors (*PRRs*). *PRRs* are essential for initiating immune defenses against invading pathogens. However, they also contribute to persistent and systemic inflammation. Heat shock proteins, fibrinogen, fibronectin, hyaluran, and high mobility group box-1 (*HMGB-1*) have been defined as danger-associated molecular patterns (*DAMPs*). Toll-like receptors (*TLRs*) are involved in the recognition of these endogenous or harmful self-antigens, which are released during noninfectious injury, suggesting their function may not be restricted to the recognition of extrinsic pathogens. RAGE, receptor for advanced glycation end products; TREM-1, triggering receptor expressed on myeloid cells-1; MyD88, myeloid differentiation factor 88; KRAS, Kirsten rat sarcoma viral oncogene homolog; MAPK, mitogen-activated protein kinase; TRAF6, tumor necrosis factor receptor-associated factor 6; IRAK1/IRAK2, IL-1 receptor-associated kinase 1 and 4; NFκB, nuclear factor-κB.

activates lipid X receptors and transforming growth factor (TGF)-β to promote a tissue reparative macrophage phenotype transformation.[44] Understanding the cellular pathways by which inflammation is resolved can open new opportunities to pharmacologically enhance the processes. Several promising proresolution therapeutic strategies have been tested in animal models with the potential for translation to human applications in the future.[41]

DIAGNOSIS OF INFLAMMATION

Utility of Inflammatory Biomarkers

Although the importance of inflammation in CKD is undisputed, there is no consensus regarding the index biomolecules to be used to identify inflamed subjects with CKD or regarding the appropriate threshold levels of inflammatory markers. Investigators have proposed different biomarkers and different circulating levels, largely based on mean values noted in CKD patients and/or correlations with clinical outcomes. Although the concentrations of proinflammatory cytokines, antiinflammatory cytokines, and acute-phase proteins show a tendency to increase together, there is discordance in the rate and magnitude of the increase of individual molecules involved in the inflammation cascade.[1] Thus, it may be important to integrate information from multiple biomarkers to describe the prevailing inflammatory state. Raj and associates computed a composite score ranging from 0 to 5 based on elevated levels of selected cytokines and acute-phase proteins (CRP, fibrinogen, IL-6, TNF-α, and IL-1β). They showed the score was inversely related to eGFR and positively related to albuminuria in a large cohort of CKD patients with a wide range of kidney function.[3] Zoccali showed an inflammation score composed of CRP, IL-6, IL-1β, IL-18, and TNF-α predicts death no better than IL-6 in patients with ESRD.[45] Thus, the utility of composite inflammation scores needs further validation.

There is substantial intraindividual variation in circulating cytokines levels over time, rendering the validity of a single measurement of cytokines in predicting clinical outcomes tenuous. Preliminary findings suggest that a single baseline measure accurately reflects healthy individuals' inflammatory status over a four- to six-month period.[46] Another study showed that despite variability over time, baseline CRP level correlated with time-averaged CRP and the individual median of serial CRP values in ESRD patients.[47] Thus, single baseline measurements are adequate, but multiple measurements may be better for predicting outcome or response to interventions.

Is CRP an Ideal Biomarker of Inflammation in CKD?

CRP belongs to the pentraxin family of calcium-dependent ligand-binding plasma proteins. It derives its name from its ability to precipitate the C-polysaccharide of *Streptococcus pneumonia.* Circulating CRP is produced primarily by hepatocytes under transcriptional control by IL-6.[48] In response to an inciting stimulus, CRP synthesis is rapidly initiated, with the serum concentration peak occurring in about 48 hours. The median concentration of CRP is 0.8 mg/L in healthy subjects, the 90th percentile is 3.0 mg/L, and the 99th percentile is 10 mg/L.[49] CRP binds to phosphocholine residues and also to a variety of autologous and extrinsic ligands and aggregates the molecules exhibiting these ligands, leading to activation of the complement cascade.[50] CRP is a highly stable analyte in serum or plasma, which can be measured with ease in a reproducible manner. CRP level is a nonspecific measure of inflammation that may be useful for screening and monitoring response to treatment. It has also emerged as an independent risk factor for adverse outcomes in diverse clinical settings. None of the other upstream mediators or downstream effectors of inflammation, including other acute-phase reactants, have such desirable characteristics, rendering CRP the most commonly used measure of inflammation.

Consequences of Inflammation

Even minor decreases in kidney function are associated with an increased risk for all-cause and CV death. Abundant evidence has accrued showing inflammation is a mediator of adverse outcomes in patients with CKD.[51–53] Inflammation could be a by-product of the original insult and thus an innocent bystander rather than a prime mover. Others claim that inflammation is a partner in crime. CKD complications linked to inflammation are depicted in Figure 24.6.

Progression of CKD

Regardless of initial causes, progressive CKD often results in glomerulosclerosis and/or tubulointerstitial fibrosis, characterized by widespread tissue scarring leading to ESRD. A variety of cytokines, chemokines, and growth factors act in concert to create an imbalance in matrix formation and degradation, leading to overall accumulation of extracellular matrix and eventually glomerulosclerosis and interstitial fibrosis.[54–59] Expression of IL-1, IL-6, IL-10, and IL-1 receptor antagonist and TGF-β have been reported in experimental and human renal diseases.[60–64] In the kidney, cytokines induce resident cells to proliferate,[65] promote aberrant

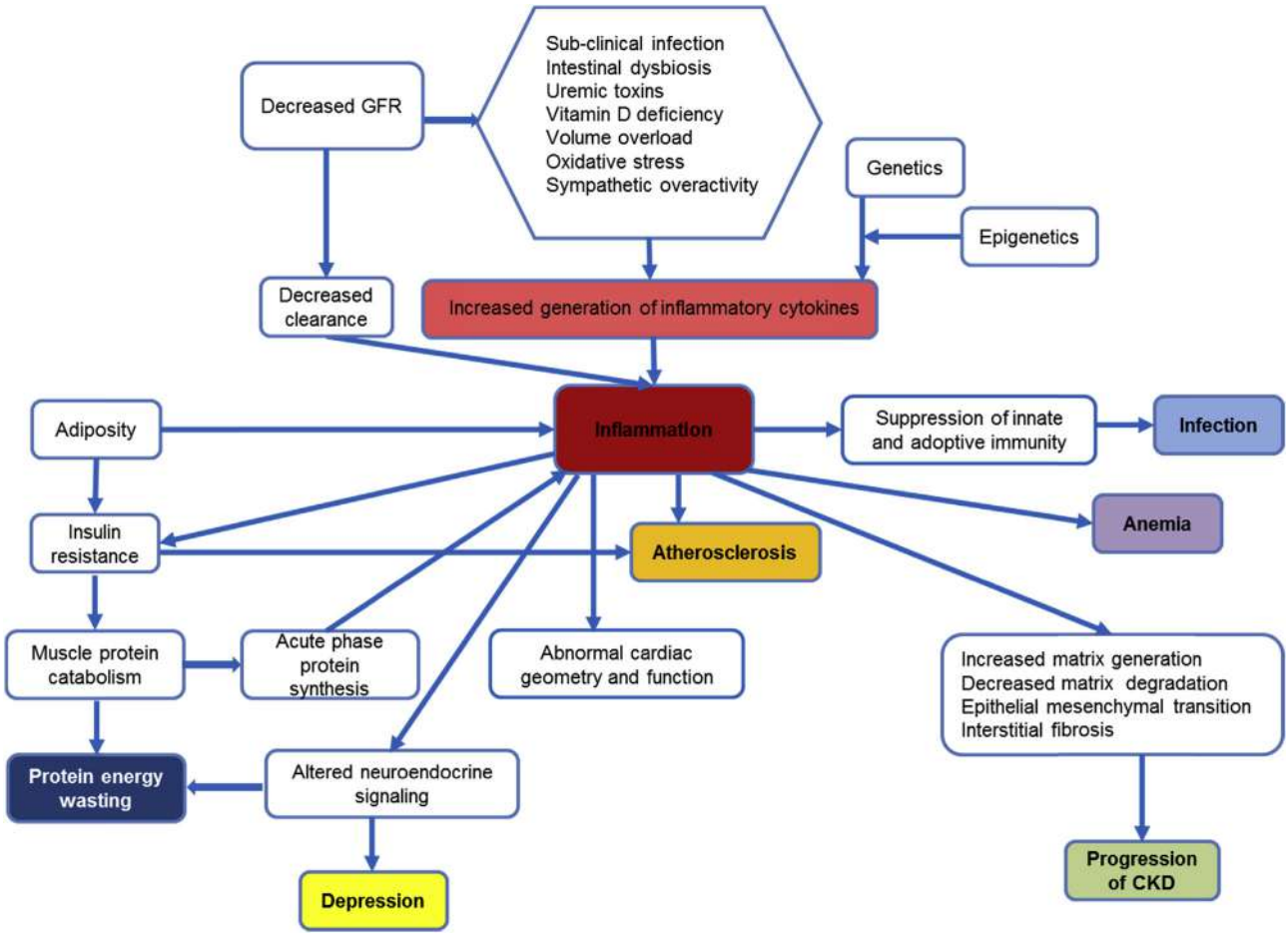


FIGURE 24.6 Inflammation in chronic kidney disease (CKD): causes and consequences. Inflammation is the result of multiple mechanisms inherent to CKD, including comorbidities such as adiposity, increased levels of inflammatory cytokines, and uremic toxicity. In turn, inflammation may increase the rate of CKD progression and cause infection, anemia, CVD, and depression.

matrix metabolism,[66,67] incite procoagulant endothelial activity,[68] generate reactive oxygen/nitrogen species,[69] and activate expression of adhesion receptors,[70] bioactive lipids,[71] and metalloproteinases.[72–75] Cytokine expression in the kidney release into the renal vein as well as excretion in the urine are increased in patients with glomerular disease.[76–79] Preliminary evidence indicates that urinary cytokine levels may be an indicator of severity and progression of renal disease.[77,78,80] Findings from the CRIC study show elevated plasma levels of fibrinogen and TNF-α and decreased serum albumin (S[Alb]) are associated with rapid loss of kidney function in patients with CKD after adjusting for traditional risk factors.[81] TNFR-1 is expressed on the cell surface of glomeruli and by the peritubular capillary endothelium of the kidney. In the Multi-Ethnic Study of Atherosclerosis study participants, elevated serum sTNFR-1 concentrations were associated with faster declines in eGFR, independent of traditional risk factors for kidney disease progression.[82] In a cross-sectional study in Japanese patients with T2D and eGFR $\geq$30 mL/min/1.73 m^2, circulating TNF-related inflammatory biomarkers (TNFα, progranulin, TNFR1, and TNFR2) were associated with albuminuria.[83]

During disease more than 30% of fibroblasts originate from tubular epithelia at the site of injury, through the process of epithelial mesenchymal transition, although such notions are controversial.[84,85] This molecular reprogramming of the cell is regulated, at least in part, by the profibrotic cytokine TGF-β. Renal arteriovenous balance studies indicate that TGF-β is released from the kidney of patients with diabetes.[78] In a population-based study of predominantly White subjects, TNF-receptor 2, WBC count, and IL-6 levels were associated with risk of developing CKD.[86] Similarly, in patients with type 2 diabetes mellitus, elevated concentrations of circulating TNF receptors at baseline are strong predictors of subsequent progression to ESRD.[58]

Hypertension and Inflammation

The roles of immune dysregulation and inflammation in the pathogenesis of hypertension have been investigated for decades. Virtually every cell type involved in innate and adaptive immunity has been implicated in the pathogenesis of hypertension. RAG1$^{-/-}$ mice, which lack both T and B cells, exhibit blunted hypertensive response to Ang II infusion, which is restored by adoptive transfer of T cells.[87] Interestingly, CD8+ T cells express the mineralocorticoid receptor, which plays a role in systemic hypertension.[88] Arterial wall inflammation is present in patients with CKD even in the absence of atherosclerosis.[89] Excess extracellular sodium activates antigen-presenting dendritic cells *via* immunogenic isolevuglandin-protein, which, in turn, promotes hypertension.[90] Proinflammatory cytokines are associated with arterial stiffness in CRIC study participants.[91] Thus, the prevalence and severity of hypertension in CKD could be related to inflammation.

Progression of Cardiovascular Disease

Atherosclerosis is described as an indolent, fibroproliferative disease fueled by chronic inflammation.[92] Immune cells dominate the atherosclerotic lesion and exhibit evidence of activation. The underlying mechanism for "accelerated atherosclerosis" in CKD may be related to chronic inflammation. Several cross-sectional studies suggest the Framingham risk equation is insufficient to capture the extent of CVD risk in CKD patients, highlighting the importance of novel risk factors such as inflammation in this population. Epidemiologic and clinical studies demonstrate strong and consistent relationships between markers of inflammation and risk for CV events in the general population and in patients with CKD.[93] Elevated CRP levels were associated with increased risk for all cause and CV mortality in Modification of Diet in Renal Disease study participants.[53] Abundant evidence from clinical studies and laboratory-based investigations suggest that abnormal cardiac geometry and function are related to inflammation in subjects with and without kidney disease.[51,94,95] Amdur et al. reported that inflammatory biomarkers and kidney function are independently associated with incident atherosclerotic vascular disease events and death in CKD patients.[96] They further showed that traditional CV risk estimates could be improved by adding measures of kidney function and markers of inflammation to traditional risk factors in evaluations.

Protein Energy Wasting

Protein energy wasting, or its extreme form, cachexia, is a maladaptive metabolic state common in inflammatory conditions, in which lean body mass is wasted, but the fat depot is relatively underutilized. Cytokines regulate neuroendocrine signaling and promote muscle wasting to sustain acute-phase protein synthesis in hemodialysis patients.[97] As a reflection of the trend in the US population, there is an epidemic of obesity among CKD patients.[98] Adiposity is associated with inflammation in the general population as well as in CKD patients. Results from the CRIC study show that fat mass and muscle mass are positively associated with hsCRP, fibrinogen, IL-1, IL-1RA, and IL-6 levels.[23] One standard deviation increases in fat and muscle mass were associated with 36% and 26% increases in log transformed hsCRP. The association between inflammation and fat mass was stronger in Caucasian than African-American patients with CKD, suggesting that abundant energy depot in conjunction with decreased burden of inflammation may explain the survival advantage observed in African Americans treated with maintenance hemodialysis.

Insulin Resistance

Epidemiologic studies show insulin resistance is a risk factor for CKD.[99] Chronic inflammation is a common feature of the metabolic syndrome and insulin resistance. Cytokines activate a number of intracellular serine/threonine kinases, including the inhibitor κB kinase (IKK) complex, a regulator of the NF-κB pathway, an important second messenger system in inflammatory cytokine signaling. The IKK complex and TNF-α activated JNK may be involved in the pathogenesis of insulin resistance.[100,101]

Anemia of CKD

Anemia is common in CKD patients. Epidemiologic studies show inflammation is an important predictor of hemoglobin variability and erythropoietin (EPO) hyporesponse in ESRD patients.[102,103] Goicoechea and associates demonstrated that EPO resistance is associated with elevated circulating levels of IL-6 and TNF-α.[104] Anemia in CKD may be related to true or functional deficiency of iron and EPO. The latter has been attributed to inflammation. Hepcidin, a 25-amino acid peptide, is produced predominantly by hepatocytes under the influence of IL-6. As the key regulator of transmembrane iron transport, hepcidin controls the absorption of iron in the intestine, the mobilization of iron from hepatic stores, and iron recycling by macrophages.[105] Furthermore, certain proinflammatory cytokines may suppress erythroid progenitor cell proliferation and inhibit EPO production.[106]

Infection and Inflammation in CKD

It has long been suspected that subclinical infections may be one of the underlying causes of inflammation in CKD. Paradoxically, systemic inflammation coexists with a state of acquired immunodeficiency in patients with CKD, predisposing to infections.[107] Persistent infection/inflammation could induce counterregulatory mechanisms that suppress innate and adaptive immunity in CKD.[108] Thus, chronic inflammation could predispose to infection, leading to a vicious cycle with poor outcomes in CKD patients.

Inflammation and Depression

The cytokine theory of depression assumes that inflammatory cytokines can trigger depression by acting on the central nervous system.[109,110] Studies in subjects without CKD have implicated TNF-α, IL-2, and IL-6 in the pathogenesis of depression. Small studies in CKD patients confirm such associations,[111] although the findings are controversial.[110]

TREATMENT OF INFLAMMATION IN CKD

A number of intervention studies targeting established risk factors for mortality in CKD have not yielded the anticipated positive results. Such negative studies could be due to the fact that inflammation in CKD has a competing and possibly overwhelming effect on outcomes, rendering these interventions ineffective.[112,113] Preliminary evidence indicates that targeting a single component of the inflammatory cascade is not sufficient in complex diseases and requires the use of broad immnomodulation therapy.[114] Alternatively, the redundancy and pleiotropy of the cytokine system renders a nontoxic intervention, a difficult proposition.

There are at least three potential therapeutic approaches using inflammation as a target that may result in clinical benefits in CKD patients: pharmacological manipulation of cell responses, reduction of the source of ligands, and direct antiinflammatory therapies. There are an increasing number of studies analyzing the potential impact of these strategies.

Targeting Inflammation Through Pharmacological Manipulation of Inflammatory Cell Responses

Renin–angiotensin system blockers, with antiinflammatory activity, have been tested in clinical trials in the dialysis population. The results of a randomized trial using fosinopril showed a slight benefit of this agent in comparison to placebo.[115] In another randomized trial with a small number of patients, candesartan significantly reduced CV events and mortality in patients treated with chronic maintenance hemodialysis.[116] Suzuki et al.[117] showed treatment with an angiotensin receptor blocker was independently associated with reduced fatal and nonfatal cardiovascular disease (CVD) events in a hemodialysis population, although this analysis may be limited because of the small sample size.

Statins are another drug class with antiinflammatory actions.[118] In observational studies, patients treated with statins had lower mortality than non-statin-using hemodialysis patients.[119] These results have not been uniformly confirmed by randomized controlled trials in ESRD hemodialysis patients.[120] Although treatment with rosuvastatin had no significant effect on the composite primary endpoint of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke, there was a reduction in mean level of plasma CRP in treated hemodialysis patients.[120] Inflammation at baseline was one of the most important risk factors for mortality.[120]

Inflammation is linked to oxidative stress, and antioxidants may be interesting drugs for antiinflammatory therapeutic interventions. One trial investigated the effect of high-dose vitamin E supplementation on CVD outcomes in hemodialysis patients with preexisting CVD.[121] After a median follow-up of 519 days, the use of vitamin E was associated with reduced CVD endpoints and myocardial infarctions.[121] In a randomized controlled trial, treatment with N-acetylcysteine, an antioxidant, reduced CV events and mortality in hemodialysis patients.[122]

Circulating levels of 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 can potentially influence the activity of many tissues and cells,[30] including cardiomyocytes, active T and B lymphocytes, and mononuclear and endothelial cells. In observational studies, dialysis patients treated with activated vitamin D and analogs have a survival advantage, perhaps related to the systemic activation of vitamin D receptors, acting as a negative endocrine regulator of renin–angiotensin synthesis and inflammation, thus reducing CV complications.[123] However, in a randomized controlled trial involving 227 patients with CKD, paricalcitrol failed to alter left ventricular mass index or improve diastolic function.[124] The Japan Dialysis Active Vitamin D study, a randomized, open-label multicenter study of 1289 hemodialysis patients without secondary hyperparathyroidism concluded oral alfacalcidol did not reduce the risk of a composite measure of fatal and nonfatal CV events.[125] Whether the results of this study are also applicable to patients with secondary hyperparathyroidism remains uncertain.[126]

Targeting Inflammation Through Reduction of Source of Ligands

Subclinical endotoxemia is associated with inflammation, protein energy wasting, and mortality in ESRD patients.[34,127] The human gut harbors 10^{14} bacteria and endotoxemia resulting from gut microbial imbalance, termed dysbiosis, could promote inflammation. Thus, restoration of gut-microbial symbiosis may have a number of potential benefits in ESRD patients. Prebiotics are nondigestible food ingredients that selectively stimulate growth and/or activity of beneficial bacteria in the colon. Preliminary evidence indicates the prebiotic oligofructose-enriched inulin (p-inulin) may reduce endotoxin generation, attenuate inflammation, and improve metabolic function in patients without kidney disease.[128,129]

Although the drug had been created to be used as a phosphate binder, sevelamer hydrochloride showed a potential endotoxin-binding effect in the intestinal lumen, reducing systemic inflammation in an experimental model.[130] Other potential pleiotropic effects of sevelamer that could have CV impact include a lipid-lowering action and reduction in CRP levels.[131,132] Stinghen et al.[133] demonstrated that sevelamer treatment leads to a decrease in CRP levels accompanied by a parallel decrease in endotoxemia in hemodialysis patients.

Periodontal disease, an occult source of inflammation, is associated with CVD.[134] CKD patients with moderate-to-severe disease compared with those with mild or no periodontal disease had higher risk of death from CV causes.[135] Intervention trials to determine if treating periodontitis (and other hidden infections) reduces CVD mortality in CKD patients would shed light in this important area.

Direct Antiinflammatory Therapies

Pentoxifylline (PTX) is a nonselective inhibitor of cyclic-3′, 5′-phosphodiesterase (PDE). Inhibition of PDE has been shown to reduce *de novo* synthesis and tissue accumulation of proinflammatory cytokines.[136] Treatment with PTX has been shown to reduce proteinuria in patients with diabetic nephropathy and glomerular diseases.[137,138] PTX slows the progression of atherosclerosis and modifies plaque morphology in patients with type 1 diabetes.[139]

Pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) is an antifibrotic drug that reduces TGF-β2 protein levels and reverses extracellular matrix accumulation. It has been shown to slow the progression of renal disease in animal models[140] as well as in clinical studies.[141] In a double-blind randomized controlled study, Sharma et al.[142] showed pirfenidone preserves renal function in patients with diabetic nephropathy. In this study, 77 subjects with diabetic nephropathy were randomized to escalating doses of pirfenidone (1200 mg/day and 2400 mg/day) or placebo. A significant number of subjects in the high dose group dropped out of the study. Among the 52 subjects who completed the study, the mean eGFR increased in the pirfenidone 1200 mg/day group, whereas the eGFR decreased in the placebo group. Pirfenidone has also been shown to improve cardiac geometry and vascular biology. Although a promising antifibrotic agent, it has a number of adverse effects and is generally not well tolerated.[143]

Tocilizumab, a humanized mouse antihuman IL-6 receptor antibody, inhibits IL-6 activity by competing for both the membrane-bound and soluble types of IL-6 receptors.[144] Preliminary findings indicate that it may be effective in the management of glomerular disease.[145] Its potential benefit in the management of anemia of CKD and CVD in patients with CKD is a fertile area for research. Treatment with etanercept, a TNF-receptor antagonist, did not have a significant effect on CRP or IL-6 but had positive effect on S[Alb] and prealbumin in hemodialysis patients.[146]

Anakinra is a nonglycosylated, recombinant form of human IL-1Ra that, like endogenous IL-1Ra, competitively inhibits IL-1 by binding the IL-1 type I receptor. In a pilot study, Hung et al. showed Anakinra reduced markers of inflammation and increased prealbumin concentrations in patients treated with hemodialysis.[147] Furthermore, an IL-1 beta receptor antagonist has been shown to improve coronary flow, left ventricular function, and endothelial function in patients with rheumatoid arthritis.[148] In a double-blind trial, 42 adult patients with stages 3−4 CKD were randomized to treatment with an IL-1 trap, rilonacept, or placebo. Rilonacept therapy improved brachial artery flow-mediated dilation and reduced systemic inflammation in patients with CKD.[149] Preliminary results from the Canakinumab Anti-inflammatory Thrombosis Outcome Study suggest that major atherosclerotic CV events were reduced with IL-1β inhibition with canakinumab in patients with moderate CKD (HR 0.82; 95% CI: 0.68−1.00, $p = 0.05$) and in those with normal kidney function (HR 0.86; 95% CI: 0.77−0.97, $p = 0.012$).[150]

An emerging therapeutic option is to directly use nanotechnology-based drug delivery systems. Various nanosized materials are currently being developed, including micelles, liposomes, polymeric nanoparticles, dendrimers, carbon nanotubes, and metallic nanoparticles. The inflammatory milieu enhances incorporation of nanosized materials into mononuclear phagocytic systems for delivery to the target organ.[151]

Bardoxolone methyl is an inducer of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway, which can suppress oxidative stress and inflammation. Initial reports showed bardoxolone methyl treatment was

TABLE 24.2 Important Issues to be Considered in the Management of Inflammation in Chronic Kidney Disease (CKD)

How should the intensity of inflammation in CKD patients be assessed?
What are the therapeutic targets for reduction of inflammation?
What is the level to which the inflammation could be reduced without compromising its physiological function?
Should specific molecules be targeted or is a broad nonspecific approach appropriate?

associated with improvement in eGFR in patients with advanced CKD and type 2 diabetes.[152] The bardoxolone methyl Evaluation in Patients with Chronic Kidney Disease and T2DM: The Occurrence of Renal Events (BEACON) trial, however, was terminated because of excess mortality in the treatment arm.[153] Thus, it is important to navigate through the maze of inflammatory pathways while selecting the target, with careful assessment of clinical risk.

CONCLUSION

Our understanding of the causes and consequences of inflammation has certainly expanded considerably, but the science is still evolving rapidly, constantly revealing new molecules and novel pathways. Besides contributing to the progression of renal disease, inflammation is now recognized as a potential catalyst that may accelerate kidney disease complications. Lack of clear understanding has hampered our progress in the management of uremia-associated inflammation, but we have made considerable strides during the last two decades. Challenges and questions still remaining to be addressed are listed in Table 24.2. While investigators are seeking answers, a number of drugs that target inflammation are in development, and small studies have reported some encouraging results.

References

1. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation [erratum appears in N Engl J Med 1999;340(17):1376.]. [Review] [64 refs] *N Engl J Med* 1999;**340**:448–54.
2. Feghali CA, Wright TM. Cytokines in acute and chronic inflammation. *Front Biosci* 1997;**2**:d12–26.
3. Gupta J, Mitra N, Kanetsky PA, Devaney J, Wing MR, Reilly M, Shah VO, Balakrishnan VS, Guzman NJ, Girndt M, Periera BG, Feldman HI, Kusek JW, Joffe MM, Raj DS. Association between albuminuria, kidney function, and inflammatory biomarker profile. *Clin J Am Soc Nephrol* 2012;**7**:1938–46.
4. Kimmel PL, Phillips TM, Simmens SJ, Peterson RA, Weihs KL, Alleyne S, Cruz I, Yanovski JA, Veis JH. Immunologic function and survival in hemodialysis patients. *Kidney Int* 1998;**54**:236–44.
5. Pereira BJ, Shapiro L, King AJ, Falagas ME, Strom JA, Dinarello CA. Plasma levels of IL-1 beta, TNF alpha and their specific inhibitors in undialyzed chronic renal failure, CAPD and hemodialysis patients. *Kidney Int* 1994;**45**:890–6.
6. Cohen SD, Phillips TM, Khetpal P, Kimmel PL. Cytokine patterns and survival in haemodialysis patients. *Nephrol Dial Transplant* 2010;**25**:1239–43.
7. Ranjit N, Diez-Roux AV, Shea S, Cushman M, Ni H, Seeman T. Socioeconomic position, race/ethnicity, and inflammation in the Multi-Ethnic Study of Atherosclerosis. *Circulation* 2007;**116**:2383–90.
8. Macaulay R, Akbar AN, Henson SM. The role of the T cell in age-related inflammation. *Age (Dordr)* 2013;**35**:563–72.
9. Jagannathan-Bogdan M, McDonnell ME, Shin H, Rehman Q, Hasturk H, Apovian CM, Nikolajczyk BS. Elevated proinflammatory cytokine production by a skewed T cell compartment requires monocytes and promotes inflammation in type 2 diabetes. *J Immunol* 2011;**186**:1162–72.
10. Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A, Hoogeveen R, Folsom AR, Heiss G. Low-grade systemic inflammation and the development of type 2 diabetes: the Atherosclerosis Risk In Communities study. *Diabetes* 2003;**52**:1799–805.
11. Luttropp K, Debowska M, Lukaszuk T, Bobrowski L, Carrero JJ, Qureshi AR, Stenvinkel P, Lindholm B, Waniewski J, Nordfors L. Genotypic and phenotypic predictors of inflammation in patients with chronic kidney disease. *Nephrol Dial Transplant* 2016;**31**:2033–40.
12. Ness RB, Haggerty CL, Harger G, Ferrell R. Differential distribution of allelic variants in cytokine genes among African Americans and White Americans. *Am J Epidemiol* 2004;**160**:1033–8.
13. Van Dyke AL, Cote ML, Wenzlaff AS, Land S, Schwartz AG. Cytokine SNPs: comparison of allele frequencies by race and implications for future studies. *Cytokine* 2009;**46**:236–44.
14. Dwivedi RS, Herman JG, McCaffrey TA, Raj DS. Beyond genetics: epigenetic code in chronic kidney disease. *Kidney Int* 2011;**79**:23–32.
15. Wilson CB, Rowell E, Sekimata M. Epigenetic control of T-helper-cell differentiation. *Nat Rev Immunol* 2009;**9**:91–105.
16. Balakrishnan VS, Schmid CH, Jaber BL, Natov SN, King AJ, Pereira BJ. Interleukin-1 receptor antagonist synthesis by peripheral blood mononuclear cells: a novel predictor of morbidity among hemodialysis patients. *J Am Soc Nephrol* 2000;**11**:2114–21.
17. Morley JJ, Kushner I. Serum C-reactive protein levels in disease. *Ann N Y Acad Sci* 1982;**389**:406–18.
18. Kimmel PL, Phillips TM, Phillips E, Bosch JP. Effect of renal replacement therapy on cellular cytokine production in patients with renal disease. *Kidney Int* 1990;**38**:129–35.
19. Raj DSC, Dominic EA, Pai A, Osman F, Morgan M, Pickett G, Shah VO, Ferrando A, Moseley P. Skeletal muscle, cytokines and oxidative stress in end-stage renal disease. *Kidney Int* 2005;**68**:2338–44.
20. Garibotto G, Sofia A, Procopio V, Villaggio B, Tarroni A, Di MM, Cappelli V, Gandolfo MT, Aloisi F, De CF, Sala MR, Verzola D. Peripheral tissue release of interleukin-6 in patients with chronic kidney diseases: effects of end-stage renal disease and microinflammatory state. *Kidney Int* 2006;**70**:384–90.
21. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. *J Clin Endocrinol Metab* 1998;**83**:847–50.
22. Boivin MA, Battah SI, Dominic EA, Kalantar-Zadeh K, Ferrando A, Tzamaloukas AH, Dwivedi R, Ma TA, Moseley P,

Raj DS. Activation of caspase-3 in the skeletal muscle during haemodialysis. *Eur J Clin Invest* 2010;**40**:903–10.
23. Wing MR, Yang W, Teal V, Navaneethan S, Tao K, Ojo A, Guzman NN, Reilly M, Wolman M, Rosas SE, Cuevas M, Fischer M, Lustigova E, Master SR, Xie D, Appleby D, Joffe M, Kusek J, Feldman HI, Raj DS. Race modifies the association between adiposity and inflammation in patients with chronic kidney disease: findings from the Chronic Renal Insufficiency Cohort study. *Obesity (Silver Spring)* 2014;**22**: 1359–66.
24. Baldus S, Heeschen C, Meinertz T, Zeiher AM, Eiserich JP, Munzel T, Simoons ML, Hamm CW. Myeloperoxidase serum levels predict risk in patients with acute coronary syndromes. *Circulation* 2003;**108**:1440–5.
25. Kalantar-Zadeh K, Brennan ML, Hazen SL. Serum myeloperoxidase and mortality in maintenance hemodialysis patients. *Am J Kidney Dis* 2006;**48**:59–68.
26. Ioannidou E, Swede H, Dongari-Bagtzoglou A. Periodontitis predicts elevated C-reactive protein levels in chronic kidney disease. *J Dent Res* 2011;**90**:1411–5.
27. Goncalves S, Pecoits-Filho R, Perreto S, Barberato SH, Stinghen AE, Lima EG, Fuerbringer R, Sauthier SM, Riella MC. Associations between renal function, volume status and endotoxaemia in chronic kidney disease patients. *Nephrol Dial Transplant* 2006;**21**:2788–94.
28. Ramos LF, Shintani A, Ikizler TA, Himmelfarb J. Oxidative stress and inflammation are associated with adiposity in moderate to severe CKD. *J Am Soc Nephrol* 2008;**19**:593–9.
29. Safieh-Garabedian B, Poole S, Haddad JJ, Massaad CA, Jabbur SJ, Saade NE. The role of the sympathetic efferents in endotoxin-induced localized inflammatory hyperalgesia and cytokine upregulation. *Neuropharmacology* 2002;**42**:864–72.
30. Sterling KA, Eftekhari P, Girndt M, Kimmel PL, Raj DS. The immunoregulatory function of vitamin D: implications in chronic kidney disease. *Nat Rev Nephrol* 2012;**8**:403–12.
31. Hida M, Aiba Y, Sawamura S, Suzuki N, Satoh T, Koga Y. Inhibition of the accumulation of uremic toxins in the blood and their precursors in the feces after oral administration of Lebenin, a lactic acid bacteria preparation, to uremic patients undergoing hemodialysis. *Nephron* 1996;**74**:349–55.
32. Vaziri ND, Wong J, Pahl M, Piceno YM, Yuan J, Desantis TZ, Ni Z, Nguyen TH, Andersen GL. Chronic kidney disease alters intestinal microbial flora. *Kidney Int* 2013;**83**(2):308–15.
33. Ramezani A, Massy ZA, Meijers B, Evenepoel P, Vanholder R, Raj DS. Role of the gut microbiome in uremia: a potential therapeutic target. *Am J Kidney Dis* 2016;**67**:483–98.
34. Raj DS, Carrero JJ, Shah VO, Qureshi AR, Barany P, Heimburger O, Lindholm B, Ferguson J, Moseley PL, Stenvinkel P. Soluble CD14 levels, interleukin 6, and mortality among prevalent hemodialysis patients. *Am J Kidney Dis* 2009; **54**:990–2.
35. Gollapudi P, Yoon JW, Gollapudi S, Pahl MV, Vaziri ND. Leukocyte toll-like receptor expression in end-stage kidney disease. *Am J Nephrol* 2010;**31**:247–54.
36. Kono H, Rock KL. How dying cells alert the immune system to danger. *Nat Rev Immunol* 2008;**8**:279–89.
37. Anders HJ, Muruve DA. The inflammasomes in kidney disease. *J Am Soc Nephrol* 2011;**22**:1007–18.
38. Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. *Mol Cell* 2002;**10**:417–26.
39. Vilaysane A, Chun J, Seamone ME, Wang W, Chin R, Hirota S, Li Y, Clark SA, Tschopp J, Trpkov K, Hemmelgarn BR, Beck PL, Muruve DA. The NLRP3 inflammasome promotes renal inflammation and contributes to CKD. *J Am Soc Nephrol* 2010;**21**: 1732–44.
40. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. *Nature* 2014;**510**:92–101.
41. Fullerton JN, Gilroy DW. Resolution of inflammation: a new therapeutic frontier. *Nat Rev Drug Discov* 2016;**15**:551–67.
42. Buckley CD, Gilroy DW, Serhan CN. Proresolving lipid mediators and mechanisms in the resolution of acute inflammation. *Immunity* 2014;**40**:315–27.
43. Serhan CN, Levy BD. Resolvins in inflammation: emergence of the pro-resolving superfamily of mediators. *J Clin Invest* 2018; **128**:2657–69.
44. Kourtzelis I, Li X, Mitroulis I, Grosser D, Kajikawa T, Wang B, Grzybek M, von RJ, Czogalla A, Troullinaki M, Ferreira A, Doreth C, Ruppova K, Chen LS, Hosur K, Lim JH, Chung KJ, Grossklaus S, Tausche AK, Joosten LAB, Moutsopoulos NM, Wielockx B, Castrillo A, Korostoff JM, Coskun U, Hajishengallis G, Chavakis T. DEL-1 promotes macrophage efferocytosis and clearance of inflammation. *Nat Immunol* 2019;**20**: 40–9.
45. Zoccali C, Tripepi G, Mallamaci F. Dissecting inflammation in ESRD: do cytokines and C-reactive protein have a complementary prognostic value for mortality in dialysis patients? *J Am Soc Nephrol* 2006;**17**:S169–73.
46. Navarro SL, Brasky TM, Schwarz Y, Song X, Wang CY, Kristal AR, Kratz M, White E, Lampe JW. Reliability of serum biomarkers of inflammation from repeated measures in healthy individuals. *Cancer Epidemiol Biomarkers Prev* 2012;**21**:1167–70.
47. Snaedal S, Heimburger O, Qureshi AR, Danielsson A, Wikstrom B, Fellstrom B, Fehrman-Ekholm I, Carrero JJ, Alvestrand A, Stenvinkel P, Barany P. Comorbidity and acute clinical events as determinants of CRP variation in hemodialysis patients: implications on patient survival. *Am J Kidney Dis* 2009;**53**:1033.
48. Castell JV, Gomez-Lechon MJ, David M, Fabra R, Trullenque R, Heinrich PC. Acute-phase response of human hepatocytes: regulation of acute-phase protein synthesis by interleukin-6. *Hepatology* 1990;**12**:1179–86.
49. Shine B, de Beer FC, Pepys MB. Solid phase radioimmunoassays for human C-reactive protein. *Clin Chim Acta* 1981;**117**:13–23.
50. Pepys MB, Rowe IF, Baltz ML. C-reactive protein: binding to lipids and lipoproteins. *Int Rev Exp Pathol* 1985;**27**:83–111.
51. Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Cutrupi S, Parlongo S, Malatino LS, Bonanno G, Rapisarda F, Fatuzzo P, Seminara G, Nicocia G, Buemi M. Fibrinogen, inflammation and concentric left ventricular hypertrophy in chronic renal failure. *Eur J Clin Invest* 2003;**33**:561–6.
52. Stenvinkel P, Heimburger O, Paultre F, Diczfalusy U, Wang T, Berglund L, Jogestrand T. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 1999;**55**:1899–911.
53. Menon V, Greene T, Wang X, Pereira AA, Marcovina SM, Beck GJ, Kusek JW, Collins AJ, Levey AS, Sarnak MJ. C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. *Kidney Int* 2005;**68**:766–72.
54. Baldwin DS. Chronic glomerulonephritis: nonimmunologic mechanisms of progressive glomerular damage. *Kidney Int* 1982; **21**:109–20.
55. Rao M, Wong C, Kanetsky P, Girndt M, Stenvinkel P, Reilly M, Raj DS. Cytokine gene polymorphism and progression of renal and cardiovascular diseases. *Kidney Int* 2007;**72**(5):549–56.
56. Wiggins JE, Patel SR, Shedden KA, Goyal M, Wharram BL, Martini S, Kretzler M, Wiggins RC. NFkappaB promotes inflammation, coagulation, and fibrosis in the aging glomerulus. *J Am Soc Nephrol* 2010;**21**:587–97.
57. Qin W, Chung AC, Huang XR, Meng XM, Hui DS, Yu CM, Sung JJ, Lan HY. TGF-{beta}/Smad3 signaling promotes renal fibrosis by inhibiting miR-29. *J Am Soc Nephrol* 2011;**22**:1462–74.

58. Niewczas MA, Gohda T, Skupien J, Smiles AM, Walker WH, Rosetti F, Cullere X, Eckfeldt JH, Doria A, Mayadas TN, Warram JH, Krolewski AS. Circulating TNF receptors 1 and 2 predict ESRD in type 2 diabetes. *J Am Soc Nephrol* 2012;**23**:507–15.
59. Suthanthiran M, Gerber LM, Schwartz JE, Sharma VK, Medeiros M, Marion R, Pickering TG, August P. Circulating transforming growth factor-beta1 levels and the risk for kidney disease in African Americans. *Kidney Int* 2009;**76**:72–80.
60. Taniguchi Y, Yorioka N, Oda H, Yamakido M. Platelet-derived growth factor, interleukin (IL)-1 beta, IL-6R and tumor necrosis factor-alpha in IgA nephropathy. An immunohistochemical study. *Nephron* 1996;**74**:652–60.
61. Chen WP, Lin CY. Augmented expression of interleukin-6 and interleukin-1 genes in the mesangium of IgM mesangial nephropathy. *Nephron* 1994;**68**:10–9.
62. Cheng J, Grande JP. Transforming growth factor-beta signal transduction and progressive renal disease. *Exp Biol Med (Maywood)* 2002;**227**:943–56.
63. Taniguchi Y, Yorioka N, Kumagai J, Katsutani M, Kuratsune M, Amimoto D, Yamakido M. Interleukin-6 localization and the prognosis of IgA nephropathy. *Nephron* 1999;**81**:94–8.
64. Boswell JM, Yui MA, Burt DW, Kelley VE. Increased tumor necrosis factor and IL-1 beta gene expression in the kidneys of mice with lupus nephritis. *J Immunol* 1988;**141**:3050–4.
65. Nakamura T, Miller D, Ruoslahti E, Border WA. Production of extracellular matrix by glomerular epithelial cells is regulated by transforming growth factor-beta 1. *Kidney Int* 1992;**41**:1213–21.
66. Coleman DL, Ruef C. Interleukin-6: an autocrine regulator of mesangial cell growth. *Kidney Int* 1992;**41**:604–6.
67. Horii Y, Muraguchi A, Iwano M, Matsuda T, Hirayama T, Yamada H, Fujii Y, Dohi K, Ishikawa H, Ohmoto Y. Involvement of IL-6 in mesangial proliferative glomerulonephritis. *J Immunol* 1989;**143**:3949–55.
68. Bevilacqua MP, Pober JS, Majeau GR, Fiers W, Cotran RS, Gimbrone Jr MA. Recombinant tumor necrosis factor induces procoagulant activity in cultured human vascular endothelium: characterization and comparison with the actions of interleukin 1. *Proc Natl Acad Sci USA* 1986;**83**:4533–7.
69. Sharma K, Cook A, Smith M, Valancius C, Inscho EW. TGF-beta impairs renal autoregulation via generation of ROS. *Am J Physiol Renal Physiol* 2005;**288**:F1069–77.
70. Park S, Chang YH, Cho YJ, Ahn H, Yang WS, Park JS, Lee JD. Cytokine-regulated expression of vascular cell adhesion molecule-1 in human glomerular endothelial cells. *Transplant Proc* 1998;**30**:2395–7.
71. Zager RA, Johnson A. Renal cortical cholesterol accumulation is an integral component of the systemic stress response. *Kidney Int* 2001;**60**:2299–310.
72. Nee LE, McMorrow T, Campbell E, Slattery C, Ryan MP. TNF-alpha and IL-1beta-mediated regulation of MMP-9 and TIMP-1 in renal proximal tubular cells. *Kidney Int* 2004;**66**:1376–86.
73. Sedor JR, Nakazato Y, Konieczkowski M. Interleukin-1 and the mesangial cell. *Kidney Int* 1992;**41**:595–9.
74. Atkins RC. Interleukin-1 in crescentic glomerulonephritis. *Kidney Int* 1995;**48**:576–86.
75. Baud L, Ardaillou R. Tumor necrosis factor alpha in glomerular injury. *Kidney Int Suppl* 1994;**45**:S32–6.
76. Goumenos DS, Tsakas S, el Nahas AM, Alexandri S, Oldroyd S, Kalliakmani P, Vlachojannis JG. Transforming growth factor-beta(1) in the kidney and urine of patients with glomerular disease and proteinuria. *Nephrol Dial Transplant* 2002;**17**:2145–52.
77. Noh JW, Wiggins R, Phan SH. Urine transforming growth factor-beta activity is related to the degree of scarring in crescentic nephritis in the rabbit. *Nephron* 1993;**63**:73–8.
78. Sharma K, Ziyadeh FN, Alzahabi B, McGowan TA, Kapoor S, Kurnik BR, Kurnik PB, Weisberg LS. Increased renal production of transforming growth factor-beta1 in patients with type II diabetes. *Diabetes* 1997;**46**:854–9.
79. Kalantarinia K, Awad AS, Siragy HM. Urinary and renal interstitial concentrations of TNF-alpha increase prior to the rise in albuminuria in diabetic rats. *Kidney Int* 2003;**64**:1208–13.
80. Harada K, Akai Y, Kurumatani N, Iwano M, Saito Y. Prognostic value of urinary interleukin 6 in patients with IgA nephropathy: an 8-year follow-up study. *Nephron* 2002;**92**:824–6.
81. Amdur RL, Feldman HI, Gupta J, Yang W, Kanetsky P, Shlipak M, Rahman M, Lash JP, Townsend RR, Ojo A, Roy-Chaudhury A, Go AS, Joffe M, He J, Balakrishnan VS, Kimmel PL, Kusek JW, Raj DS. Inflammation and progression of CKD: the CRIC study. *Clin J Am Soc Nephrol* 2016;**11**:1546–56.
82. Bhatraju PK, Zelnick LR, Shlipak M, Katz R, Kestenbaum B. Association of soluble TNFR-1 concentrations with long-term decline in kidney function: the Multi-Ethnic Study of Atherosclerosis. *J Am Soc Nephrol* 2018;**29**:2713–21.
83. Kamei N, Yamashita M, Nishizaki Y, Yanagisawa N, Nojiri S, Tanaka K, Yamashita Y, Shibata T, Murakoshi M, Suzuki Y, Gohda T. Association between circulating tumor necrosis factor-related biomarkers and estimated glomerular filtration rate in type 2 diabetes. *Sci Rep* 2018;**8**:15302.
84. Iwano M, Plieth D, Danoff TM, Xue C, Okada H, Neilson EG. Evidence that fibroblasts derive from epithelium during tissue fibrosis. *J Clin Invest* 2002;**110**:341–50.
85. LeBleu VS, Taduri G, O'Connell J, Teng Y, Cooke VG, Woda C, Sugimoto H, Kalluri R. Origin and function of myofibroblasts in kidney fibrosis. *Nat Med* 2013;**19**:1047–53.
86. Shankar A, Sun L, Klein BE, Lee KE, Muntner P, Nieto FJ, Tsai MY, Cruickshanks KJ, Schubert CR, Brazy PC, Coresh J, Klein R. Markers of inflammation predict the long-term risk of developing chronic kidney disease: a population-based cohort study. *Kidney Int* 2011;**80**:1231–8.
87. Norlander AE, Madhur MS, Harrison DG. The immunology of hypertension. *J Exp Med* 2018;**215**:21–33.
88. Sun XN, Li C, Liu Y, Du LJ, Zeng MR, Zheng XJ, Zhang WC, Liu Y, Zhu M, Kong D, Zhou L, Lu L, Shen ZX, Yi Y, Du L, Qin M, Liu X, Hua Z, Sun S, Yin H, Zhou B, Yu Y, Zhang Z, Duan SZ. T-cell mineralocorticoid receptor controls blood pressure by regulating interferon-gamma. *Circ Res* 2017;**120**:1584–97.
89. Bernelot Moens SJ, Verweij SL, van der Valk FM, van Capelleveen JC, Kroon J, Versloot M, Verberne HJ, Marquering HA, Duivenvoorden R, Vogt L, Stroes ES. Arterial and cellular inflammation in patients with CKD. *J Am Soc Nephrol* 2017;**28**:1278–85.
90. Barbaro NR, Foss JD, Kryshtal DO, Tsyba N, Kumaresan S, Xiao L, Mernaugh RL, Itani HA, Loperena R, Chen W, Dikalov S, Titze JM, Knollmann BC, Harrison DG, Kirabo A. Dendritic cell amiloride-sensitive channels mediate sodium-induced inflammation and hypertension. *Cell Rep* 2017;**21**:1009–20.
91. Peyster E, Chen J, Feldman HI, Go AS, Gupta J, Mitra N, Pan Q, Porter A, Rahman M, Raj D, Reilly M, Wing MR, Yang W, Townsend RR. Inflammation and arterial stiffness in chronic kidney disease: findings from the CRIC study. *Am J Hypertens* 2017;**30**:400–8.
92. Reiss AB, Glass AD. Atherosclerosis: immune and inflammatory aspects. *J Investig Med* 2006;**54**:123–31.
93. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, Sarnak MJ. Inflammation and cardiovascular events in individuals with and without chronic kidney disease. *Kidney Int* 2008;**73**:1406–12.

94. Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. *Circ Res* 2002;**91**:988–98.
95. Oral H, Sivasubramanian N, Dyke DB, Mehta RH, Grossman PM, Briesmiester K, Fay WP, Pagani FD, Bolling SF, Mann DL, Starling MR. Myocardial proinflammatory cytokine expression and left ventricular remodeling in patients with chronic mitral regurgitation. *Circulation* 2003;**107**:831–7.
96. Amdur RL, Feldman HI, Dominic EA, Anderson AH, Beddhu S, Rahman M, Wolf M, Reilly M, Ojo A, Townsend RR, Go AS, He J, Xie D, Thompson S, Budoff M, Kasner S, Kimmel PL, Kusek JW, Raj DS. Use of measures of inflammation and kidney function for prediction of atherosclerotic vascular disease events and death in patients with CKD: findings from the CRIC study. *Am J Kidney Dis* 2019;**73**(3):344–53.
97. Raj DS, Moseley P, Dominic EA, Onime A, Tzamaloukas AH, Boyd A, Shah VO, Glew R, Wolfe R, Ferrando A. Interleukin-6 modulates hepatic and muscle protein synthesis during hemodialysis. *Kidney Int* 2008;**73**:1061.
98. Kramer HJ, Saranathan A, Luke A, Durazo-Arvizu RA, Guichan C, Hou S, Cooper R. Increasing body mass index and obesity in the incident ESRD population. *J Am Soc Nephrol* 2006; **17**:1453–9.
99. Chen J, Muntner P, Hamm LL, Fonseca V, Batuman V, Whelton PK, He J. Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. *J Am Soc Nephrol* 2003;**14**:469–77.
100. Yuan M, Konstantopoulos N, Lee J, Hansen L, Li ZW, Karin M, Shoelson SE. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikkbeta. *Science* 2001;**293**:1673–7.
101. Hirosumi J, Tuncman G, Chang L, Gorgun CZ, Uysal KT, Maeda K, Karin M, Hotamisligil GS. A central role for JNK in obesity and insulin resistance. *Nature* 2002;**420**:333–6.
102. Barany P, Divino Filho JC, Bergstrom J. High C-reactive protein is a strong predictor of resistance to erythropoietin in hemodialysis patients. *Am J Kidney Dis* 1997;**29**:565–8.
103. de Francisco AL, Stenvinkel P, Vaulont S. Inflammation and its impact on anaemia in chronic kidney disease: from haemoglobin variability to hyporesponsiveness. *NDT Plus* 2009;**2**:i18–26.
104. Goicoechea M, Martin J, de Sequera P, Quiroga JA, Ortiz A, Carreno V, Caramelo C. Role of cytokines in the response to erythropoietin in hemodialysis patients. *Kidney Int* 1998;**54**:1337–43.
105. De D I, Ward DM, Langelier C, Vaughn MB, Nemeth E, Sundquist WI, Ganz T, Musci G, Kaplan J. The molecular mechanism of hepcidin-mediated ferroportin down-regulation. *Mol Biol Cell* 2007;**18**:2569–78.
106. Faquin WC, Schneider TJ, Goldberg MA. Effect of inflammatory cytokines on hypoxia-induced erythropoietin production. *Blood* 1992;**79**:1987–94.
107. Girndt M, Sester M, Sester U, Kaul H, Kohler H. Molecular aspects of T- and B-cell function in uremia. *Kidney Int Suppl* 2001; **78**:S206–11.
108. Moser B, Roth G, Brunner M, Lilaj T, Deicher R, Wolner E, Kovarik J, Boltz-Nitulescu G, Vychytil A, Ankersmit HJ. Aberrant T cell activation and heightened apoptotic turnover in end-stage renal failure patients: a comparative evaluation between non-dialysis, haemodialysis, and peritoneal dialysis. *Biochem Biophys Res Commun* 2003;**308**:581–5.
109. Smith RS. The macrophage theory of depression. *Med Hypotheses* 1991;**35**:298–306.
110. Cukor D, Cohen SD, Peterson RA, Kimmel PL. Psychosocial aspects of chronic disease: ESRD as a paradigmatic illness. *J Am Soc Nephrol* 2007;**18**:3042–55.
111. Kalender B, Ozdemir AC, Koroglu G. Association of depression with markers of nutrition and inflammation in chronic kidney disease and end-stage renal disease. *Nephron Clin Pract* 2006;**102**: c115–21.
112. Carrero JJ, Stenvinkel P. Persistent inflammation as a catalyst for other risk factors in chronic kidney disease: a hypothesis proposal. *Clin J Am Soc Nephrol* 2009;**4**(Suppl. 1):S49–55.
113. Raj DS, Adeniyi O, Dominic EA, Boivin MA, McClelland S, Tzamaloukas AH, Morgan N, Gonzales L, Wolfe R, Ferrando A. Amino acid repletion does not decrease muscle protein catabolism during hemodialysis. *Am J Physiol Endocrinol Metab* 2007; **292**:E1534–42.
114. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, Djian J, Drexler H, Feldman A, Kober L, Krum H, Liu P, Nieminen M, Tavazzi L, van Veldhuisen DJ, Waldenstrom A, Warren M, Westheim A, Zannad F, Fleming T. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation* 2004;**109**:1594–602.
115. Zannad F, Kessler M, Lehert P, Grunfeld JP, Thuilliez C, Leizorovicz A, Lechat P. Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. *Kidney Int* 2006;**70**:1318–24.
116. Takahashi A, Takase H, Toriyama T, Sugiura T, Kurita Y, Ueda R, Dohi Y. Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis–a randomized study. *Nephrol Dial Transplant* 2006;**21**:2507–12.
117. Suzuki H, Kanno Y, Sugahara S, Ikeda N, Shoda J, Takenaka T, Inoue T, Araki R. Effect of angiotensin receptor blockers on cardiovascular events in patients undergoing hemodialysis: an open-label randomized controlled trial. *Am J Kidney Dis* 2008;**52**: 501–6.
118. Krane V, Wanner C. Statins, inflammation and kidney disease. *Nat Rev Nephrol* 2011;**7**:385–97.
119. Seliger SL, Weiss NS, Gillen DL, Kestenbaum B, Ball A, Sherrard DJ, Stehman-Breen CO. HMG-CoA reductase inhibitors are associated with reduced mortality in ESRD patients. *Kidney Int* 2002;**61**:297–304.
120. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Gronhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Suleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wuthrich RP, Gottlow M, Johnsson E, Zannad F. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;**360**:1395–407.
121. Boaz M, Smetana S, Weinstein T, Matas Z, Gafter U, Iaina A, Knecht A, Weissgarten Y, Brunner D, Fainaru M, Green MS. Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomised placebo-controlled trial. *Lancet* 2000;**356**:1213–8.
122. Tepel M, Echelmeyer M, Orie NN, Zidek W. Increased intracellular reactive oxygen species in patients with end-stage renal failure: effect of hemodialysis. *Kidney Int* 2000;**58**:867–72.
123. Valdivielso JM, Ayus JC. Role of vitamin D receptor activators on cardiovascular risk. *Kidney Int Suppl* 2008;**111**:S44–9.
124. Thadhani R, Appelbaum E, Pritchett Y, Chang Y, Wenger J, Tamez H, Bhan I, Agarwal R, Zoccali C, Wanner C, Lloyd-Jones D, Cannata J, Thompson BT, Andress D, Zhang W, Packham D, Singh B, Zehnder D, Shah A, Pachika A, Manning WJ, Solomon SD. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. *J Am Med Assoc* 2012;**307**: 674–84.
125. Shoji T, Inaba M, Fukagawa M, Ando R, Emoto M, Fujii H, Fujimori A, Fukui M, Hase H, Hashimoto T, Hirakata H, Honda H, Hosoya T, Ikari Y, Inaguma D, Inoue T, Isaka Y, Iseki K, Ishimura E, Itami N, Ito C, Kakuta T, Kawai T, Kawanishi H, Kobayashi S, Kumagai J, Maekawa K, Masakane I, Minakuchi J, Mitsuiki K, Mizuguchi T, Morimoto S,

Murohara T, Nakatani T, Negi S, Nishi S, Nishikawa M, Ogawa T, Ohta K, Ohtake T, Okamura M, Okuno S, Shigematsu T, Sugimoto T, Suzuki M, Tahara H, Takemoto Y, Tanaka K, Tominaga Y, Tsubakihara Y, Tsujimoto Y, Tsuruya K, Ueda S, Watanabe Y, Yamagata K, Yamakawa T, Yano S, Yokoyama K, Yorioka N, Yoshiyama M, Nishizawa Y. Effect of oral alfacalcidol on clinical outcomes in patients without secondary hyperparathyroidism receiving maintenance hemodialysis: the J-DAVID randomized clinical trial. *J Am Med Assoc* 2018;**320**:2325–34.

126. Hall RK, Scialla JJ. Vitamin D receptor agonists for patients undergoing hemodialysis. *J Am Med Assoc* 2018;**320**:2319–21.
127. Raj DS, Shah VO, Rambod M, Kovesdy CP, Kalantar-Zadeh K. Association of soluble endotoxin receptor CD14 and mortality among patients undergoing hemodialysis. *Am J Kidney Dis* 2009;**54**(6):1062–71.
128. Cani PD, Neyrinck AM, Fava F, Knauf C, Burcelin RG, Tuohy KM, Gibson GR, Delzenne NM. Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. *Diabetologia* 2007;**50**:2374–83.
129. Gibson GR, Beatty ER, Wang X, Cummings JH. Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin. *Gastroenterology* 1995;**108**:975–82.
130. Perianayagam MC, Jaber BL. Endotoxin-binding affinity of sevelamer hydrochloride. *Am J Nephrol* 2008;**28**:802–7.
131. Ferramosca E, Burke S, Chasan-Taber S, Ratti C, Chertow GM, Raggi P. Potential antiatherogenic and anti-inflammatory properties of sevelamer in maintenance hemodialysis patients. *Am Heart J* 2005;**149**:820–5.
132. Evenepoel P, Selgas R, Caputo F, Foggensteiner L, Heaf JG, Ortiz A, Kelly A, Chasan-Taber S, Duggal A, Fan S. Efficacy and safety of sevelamer hydrochloride and calcium acetate in patients on peritoneal dialysis. *Nephrol Dial Transplant* 2009;**24**:278–85.
133. Stinghen AE, Gonçalves SM, Bucharles S, Branco FS, Gruber B, Hauser AB, Pecoits-Filho R. Sevelamer decreases systemic inflammation in parallel to a reduction in endotoxemia. *Blood Purif* 2010;**29**(4):352–6. https://doi.org/10.1159/000302723. Epub 2010 March 31.
134. Pussinen PJ, Tuomisto K, Jousilahti P, Havulinna AS, Sundvall J, Salomaa V. Endotoxemia, immune response to periodontal pathogens, and systemic inflammation associate with incident cardiovascular disease events. *Arterioscler Thromb Vasc Biol* 2007;**27**:1433–9.
135. Craig RG, Pernat AM, Pecoits-Filho R, Levin NW, Kotanko P. Periodontal diseases and systemic inflammation. *Semin Dial* 2013;**26**:23–8.
136. D'Hellencourt CL, Diaw L, Cornillet P, Guenounou M. Differential regulation of TNF alpha, IL-1 beta, IL-6, IL-8, TNF beta, and IL-10 by pentoxifylline. *Int J Immunopharmacol* 1996;**18**:739–48.
137. McCormick BB, Sydor A, Akbari A, Fergusson D, Doucette S, Knoll G. The effect of pentoxifylline on proteinuria in diabetic kidney disease: a meta-analysis. *Am J Kidney Dis* 2008;**52**:454–63.
138. Ducloux D, Bresson-Vautrin C, Chalopin J. Use of pentoxifylline in membranous nephropathy. *Lancet* 2001;**357**:1672–3.
139. Atabek ME, Kurtoglu S, Selver B, Baykara M. Effectiveness of pentoxifylline on the cross-sectional area of intima media thickness and functions of the common carotid artery in adolescents with type 1 diabetes. *J Pediatr Endocrinol Metab* 2011;**24**:945–51.
140. Shimizu T, Fukagawa M, Kuroda T, Hata S, Iwasaki Y, Nemoto M, Shirai K, Yamauchi S, Margolin SB, Shimizu F, Kurokawa K. Pirfenidone prevents collagen accumulation in the remnant kidney in rats with partial nephrectomy. *Kidney Int Suppl* 1997;**63**:S239–43.
141. Cho ME, Smith DC, Branton MH, Penzak SR, Kopp JB. Pirfenidone slows renal function decline in patients with focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol* 2007;**2**:906–13.
142. Sharma K, Ix JH, Mathew AV, Cho M, Pflueger A, Dunn SR, Francos B, Sharma S, Falkner B, McGowan TA, Donohue M, Ramachandrarao S, Xu R, Fervenza FC, Kopp JB. Pirfenidone for diabetic nephropathy. *J Am Soc Nephrol* 2011;**22**:1144–51.
143. Jiang C, Huang H, Liu J, Wang Y, Lu Z, Xu Z. Adverse events of pirfenidone for the treatment of pulmonary fibrosis: a meta-analysis of randomized controlled trials. *PLoS One* 2012;**7**:e47024.
144. Alten R, Maleitzke T. Tocilizumab: a novel humanized anti-interleukin 6 (IL-6) receptor antibody for the treatment of patients with non-RA systemic, inflammatory rheumatic diseases. *Ann Med* 2013;**45**:357–63.
145. Iijima T, Suwabe T, Sumida K, Hayami N, Hiramatsu R, Hasegawa E, Yamanouchi M, Hoshino J, Sawa N, Takaichi K, Oohashi K, Fujii T, Ubara Y. Tocilizumab improves systemic rheumatoid vasculitis with necrotizing crescentic glomerulonephritis. *Mod Rheumatol* 2015;**25**(1):138–42.
146. Don BR, Kim K, Li J, Dwyer T, Alexander F, Kaysen GA. The effect of etanercept on suppression of the systemic inflammatory response in chronic hemodialysis patients. *Clin Nephrol* 2010;**73**:431–8.
147. Hung AM, Ellis CD, Shintani A, Booker C, Ikizler TA. IL-1beta receptor antagonist reduces inflammation in hemodialysis patients. *J Am Soc Nephrol* 2011;**22**:437–42.
148. Ikonomidis I, Lekakis JP, Nikolaou M, Paraskevaidis I, Andreadou I, Kaplanoglou T, Katsimbri P, Skarantavos G, Soucacos PN, Kremastinos DT. Inhibition of interleukin-1 by anakinra improves vascular and left ventricular function in patients with rheumatoid arthritis. *Circulation* 2008;**117**:2662–9.
149. Nowak KL, Chonchol M, Ikizler TA, Farmer-Bailey H, Salas N, Chaudhry R, Wang W, Smits G, Tengesdal I, Dinarello CA, Hung AM. IL-1 inhibition and vascular function in CKD. *J Am Soc Nephrol* 2017;**28**:971–80.
150. Ridker PM, MacFadyen JG, Glynn RJ, Koenig W, Libby P, Everett BM, Lefkowitz M, Thuren T, Cornel JH. Inhibition of interleukin-1beta by canakinumab and cardiovascular outcomes in patients with chronic kidney disease. *J Am Coll Cardiol* 2018;**71**:2405–14.
151. Katsuki S, Matoba T, Nakashiro S, Sato K, Koga J, Nakano K, Nakano Y, Egusa S, Sunagawa K, Egashira K. Nanoparticle-mediated delivery of pitavastatin inhibits atherosclerotic plaque destabilization/rupture in mice by regulating the recruitment of inflammatory monocytes. *Circulation* 2014;**129**:896–906.
152. Pergola PE, Raskin P, Toto RD, Meyer CJ, Huff JW, Grossman EB, Krauth M, Ruiz S, Audhya P, Christ-Schmidt H, Wittes J, Warnock DG. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. *N Engl J Med* 2011;**365**:327–36.
153. de Zeeuw D, Akizawa T, Agarwal R, Audhya P, Bakris GL, Chin M, Krauth M, Lambers Heerspink HJ, Meyer CJ, McMurray JJ, Parving HH, Pergola PE, Remuzzi G, Toto RD, Vaziri ND, Wanner C, Warnock DG, Wittes J, Chertow GM. Rationale and trial design of bardoxolone methyl evaluation in patients with chronic kidney disease and type 2 diabetes: the occurrence of renal events (BEACON). *Am J Nephrol* 2013;**37**:212–22.
154. Goicoechea M, de Vinuesa SG, Gomez-Campdera F, Aragoncillo I, Verdalles U, Mosse A, Luno J. Serum fibrinogen levels are an independent predictor of mortality in patients with chronic kidney disease (CKD) stages 3 and 4. *Kidney Int Suppl* 2008:S67–70.
155. Kumon Y, Hosokawa T, Suehiro T, Ikeda Y, Sipe JD, Hashimoto K. Acute-phase, but not constitutive serum amyloid A (SAA) is chemotactic for cultured human aortic smooth muscle cells. *Amyloid* 2002;**9**:237–41.
156. Jones SA, Horiuchi S, Topley N, Yamamoto N, Fuller GM. The soluble interleukin 6 receptor: mechanisms of production and implications in disease. *FASEB J* 2001;**15**:43–58.
157. Xing Z, Gauldie J, Cox G, Baumann H, Jordana M, Lei XF, Achong MK. IL-6 is an antiinflammatory cytokine required for

controlling local or systemic acute inflammatory responses. *J Clin Invest* 1998;**101**:311–20.
158. Raj DS. Role of interleukin-6 in the anemia of chronic disease. *Semin Arthritis Rheum* 2009;**38**(5):382–8.
159. Stenvinkel P, Heimburger O, Jogestrand T. Elevated interleukin-6 predicts progressive carotid artery atherosclerosis in dialysis patients: association with *Chlamydia pneumoniae* seropositivity. *Am J Kidney Dis* 2002;**39**:274–82.
160. Rao M, Guo D, Perianayagam MC, Tighiouart H, Jaber BL, Pereira BJ, Balakrishnan VS. Plasma interleukin-6 predicts cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 2005; **45**:324–33.
161. Biasucci LM, Liuzzo G, Fantuzzi G, Caligiuri G, Rebuzzi AG, Ginnetti F, Dinarello CA, Maseri A. Increasing levels of interleukin (IL)-1Ra and IL-6 during the first 2 days of hospitalization in unstable angina are associated with increased risk of in-hospital coronary events. *Circulation* 1999;**99**:2079–84.
162. Girndt M, Kaul H, Sester U, Ulrich C, Sester M, Georg T, Kohler H. Anti-inflammatory interleukin-10 genotype protects dialysis patients from cardiovascular events. *Kidney Int* 2002;**62**:949–55.
163. Balakrishnan VS, Guo D, Rao M, Jaber BL, Tighiouart H, Freeman RL, Huang C, King AJ, Pereira BJ. Cytokine gene polymorphisms in hemodialysis patients: association with comorbidity, functionality, and serum albumin. *Kidney Int* 2004;**65**: 1449–60.
164. Nilsson J, Jovinge S, Niemann A, Reneland R, Lithell H. Relation between plasma tumor necrosis factor-alpha and insulin sensitivity in elderly men with non-insulin-dependent diabetes mellitus. *Arterioscler Thromb Vasc Biol* 1998;**18**:1199–202.
165. Ridker PM, Rifai N, Pfeffer M, Sacks F, Lepage S, Braunwald E. Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction. *Circulation* 2000;**101**:2149–53.
166. Egido J, Gomez-Chiarri M, Ortiz A, Bustos C, Alonso J, Gomez-Guerrero C, Gomez-Garre D, Lopez-Armada MJ, Plaza J, Gonzalez E. Role of tumor necrosis factor-alpha in the pathogenesis of glomerular diseases. *Kidney Int Suppl* 1993;**39**: S59–64.
167. Carrero JJ, Ortiz A, Qureshi AR, Martin-Ventura JL, Barany P, Heimburger O, Marron B, Metry G, Snaedal S, Lindholm B, Egido J, Stenvinkel P, Blanco-Colio LM. Additive effects of soluble TWEAK and inflammation on mortality in hemodialysis patients. *Clin J Am Soc Nephrol* 2008;**4**:110–8.
168. Grainger DJ, Metcalfe JC, Grace AA, Mosedale DE. Transforming growth factor-beta dynamically regulates vascular smooth muscle differentiation in vivo. *J Cell Sci* 1998;**111**(Pt 19): 2977–88.
169. Segal R, Fine LG. Polypeptide growth factors and the kidney. *Kidney Int Suppl* 1989;**27**:S2–10.
170. Bruchfeld A, Qureshi AR, Lindholm B, Barany P, Yang L, Stenvinkel P, Tracey KJ. High Mobility Group Box Protein-1 correlates with renal function in chronic kidney disease (CKD). *Mol Med* 2008;**14**:109–15.
171. Tang WH, Brennan ML, Philip K, Tong W, Mann S, Van LF, Hazen SL. Plasma myeloperoxidase levels in patients with chronic heart failure. *Am J Cardiol* 2006;**98**:796–9.
172. Zhang R, Brennan ML, Fu X, Aviles RJ, Pearce GL, Penn MS, Topol EJ, Sprecher DL, Hazen SL. Association between myeloperoxidase levels and risk of coronary artery disease. *J Am Med Assoc* 2001;**286**:2136–42.
173. Pugin J, Heumann ID, Tomasz A, Kravchenko VV, Akamatsu Y, Nishijima M, Glauser MP, Tobias PS, Ulevitch RJ. CD14 is a pattern recognition receptor. *Immunity* 1994;**1**:509–16.
174. Wiedermann CJ, Kiechl S, Dunzendorfer S, Schratzberger P, Egger G, Oberhollenzer F, Willeit J. Association of endotoxemia with carotid atherosclerosis and cardiovascular disease: prospective results from the Bruneck Study. *J Am Coll Cardiol* 1999;**34**: 1975–81.
175. Stoll LL, Denning GM, Weintraub NL. Potential role of endotoxin as a proinflammatory mediator of atherosclerosis. *Arterioscler Thromb Vasc Biol* 2004;**24**:2227–36.
176. Panichi V, Paoletti S, Mantuano E, Manca-Rizza G, Filippi C, Santi S, Taccola D, Donadio C, Tramonti G, Innocenti M, Casto G, Consani C, Sbragia G, Franzoni F, Galetta F, Panicucci E, Barsotti G. In vivo and in vitro effects of simvastatin on inflammatory markers in pre-dialysis patients. *Nephrol Dial Transplant* 2006;**21**:337–44.
177. Brull DJ, Sanders J, Rumley A, Lowe GD, Humphries SE, Montgomery HE. Impact of angiotensin converting enzyme inhibition on post-coronary artery bypass interleukin 6 release. *Heart* 2002;**87**:252–5.
178. Gunnell J, Yeun JY, Depner TA, Kaysen GA. Acute-phase response predicts erythropoietin resistance in hemodialysis and peritoneal dialysis patients. *Am J Kidney Dis* 1999;**33**:63–72.
179. Sarnak MJ, Coronado BE, Greene T, Wang SR, Kusek JW, Beck GJ, Levey AS. Cardiovascular disease risk factors in chronic renal insufficiency. *Clin Nephrol* 2002;**57**:327–35.
180. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 1999;**55**:648–58.
181. Ballmer PE, McNurlan MA, Grant I, Garlick PJ. Down-regulation of albumin synthesis in the rat by human recombinant interleukin-1 beta or turpentine and the response to nutrients. *JPEN J Parenter Enteral Nutr* 1995;**19**:266–71.
182. Steensberg A, Febbraio MA, Osada T, Schjerling P, van Hall G, Saltin B, Pedersen BK. Interleukin-6 production in contracting human skeletal muscle is influenced by pre-exercise muscle glycogen content. *J Physiol* 2001;**537**:633–9.
183. Febbraio MA, Steensberg A, Keller C, Starkie RL, Nielsen HB, Krustrup P, Ott P, Secher NH, Pedersen BK. Glucose ingestion attenuates interleukin-6 release from contracting skeletal muscle in humans. *J Physiol* 2003;**549**:607–12.
184. Higuchi T, Kuno T, Takahashi S, Kanmatsuse K. Influence of dialysis membranes on interleukin-1 beta and interleukin-1 receptor antagonist production by peripheral blood mononuclear cells. *Artif Organs* 1997;**21**:265–71.
185. Lopez-Gomez JM, Perez-Flores I, Jofre R, Carretero D, Rodriguez-Benitez P, Villaverde M, Perez-Garcia R, Nassar GM, Niembro E, Ayus JC. Presence of a failed kidney transplant in patients who are on hemodialysis is associated with chronic inflammatory state and erythropoietin resistance. *J Am Soc Nephrol* 2004;**15**:2494–501.
186. Nassar GM, Fishbane S, Ayus JC. Occult infection of old nonfunctioning arteriovenous grafts: a novel cause of erythropoietin resistance and chronic inflammation in hemodialysis patients. *Kidney Int Suppl* 2002:49–54.

QUESTIONS AND ANSWERS

Question 1

A 52-year-old African-American man with CKD was seen in the nephrology clinic. He complained of fatigue and diffuse joint pain. He denied any urinary symptoms. On physical examination, he was afebrile; his blood pressure was 154/98 mm Hg with a pulse rate of 78 beats per minute. Oral cavity was normal. No lymphadenopathy was noted nor was there any focus of infection. His current medications include amlodipine 10 mg/day, asprin 75 mg daily, and a multivitamin.

The following laboratory investigations were obtained:

WBC 4.7, neutrophils 31%, hemoglobin 9.8 g/dL
Albuminuria by spot urine albumin:creatinine ratio (UACR): 3.1 g/day
BUN: 32 mg/dL
Serum creatinine (S[Cr]): 2.5 mg/dL
Glucose: 289 mg/dL.
HbAIC: 9%
hsCRP 4.5 mg/L

Which one of these statements is true?

A. Stable patients with CKD who are not yet on dialysis do not have elevated CRP
B. A single measurement of CRP has no clinical significance. Multiple measurements are required to determine the level of inflammation in a given patient
C. The contribution of traditional risk factors for inflammation such as age, sex, obesity, and diabetic status are minimal and attenuated by the presence of CKD
D. Proteinuria is an independent predictor of inflammation

Answer: D[3]

A is not correct. Plasma levels of cytokines are not significantly different in dialysis patients and CKD patients not yet on dialysis.[5]

B is not true. CRP levels fluctuate over time, but baseline CRP levels correlate with time-averaged CRP measurements and the median of serial CRP values in patients with kidney disease.[47]

C is not true. Older age, male sex, obesity, and diabetic status are associated with inflammation in patients with CKD.[3]

Question 2

The same patient returns for a follow-up visit six months later. His blood pressure remains elevated at 158/94 mm Hg. Laboratory investigations showed WBC 4.2, hemoglobin 9.7 g/dL. Total cholesterol 230 mg/dL, BUN 30 mg/dL, S[Cr] 2.8 mg/dL, K+ 3.4 mEq/dL, HCO3- 21 mEq/L, Ca++ 9.6 mg/dL, PO_4 5.2 mg/dL, hsCRP 5.2 mg/L. Albuminuria by spot UACR suggests urinary losses of 3.4 g/day

Choose the most appropriate response

A. Lisinopril will not reduce albuminuria and preserve GFR in this patient
B. Besides a cardioprotective effect, statins therapy may reduce inflammation in this patient
C. Sevelamer has no advantage over calcium-based phosphate binders in reducing systemic inflammation in CKD patients
D. Pirfenidone will be an established adjunct therapy, which should be considered in this patient, to slow the progression of CKD

Answer: B

B is correct. Treatment with statins reduces CRP and proinflammatory cytokine levels in patients with and without CKD.[176]

A is not correct. Preliminary evidence indicates that ACE inhibitor treatment is associated with reduction in markers of inflammation.[177,178]

C is not correct. Treatment with sevelamer hydrochloride lowers circulating biomarkers of inflammation in patients with CKD.

D is not correct. Studies in human subjects and animal models suggest that pirfenidone has antifibrotic properties, but it has a number of adverse effects precluding clinical use.

Question 3

The patient subsequently underwent angioplasty with stent placement for acute myocardial infarction. He was started on atorvastatin 40 mg/day and metoprolol 50 mg twice daily. Laboratory investigation showed WBC 4.4, hemoglobin 9.7 g/dL. Total cholesterol 170 mg/dL. BUN 34 mg/dL, S[Cr] increased to 3.1 mg/dL, hsCRP 4.9 mg/L, S[Alb] decreased to 3.1 g/dL. Fibrinogen was 4 g/L.

Which of the following statements is correct?

A. Augmented inflammation in CKD contributes to accelerated atherogenesis in CKD
B. S[Alb] is a marker of nutrition. Nutrient supplementation alone is sufficient to improve the level of S[Alb] in this patient
C. In CKD patients, cytokines are derived exclusively from macrophages and adipocytes
D. Excess inflammation is this patient is due to decreased clearance of cytokines. There is insufficient evidence that cytokines contribute to the progression of CKD beyond traditional risk factors

Answer: A

A is correct. In an analysis that applied the Framingham risk equation to a population with CKD, the predicted CVD risk was similar to and not substantially higher than that of the general population,[179] leading to the speculation that traditional risk factors may have a qualitatively and quantitatively different risk relationship with CVD in CKD patients compared with the general population. Several studies have demonstrated a relationship between chronic inflammation and presence of atherosclerosis and CV mortality in patients with CKD and ESRD.[52,180]

B is not correct. In addition to being nutritionally modulated, albumin is also a negative acute-phase protein. Ballmer et al.[181] showed that proinflammatory cytokines stimulated total liver protein synthesis, but decreased albumin synthesis rate and also inhibited nutrient-induced increases in albumin synthesis

C is not correct. Human skeletal muscle cells have the ability to express a variety of cytokines, including IL-6.[19,182] Muscle-derived IL-6 functions as an exocrine hormone, exerting its effect on the liver and adipose tissue.[183]

D is not correct. Cytokine production by mononuclear cells in undialyzed CKD patients and in patients treated with maintenance hemodialysis is increased.[184] There is evidence that many inflammatory cytokines and chemokines play significant roles in the progression of CKD. They may be potential therapeutic targets.

Question 4

The patient returned after 3 months and had no specific complaints except fatigue. On examination he appeared pale. His blood pressure was 138/74 mm Hg. Laboratory investigations showed WBC 4.2, hemoglobin 7.9 g/dL. Total cholesterol 130 mg/dL. BUN 34 mg/dL, S[Cr] 3.4 mg/dL, hsCRP 5.2 mg/L. He had hypochromic microcytic anemia. Iron profile and PTH were appropriate.

Which of the statement is true?

A. The primary function of hepcidin is host defense against infection
B. This patient will show a robust response to erythropoiesis-stimulating agents
C. With EPO therapy, the patient will effectively utilize iron for hematopoiesis
D. Reducing inflammation will improve EPO hyporesponsiveness in this patient

Answer: D

D is correct. Reducing inflammation (such as removal of a rejected kidney allograft[185] or nonfunctioning arteriovenous grafts with occult infection[186]) and treatment directed toward reducing inflammation improve response to EPO therapy.

A is not correct. In addition to its antimicrobial properties, hepcidin is the main regulator of iron metabolism and controls both the amount of dietary iron absorbed in the duodenum and iron release by reticuloendothelial cells. Elevated serum hepcidin levels in CKD may contribute to the development and severity of anemia and to resistance to erythropoiesis-stimulating agents.

B is not correct. EPO resistance is manifested in the presence of elevated cytokines and positive acute-phase response.[178]

C is not correct. There is a functional iron deficiency in patients with CKD. Iron is not effectively utilized for hematopoiesis.

CHAPTER

25

Genetics and Chronic Kidney Disease

Nicholette D. Palmer[a], *Fiona E. Karet Frankl*[b], *Etty Kruzel-Davila*[c], *Barry I. Freedman*[d]

[a]Department of Biochemistry, Wake Forest School of Medicine, Medical Center Boulevard, Winston–Salem, NC, United States; [b]Department of Medical Genetics and Division of Renal Medicine, University of Cambridge, Cambridge, United Kingdom; [c]Department of Nephrology, Rambam Health Care Campus, Rappaport Faculty of Medicine and Research Institute, Technion—Israel Institute of Technology, Haifa, Israel; [d]Department of Internal Medicine; Section on Nephrology, Wake Forest School of Medicine, Medical Center Boulevard, Winston–Salem, NC, United States

Abstract

Several genes associated with the development of chronic glomerular and tubulointerstitial kidney diseases have been detected. Recent developments include an improved understanding of potential mechanisms involved in nondiabetic glomerulosclerosis, including apolipoprotein L1 gene (*APOL1*)-associated nephropathy, as well as autosomal dominant tubulointerstitial kidney disease. The identification of genes associated with diabetic kidney disease has proven more challenging. Nephropathy susceptibility genes are changing the classification of common complex kidney diseases, offering new insights into pathogenesis and providing hope for novel treatments. This chapter reviews genetic associations and mechanisms of injury in diabetic and nondiabetic glomerular and tubulointerstitial kidney diseases.

INTRODUCTION

The past decade has seen advances in the identification of genes associated with chronic kidney disease (CKD) and improved methodologies for detecting associated gene variants. Linkage analyses useful for detecting genomic regions coinherited with a trait in families, genome-wide association studies (GWAS), and candidate gene association studies capable of detecting common variants in unrelated cases and controls samples, and admixture mapping (useful for detecting associated variants more common in one ancestral population of admixed groups) have all been performed in CKD. Major breakthroughs include the identification of a newly recognized spectrum of nondiabetic apolipoprotein L1 gene (*APOL1*)-associated nephropathy, untangling of structural and signaling pathways involved in maintaining the delicate glomerular filtration barrier critical for preventing glomerulosclerosis, and identification of mutations producing rare interstitial kidney diseases. Nephropathy susceptibility genes have altered the classification of common complex kidney disease, offer new insights in pathogenesis, and provide hope for novel treatments.

STEROID-RESISTANT NEPHROTIC SYNDROME

Nephrotic syndrome (NS) is characterized by proteinuria caused by disruption of the glomerular filtration barrier. Approximately 10%–20% of affected children and 40% of affected adults exhibit steroid-resistant nephrotic syndrome (SRNS).[1] This disorder manifests histologically as focal segmental glomerulosclerosis (FSGS) or as the early-onset developmental variant "diffuse mesangial sclerosis" (DMS). These histologic variants may progress to end-stage renal disease (ESRD). A mutation in the nephrin gene (*NPHS1*) was the first to be reported to cause early-onset NS.[2] Since then, mutations in more than 50 genes causing FSGS have been identified. The rate of mutation detection is inversely correlated with age. Approximately 30% detection rates are seen in individuals with SRNS less than 25 years old.[1] Mutations in genes with recessive inheritance (e.g., *NPHS1*, *LAMB2*, and *PLCEI*) usually manifest as SRNS in early childhood with DMS.

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00025-5

Mutations in other genes with recessive inheritance (podocin or *NPHS2*) or genes with dominant inheritance (e.g., *ACTN4*, *TRPC6*, *INF2*, *ANLN*, and *ARHGAP24*) lead to late childhood/adult-onset SRNS with FSGS. The sole exception is dominant *WT1* mutations presenting in early childhood.[1] Notably, the inheritance mode of R229Q in *NPHS2* deviates from the classic autosomal recessive paradigm. This mutation is innocuous in homozygotes and only pathogenic when associated with another specific C-terminal *NPHS2* mutation (compound heterozygous), exerting a dominant-negative effect through altered dimerization and mislocalization of the protein.[3]

Some mutations causing NS manifest a heterogeneous syndromic phenotype. The best example is *WT1*, where mutations in the KTS domain (deletion of lysine−threonine−serine) cause Frasier syndrome with streak gonads and pseudohermaphroditism and harbor increased risk for gonadoblastoma in XY phenotypic females or lead to isolated NS in XX phenotypic females. In contrast, missense mutations can cause Denys−Drash syndrome with pseudohermaphroditism and Wilms tumor or isolated NS.[1]

The proteins encoded by the NS-causing genes have coalesced to complexes and cellular pathways in podocytes, including podocyte slit membrane components (*NPHS1*, *NPHS2*, *CD2AP*, *PLCE1*), laminin/integrin signaling components (*LAMB2* and *ITGA3*), actin-binding proteins (*ACTN4*, *INF2*, *MYO1E*, and *ANLN*), Rho-like small GTPase regulatory cluster (*RHO/RAC/CDC42*, *ARHGAP24*, *ARHGDIA*, *KANK1*, 2, and 4, *FAT1*, *MAGI2*, *TNS2*, *DLC1*, *CDK20*, *ITSN1*, *ITSN2*), lysosomal proteins (lysosomal integral membrane protein type-2, encoded by *SCARB2*), calcium signaling (*TRPC6*), transcription factors (*WT1*, *LMX1B*, and *SMARCAL1*), proteins of coenzyme Q10 biosynthesis (*COQ2*, *COQ6*, *PDSS2*, and *ADCK4*), and nuclear pore complex components (*NUP93/107/205* and *EXPORTIN5*).[1,4,5]

Although the majority of patients with NS and monogenic mutations rarely respond to steroid treatment or immunomodulation, exceptions exist. Steroid-sensitive nephrotic syndrome (SSNS) caused by mutations in the *EMP2* gene can respond to glucocorticoids.[1] The absence of *EMP2* upregulates caveolin-1 in podocytes, and this phenotype is ameliorated by glucocorticoid therapy.[6] Furthermore, NS due to mutations in *PLCE1*, *NUP93*, *TRPC6*, or regulators of Rho-like GTPase may partially respond to steroid or cyclosporine A treatment.[1,4,5] Therefore, resistance and sensitivity to steroid and calcineurin inhibitors represent a phenotypic spectrum of FSGS, reflecting the pleiotropic effects of the medications on podocyte biology.

In the case of mutations in genes encoding proteins essential for coenzyme Q10 biosynthesis in SRNS (*COQ2*, *COQ6*, *ADCK4*, or *PDSS2*), treatment with coenzyme Q10 may be warranted.[1] Eplerenone may also ameliorate NS in individuals harboring *ARHGDIA* mutations through modulation of Rac I−mineralocorticoid interactions.[1,4,5,7]

Mutations in genes that lead to clinical phenocopies of SRNS, such as cystinosis, hyperoxaluria, or Fabry's disease, can also require specific therapy. Although these disorders may present with proteinuria, edema, and CKD, mutations in these genes would be missed in panel sequencing because they are not canonical NS genes. The ability to detect mutations in genes that represent phenocopies of NS is an advantage of whole exome sequencing.[7] Patients with monogenic forms of FSGS known to confer resistance to immune modulation therapy should avoid unnecessary immune-modulating therapy.[1] Appropriate selection and counseling of potential living-related kidney donors should be based on causative mutations, especially in families harboring a dominant mutation with variable penetrance.[1,7] Mutations associated with kidney disease recurrence following kidney transplantation due to antibody formation (e.g., mutations leading to the absence of nephrin, which can trigger antibody formation against the "neoantigen" nephrin in the allograft) should be identified to direct immunomodulatory therapy that may ameliorate recurrence.[8]

CKD affects approximately 10% of the population worldwide. Heritability of impaired kidney function in the general population is estimated to range between 29% and 46%.[9] GWAS investigate the contribution of multiple common gene variants to CKD, each with a potentially small effect. In contrast to candidate gene studies, GWAS offer an unbiased hypothesis-free approach with the potential to identify novel therapeutic targets. The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium provided the basis for the first CKD GWAS meta-analysis that identified several CKD-associated single-nucleotide polymorphisms (SNPs) for the estimated glomerular filtration rate (eGFR) computed using serum creatinine concentration (S[Cr]) [eGFRcrea] and cystatin C levels [eGFRcys]).[10] The three most significant SNPs were located near or within genes encoding for the uromodulin/Tamm−Horsfall protein (*UMOD*), shroom family member 3 (*SHROOM3*), and stanniocalcin-1(*STC1*).[10] Subsequent GWAS have been conducted on the CKDGen Consortium including 16 population-based cohorts joined to the CHARGE Consortium,[11] as well as European and cross-ethnic cohorts.[12] These GWAS expanded the spectrum of CKD-associated

variants. More than 50% of associated SNPs shared effects across all ethnicities.[12,13] Cohorts that examined CKD progression or ESRD discovered fewer associated variants due to the reduced power of dichotomous disease traits versus continuous clinical measures.

The CKD-associated SNPs shared several common pathways including kidney development and nephrogenesis (*ALMS1*, *VEGFA*, and *DACH1*), podocyte function and glomerular filtration barrier formation (*DAB2* and *VEGFA*), angiogenesis (*VEGFA*), solute transport (*SLC7A9* and *SLC34A1*), kidney metabolism (*PRKAG2*, *GCKR*, and *LASS2*), primary cilia function (*ALMS1, GCKR/IFT172, PARD3B*), drugs and toxin metabolism (*NAT8*), and ion channels (*KCNQ1)*.[11–14] Some loci are located near genes causing monogenic kidney diseases, such as autosomal dominant tubulointerstitial kidney disease or ADTKD (*UMOD*), nephrolithiasis (*SLC7A9*), phosphaturia (*SLC34A1*), tubular dysfunction (*SLC7A9* and *DAB2*), cystinuria (*SLC7A9*), ciliopathies (*ALMS1*), and congenital kidney disease (*DACH1*).[11,12] This suggests that rare disruptive mutations in genes causing monogenic kidney diseases are at the extreme of a continuum with common regulatory variants in these genes that elicit subtler effects on kidney function. Many variants are located at regulatory regions, specifically enhancer regions that control the expression of multiple genes in kidney tissues[12,14,15] (also called expression quantitative trait loci [eQTL]). The majority of these are enriched for pathways important in kidney development, transmembrane transporter activity, kidney structure, regulation of glucose metabolism, and lysosomal proteins.[12,14,15]

A GWAS meta-analysis for the urine albumin:creatinine ratio (UACR) combined data from >80,000 individuals in the international CKDGen and CARe Consortia, including populations of European and African descent. The authors identified a common missense variant (allele frequency 0.1 in the general population) in the cubilin gene (*CUBN*) associated with UACR and incident microalbuminuria, but not eGFR.[16] The association was also significant in diabetic patients from the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications.[16] Cubilin mediates reuptake of filtered albumin in the proximal tubule. The involvement of this variant in albuminuria is further supported by the fact that rare *CUBN* mutations can cause Imerslund–Gräsbeck syndrome, resulting in megaloblastic anemia with varying degrees of proteinuria.

Coupling genomics and metabolomics in genome-wide association analyses of metabolites can illuminate mechanisms underlying CKD progression. It may be difficult, however, to discriminate between causality versus consequence of CKD.[17] Moreover, even an extremely high correlation between an eQTL and a GWAS signal does not establish causality and requires functional studies to determine the biologic significance of discovered variants. In this regard, the *UMOD* locus stands out by virtue of cell biology studies, animal models, and data from human populations. These studies provide evidence that common eGFR-associated GWAS variants upstream of *UMOD* induce salt-sensitive hypertension and kidney disease by increasing renal uromodulin expression, leading to increased activation of the sodium cotransporter NKCC2 (Table 25.1).[18] Individuals with the genetic *UMOD* risk variant have higher Tamm–Horsfall protein concentrations in their urine and are at increased CKD risk.[19] The role of *UMOD* as causal mediator in CKD has also been demonstrated by a Mendelian randomization approach.[20]

Similarly, *SHROOM3* function was characterized in various experimental models. SHROOM3 participates in maintaining the glomerular filtration barrier in rat models of kidney disease and zebrafish (Table 25.1).[21] Additionally, *SHROOM3* null mice show glomerular abnormalities and podocyte pathology, and heterozygous mice develop adult-onset glomerulosclerosis.[22] In spite of these findings suggesting a loss-of-function mechanism, significantly elevated *SHROOM3* expression in kidney allografts homozygous for the CKD risk SNP (rs17319721) was correlated with increasing allograft fibrosis and reduced posttransplant eGFR.[23] SHROOM3 expression is enhanced by rs17319721, functioning by a cis-acting element with specific TCF7L2-dependent enhancer binding β-catenin and facilitating TGF-β downstream profibrotic pathways.[23] Prokop et al. demonstrated that rs17319721 increased transcription of the *SHROOM3* short isoform in the kidney with altered binding of TCF7L2.[24] Further studies are required to explore the biologic mechanism of this intronic variant. Table 25.1 lists additional variants whose causality in CKD have been partially validated.[13,15,25,26]

Although large sample sizes are required for the detection of variants associated with a heterogenous kidney phenotype such as CKD, identification of variants associated with well-defined kidney disease phenotypes can be achieved with moderately sized cohorts. Genetic variants in the phospholipase A2 receptor 1 gene (*PLA2R1*) and *HLA-DQA1/HLA-DQB1* locus were identified by GWAS in European patient/control cohorts with membranous nephropathy (MN).[27] The odds ratio for the homozygous risk genotype for HLA-DQA1 was 20.2 (95% confidence interval [CI], 5.5 to 74.4) and for *PLA2R1* was 4.2 (95% CI, 2.4 to 7.5). Moreover, the odds ratios were additive, with each additional copy of the risk allele at either locus being 78.5, compared to individuals homozygous for the protective genotype at both loci. Follow-up clinical studies

TABLE 25.1 List of Gene Variants With Potential Roles in Chronic Kidney Disease (CKD)

Gene	GWAS Allele	Chr	Organism/Model	Genetic Manipulation	Experimental Results	Other Supportive Findings	References
UROMODULIN	rs4293393	16	Mice	Transgenic mice	Salt-sensitive hypertension. Age-dependent renal lesions similar to elderly individuals homozygous for UMOD promoter risk variants. Uromodulin causes hypertension by activation of the renal sodium cotransporter NKCC2	Carriers of UMOD promoter risk variants have higher UMOD expression in kidney and urine versus carriers of protective haplotype. Pharmacological inhibition of NKCC2 more effective in lowering blood pressure in hypertensive patients homozygous for UMOD promoter risk variants than others	18,19
SHROOM3	No specific SNP examined	4	Rat	Congenic rat introgression of Brown Norway rat Shroom3 gene onto fawn-hooded hypertensive (FHH) rat genetic background; 13 protein coding variants in the SHROOM3 gene	Improvement of glomerular function		21
	rs181194611-rare coding variant-P1244L	4	Zebrafish	Knockdown and rescue	Wild-type SHROOM3a allele, not FHH SHROOM3 allele or P1244L mRNA, rescued glomerular defects induced by knockdown of endogenous SHROOM3	P1224L attenuates the interaction of SHROOM3 with 14-3-3, suggesting alterations to the Hippo pathway, a known mediator of CKD	21,24
	rs17319721	4	Podocytes and HEK293T	CRISPR/Cas9 to generate the homozygous A allele	Disrupted allele binding to transcription factor TCF7L2 in podocyte cell nuclear extracts and altered transcription levels of SHROOM3 short isoform in cultured cells		24
	No specific SNP examined	4	Mice	Knockdown of SHROOM3	Impaired kidney development and morphology Abrogation of interstitial fibrosis in mice with unilateral ureteric obstruction	Rs7319721 allele in donors correlated with increased SHROOM3 expression in allografts, and with fibrosis and decreased kidney function. rs17319721 functions as a cis-acting expression quantitative trait locus of SHROOM3 that facilitates TGF-B1 signaling	22,23

KCNQ1	No specific SNP examined	11	Zebrafish	Knockdown	Abnormal kidney development		13
CDH23	No specific SNP examined	10	Zebrafish	Knockdown	Severe edema 72h after gentamicin compared with controls; no gross renal abnormalities before gentamicin		25
GALNT11	No specific SNP examined	7	Zebrafish	Knockdown	Severe edema 72h after gentamicin compared with controls; no gross renal abnormalities before gentamicin		25
ACP1	No specific SNP examined	2	Zebrafish	Knockdown	Altered glomerular gene expression and renal tubule morphology in the embryonic kidney; impaired kidney function		26
S0S2	No specific SNP examined	14	Zebrafish	Knockdown	Altered glomerular gene expression and renal tubule morphology in the embryonic kidney; impaired kidney function		26
MANBA	No specific SNP examined	4	Zebrafish	Knockdown	Renal tubule defects and pericardial edema	The expression of MANBA was significantly lower in kidneys of subjects with risk alleles	15

GWAS, genome-wide association studies; *SNP*, single-nucleotide polymorphism.

demonstrated that 73% of individuals carrying these susceptibility genotypes had anti-PLA2R antibodies, whereas antibodies were absent in carriers of protective genotypes.[12] In addition, immunosuppressive therapy was more effective in patients carrying the combined susceptibility genotype, likely by decreasing anti-PLA2R levels.[12] Cui et al. investigated the HLA class II gene profile in Chinese MN patients and controls.[28] *DRB1*1501* and *DRB1*0301* were independent risk alleles for MN and associated with circulating anti-PLA2R antibodies. Strong gene−gene interactions were identified between rs4664308(A) (top intronic SNP within *PLA2R1*) and *HLA-DRB1*1501/DRB1*0301*. Structural models identified specific amino acids in these HLA loci that facilitate interactions with T-cell epitopes of PLA2R and thereby enhance antibody production, thus translating the GWAS findings to an immunologic mechanism.[28]

SSNS accounts for 80% of cases of childhood NS. Gbadegesin et al. reported association of an *HLA-DQA1* (rs1129740) risk allele with SSNS in children of South Asian and European ancestry.[29] A trans-ethnic GWAS discovered three independent risk SNPs for pediatric SSNS.[30] Two were located in noncoding regions in *HLA-DQB1* and *HLA-DRB1* and the third in the 3′ untranslated region of the butyrophilin like-2 gene (*BTNL2*) within introns of *HCG23* and *LOC101929163* (long noncoding RNA). Increased burden of risk alleles across independent loci was associated with higher odds of SSNS, younger age at onset and increased odds of complete remission. Reassuringly, one of the leading SNPs (rs1063348) was in strong linkage disequilibrium with the SNPs identified by Gbadegesin et al.[29] and was associated with decreased HLA transcript expression across tissues, including glomeruli.[30] These studies establish SSNS as another primary glomerular disease caused by genetic susceptibility that leads to immune dysregulation.

Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis worldwide. IgAN is most prevalent in East Asians, less frequent in individuals of European ancestry, and relatively rare in individuals of African ancestry. Although most cases are sporadic, familial aggregation of biopsy-proven IgAN is widely recognized.[31] GWAS in European, Han Chinese, and Asian cohorts identified multiple IgAN susceptibility loci.[31−33] Implicated pathways include antigen processing and presentation (*HLA-DQB1*, *DRB1*, and *DQA1* loci on chromosome 6p21), mucosal immunity and maintenance of the intestinal mucosal barrier, activation of mucosal IgA production, NF-κB signaling and defense against intracellular pathogens (chromosomes 22q12 *LIF, OSM, HORMAD2, MTMR3* loci, 8p23 *alpha-DEFENSIN* locus, 17p13 *TNFSF13* locus, 6p21 *PSMB9/TAP1* locus, 1p13 *VAV3* locus, 9q34 *CARD9* locus, 16p11 *ITGAM-ITGAX* locus, 3q27 *ST6GAL1* locus, 8q22.3 *ODF1-KLF10*, and 11p11 *ACCS* locus), and the alternative complement pathway (chromosome 1q32 complement factor H [*CFH/CFHR*] locus).[31−33] GWAS findings generated new insights into the pathogenesis of IgAN, highlighting a common role for the intestinal immune response and the alternative complement pathway. A genetic risk score has been developed, explaining nearly 5% of disease variance. The polygenic score paralleled the known East−West gradient in disease risk (Asian > Northern Europe > African ancestry population) and was similar to other autoimmune diseases correlated with North−South risk. One standard deviation increase in score was associated with nearly 50% increase in disease risk, translating into a fivefold increase in risk between individuals from the extremes of the risk score distribution and strongly correlated with distance from the African continent and disease prevalence.[31] Moreover, the cumulative effect of multiple genic risk loci was correlated with age at diagnosis, specifically after ancestry adjustment.[32] Risk variants at 3q27 and 11p11 also show strong association with mRNA expression levels of *ITGAX, ITGAM, ACCS, EXT2,* and *ST6GAL1* in peripheral blood cells, whereas allele frequencies of the risk variants within *ST6GAL1*, *ACCS*, and *DEFENSIN* correlate with geographical variation in IgAN prevalence.[33] This suggests that many common risk alleles influence IgAN through effects on regulation of gene expression.

Some GWAS findings provide insights from an evolutionary perspective. For example, the lead *UMOD* risk variant (allele T at rs4293393) associated with CKD and hypertension is the ancestral allele. Its prevalence ranges from 70% to 80% in Africans and Europeans to 90% in East Asians. The ancestral allele shows a global correlation with bacterial diversity (the Human Genome Diversity Project) and the prevalence of antibiotic resistance to gram-negative uropathogens.[19] High urinary levels of uromodulin are associated with lower risk for urinary tract infection (UTI) in older adults from the Cardiovascular Health Study, independent of traditional risk factors. These studies suggest that the ancestral *UMOD* allele has been kept at a high frequency due to its protective effect against UTI, which mainly affects young women and has important fitness and reproductive consequences.[19]

Regarding geospatial correlations in IgAN, Kiryluk et al. elegantly demonstrated a strong association of the IgAN genetic risk score with local pathogen diversity.[32] In the final combined model, only helminth diversity and geographical location were independently associated with the IgAN genetic risk score. This suggests that helminth infection serves as a potential source of selective pressure that has shaped the genetic diversity at IgAN risk loci.[32]

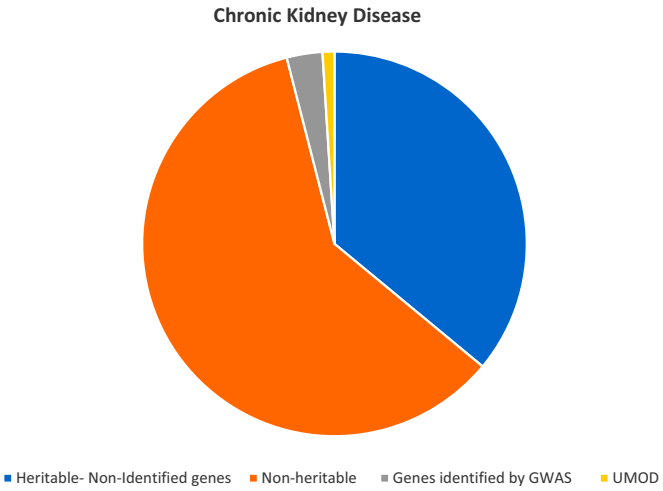


FIGURE 25.1 Heritability of glomerular filtration rate. Heritability of impaired kidney function in the general population ranges between 29% and 46% (*blue*, *yellow* and *gray*). The identified variants by genome-wide association studies explain less than 4% of the eGFRcrea variance (*gray* and *yellow*), including *UMOD* that explains approximately 1% (*yellow*). There is an unexplained gap of nonidentified genes termed the "missing heritability" (*blue*).

Notwithstanding these discoveries, identified variants in CKD GWAS explain <4% of eGFRcrea variance.[19,34] The small effect size leaves an unexplained gap that has been termed "missing heritability" (Figure 25.1).[26,34] Therefore, questions persist related to the extent by which genetic variation currently undetectable through GWAS (e.g., rare variants and non-SNP variants), as well as gene–environment interactions, explains missing heritability.

APOLIPOPROTEIN L1 GENE (*APOL1*)-ASSOCIATED NONDIABETIC KIDNEY DISEASE

Approximately 50% of patients with advanced renal disease have nondiabetic forms of nephropathy.[35] Disease etiologies were often unknown, as renal biopsies are performed mainly in patients with nephrotic syndrome or heavy proteinuria. Those with isolated hematuria or low level proteinuria were deemed less likely to have a treatable lesion identified on biopsy, beyond the usual supportive measures of controlling blood pressure and lipids and use of renin–angiotensin–aldosterone system (RAAS) blockade. Renal diagnoses in the absence of histology were most often ascribed to the effects of essential hypertension in those with low to absent proteinuria or IgAN or familial hematuria in those with isolated hematuria.

TABLE 25.2 Apolipoprotein L1 (*APOL1*)-Associated Forms of Nephropathy in African Ancestry Populations

Idiopathic focal segmental glomerulosclerosis (FSGS)
Solidified glomerulosclerosis with interstitial fibrosis and vascular injury (historically termed hypertension-attributed nephrosclerosis)
HIV-associated nephropathy and other forms of collapsing glomerulopathy
Sickle cell disease-associated nephropathy
Lupus nephritis-associated kidney disease
Shorter renal allograft survival in recipients of *APOL1* high-risk genotype deceased donor kidneys
Nephropathy in living kidney donors with *APOL1* high-risk genotypes

A paradigm shift occurred in 2010 with demonstration that the complex disorders idiopathic FSGS, focal global glomerulosclerosis (FGGS) with interstitial scarring and vascular changes (previously labeled "hypertension-attributed nephrosclerosis"), and human immunodeficiency virus-associated nephropathy (HIVAN) were strongly associated with two coding variants in the *APOL1* gene on chromosome 22q13 in patients of African ancestry.[36,37] Individuals inheriting two *APOL1* nephropathy risk variants (G1: nonsynonymous coding variant 342G:384M and G2: 6 bp deletion) have impressive 29-89-, 17-, and 7.3-fold increases in risk for HIVAN, FSGS, and nondiabetic (hypertension-attributed nephrosclerosis) ESRD, respectively. Odds ratios of this magnitude had not been seen before in complex disorders. Development of nephropathy in patients with sickle cell disease and progressive lupus nephritis (LN) were subsequently found to reside within the *APOL1* disease spectrum (Table 25.2).[38]

The *APOL1* discovery explained the marked familial aggregation of ESRD in African American families, with disparate causes of ESRD.[39] More than 30% of incident African American patients with ESRD had close relatives already receiving renal replacement therapy (RRT), excluding families with Mendelian disorders such as polycystic kidney disease.[40] Far greater numbers had relatives with CKD not yet undergoing RRT. Familial clustering of ESRD is present, albeit weaker in European Americans. Importantly, aggregation of different types of CKD was often observed in African American families. This is in dramatic contrast to other populations groups, where one type of kidney disease (e.g., IgAN or diabetic kidney disease [DKD]) clusters in families. Together, these findings supported the existence of an overarching kidney failure susceptibility gene in African American families, with multiple potential inciting events (such as the presence of antinuclear antibodies or HIV infection) that could trigger progressive kidney failure.[39]

The *APOL1* encodes APOL1, a secretory protein that associates with trypanosome lytic factor in plasma.[41] Selection for *APOL1* renal-risk variants confers ability to kill *Trypanosoma brucei rhodesiense*, a parasite causing African sleeping sickness.[36] This spectrum of kidney disorders is of great public health and personal importance. Population ancestry differences in *APOL1* allele frequency explain the excess risk of nondiabetic ESRD in African Americans, relative to European Americans, as well as the poorer allograft survival of deceased donor kidneys transplanted from donors of African ancestry.[42] The mechanisms whereby *APOL1* gene renal-risk variants lead to podocyte loss and clinically evident nephropathy remain unknown. APOL1 exhibits homology with the bacterial colicin family of toxic proteins that possess pore-forming capability.[43] APOL1 G1 and G2 nephropathy risk-variant proteins are toxic to (or form ion channels for cations or anions) in cell membranes and membrane-bound organelles.[44,45] Mitochondrial dysfunction with energy depletion appears to be an early manifestation of *APOL1*-associated renal injury and can result from damage to the mitochondrial membrane.[46,47] Other potential mechanisms of renal cell injury reported in animal and cell-based models of *APOL1*-associated nephropathy include defective endocytic fusion with lysosomes altering intracellular trafficking,[48–50] autophagic cell death,[51] and intracellular potassium depletion with secondary activation of stress kinases.[45] A single mechanism of renal injury has not been seen in all disease models. It is uncertain how closely transgenic and *in vitro* models reproduce the human condition.

Experiments in transgenic mice expressing the *APOL1* G0 (wild type) variant, and the G1 and G2 renal-risk variants in podocytes and renal tubule cells, reveal that expression of only the renal-risk variants in podocytes led to albuminuria and podocyte loss.[48,52] This study demonstrated that *APOL1* renal-risk variants cause kidney disease and are not simply disease-associated. In contrast, plasma *APOL1* protein concentrations are not associated with presence (vs. absence) of nephropathy.[53,54] Presence of two *APOL1* renal-risk variants in kidney donors, but not kidney transplant recipients, is associated with more rapid failure of the transplanted kidney and a higher risk for post-donation kidney disease in living kidney donors.[54,55] These studies support intrinsic renal expression of *APOL1*, not circulating APOL1 protein, as important in the pathogenesis of nephropathy.

APOL1 nephropathy variants are present in approximately 52% of African Americans; 13% of whom possess two renal-risk variants and are at increased risk for kidney disease.[36] These frequencies are higher in people from West Africa.[56] G1 and G2 risk variants are virtually absent in Asians, Europeans, and non-admixed Hispanic populations, suggesting relatively recent origin (<10,000 years ago), after early humans departed the African continent. Importantly, approximately 20% of individuals possessing two *APOL1* renal-risk variants will develop nephropathy, and only a minority of kidneys transplanted from *APOL1* high-risk donors fail shortly after transplantation. These findings suggest that requisite gene–gene or gene–environment interactions are necessary for development of kidney disease.[57] *APOL1*-associated nephropathy in individuals with low levels of proteinuria appears resistant to treatment with RAAS blockade or aggressively lowering blood pressure, although these therapies are often indicated in affected patients to reduce the risk of cardiovascular complications.[58]

HIV infection is a major environmental trigger for *APOL1*-associated kidney disease, with a population attributable risk of 70%. This means that 7 of 10 cases of HIVAN would not develop in the absence of the G1 and G2 *APOL1* variants.[59] The kidney serves as a reservoir for HIV replication, and HIV infection produces the highest attack rates of nephropathy among genetically susceptible hosts. Approximately half of patients with untreated HIV infection and two *APOL1* nephropathy variants develop nephropathy.[60] Aberrant replacement of partially differentiated podocytes develops in HIVAN, and renal histology reveals the most aggressive form of FSGS, the collapsing variant. Individuals with these risk variants but without HIV infection develop different renal histologic patterns of FSGS, solidified glomerulosclerosis with interstitial fibrosis and vascular changes, whereas others develop nonspecific FSGS variants. It has been proposed that different second hits likely determine the final renal histopathologic lesion in the spectrum. Solidified glomerulosclerosis has the lowest levels of proteinuria and slowest rate of loss of kidney function, whereas FSGS nonspecific variants appear to have intermediate degrees of proteinuria and rates of nephropathy progression relative to HIVAN and other forms of collapsing glomerulopathy.[61]

Based on this paradigm, there is reason for optimism. Rates of HIVAN have fallen dramatically with the introduction of highly active antiretroviral therapy (HAART).[35] This supports the concept that successful treatment of an environmental exposure can prevent kidney disease in those at high genetic risk. In this sense, HAART can be viewed as a novel treatment for kidney disease, whereas conventional therapies (i.e., blood pressure control and RAAS inhibitors) failed to reliably halt the progression of *APOL1*-associated nephropathy in cases with hypertension-attributed kidney disease,

predominantly solidified glomerulosclerosis, in the National Institute of Health-Sponsored African American Study of Kidney Disease and Hypertension (AASK).[58,62] In contrast to HIVAN, the inciting cause(s) of solidified glomerulosclerosis remain unknown.

As HIV infection is a modifiable risk factor for nephropathy, non-HIV viral infections were sought to identify other pathogens potentially influencing risk of kidney disease *via* interaction with *APOL1*. *APOL1* genotypes and presence of urine JC polyoma virus (JCV) were assessed for their joint impact on parameters of kidney disease phenotypes in first-degree relatives of African Americans with nondiabetic nephropathy.[63] Adjusting for family age at start of ESRD, sex and ancestry, an additive model testing for presence of urinary JCV genomic DNA and *APOL1* genotype (recessive) were *negatively* associated with high cystatin C concentration ($p = 0.006$), albuminuria ($p = 0.0002$), and presence of nephropathy based on low estimated eGFR or albuminuria ($p = 0.000017$). Thus, African Americans at risk for kidney disease based on two *APOL1* risk variants and with JC viruria had a *lower* prevalence of kidney disease. Similar results have been observed in nondiabetic African Americans without *APOL1*-mediated kidney diseases, suggesting that urinary tract JCV replication may be a marker for reduced host immune system activation and lower risk of renal fibrosis.[64] Additional work is being done to detect modifiable environmental factors that modulate risk of *APOL1*-associated nephropathy. Elevated levels of soluble urinary plasminogen activator receptor (suPAR) have been reported to interact with *APOL1* risk genotypes and contribute to kidney disease.[65]

Several genes and genomic regions have been reported to interact with *APOL1* (gene−gene interactions) to alter the risk for nondiabetic ESRD, including *NPHS2* (podocin), *SDCCAG8* (serologically defined colon cancer antigen 8), *BMP4* (bone morphogenetic protein 4), *GSTM1* (glutathione-*S*-transferase-μ1), and *UBD* (ubiquitin D or FAT10).[57,66,67] However, a recent GWAS in 4306 African Americans (2650 with nondiabetic ESRD; 1656 nonnephropathy controls) failed to identify significant genome-wide associations with ESRD beyond *APOL1*.[68] In addition, no SNP showed significant genome-wide evidence of interaction with *APOL1*. Thus, although variants with small individual effects likely exist, results from a large GWAS in African American nondiabetic ESRD suggest that *APOL1*−environment interactions may be of greater clinical importance in triggering nephropathy than *APOL1* interactions with other genes and SNPs.

APOL1 appears to impact CKD progression to ESRD more strongly than the initiation of nephropathy. This concept is based on weaker association with mild renal phenotypes (albuminuria and slightly reduced GFR) compared to ESRD.[56,58,69,70] The longitudinal AASK, Chronic Renal Insufficiency Cohort, and Coronary Artery Risk Development in Young Adults studies strongly support *APOL1* playing a predominant role in the progression of albuminuria and kidney disease.[71,72]

In the future, there will likely be benefits to screening potential living and deceased kidney donors for *APOL1* renal-risk variants. *APOL1* risk genotypes in deceased organ donors have been associated with shorter renal allograft survival in retrospective studies.[42,55,73] A multivariate analysis in 1153 kidney transplants from 624 unique African-American deceased kidney donors revealed that donor *APOL1* genotypes had similar (or stronger) effects on the time to renal allograft failure than did the degree of match for human leukocyte antigens (HLA), cold ischemia time, recipient sensitization based on panel reactive antibodies, expanded (vs. standard) criteria donors, and donor or recipient age.[55] Of great concern are the potential effects of *APOL1* renal-risk genotypes in healthy living African American kidney donors. Doshi et al. examined post-donation kidney health in 136 African American living kidney donors with median 12 year follow-up. Fourteen percent (19/136) had two *APOL1* renal-risk variants.[74] Living kidney donors with high-risk *APOL1* genotypes had significantly faster rates of decline in eGFR compared to those with low-risk genotypes. In addition, 67% of *APOL1* high-risk donors had a follow-up eGFR $<60\ mL/min/1.73\ m^2$ versus 36% of *APOL1* low-risk donors ($p < 0.01$) and 11% developed ESRD compared with 0% of low-risk donors ($p = 0.02$). Case reports document that recipients of kidneys from living donors with *APOL1* renal-risk genotypes can develop proteinuric FSGS with subsequent loss of the graft. The National Institutes of Health recently initiated the "*APOL1* Long-term Kidney Transplant Outcomes Network" (APOLLO) to prospectively assess effects of *APOL1* in kidney transplantation. APOLLO results have the potential to optimize the allocation of kidneys from deceased African American donors, reduce rates of organ discard, and maximize safety after living kidney donation in populations with recent African ancestry.[75,76] Hence, *APOL1* genotypic data will likely alter the clinical practice of transplant medicine, as the search for a cure in *APOL1*-associated nephropathy continues.

INHERITED TUBULOINTERSTITIAL NEPHROPATHIES

Rather than primarily affecting glomerular or excretory function, a variety of inherited disorders involve dysfunction of one or more segments of the renal tubule downstream of the glomerulus. These disorders cause

specific physiological disturbances that may or may not also be associated with CKD and anatomical abnormalities (e.g., cysts). Those that classically lead to CKD are discussed below. Typically, the primary defect is in only one cell type or nephron segment, and this "geography" is how such disorders are typically classified, when understood (Table 25.3). The downstream consequence and final common pathway is interstitial fibrosis with ensuing CKD.

Tubulointerstitial nephropathies can also be considered from a mechanistic perspective. Although disease-causing mutations may result in complete failure of transcription and thus loss of function because of RNA instability or failure to translate the encoded protein, many others will result in structurally and/or functionally abnormal proteins. Such mutated proteins may be either misfolded and therefore intracellularly retained or, because of disturbed protein–protein interactions be intracellularly misrouted, reach the "wrong" domain of the polarized plasma membrane, be prematurely internalized, or not be retrieved from the cell surface for appropriate disposal.

ADTKD is a classic protein misfolding disorder. Newly synthesized proteins are normally assembled in the endoplasmic reticulum (ER), where a quality control and degradation system ensures that only properly folded and assembled proteins pass through the Golgi apparatus before being directed to their final cellular destination.[77] If proteins fail to assume their correct structure and are unfolded or misfolded because of amino acid alterations consequent on specific mutations, they are retained in the ER by the association of chaperone molecules and become destined for ubiquitination and degradation by the 26S proteasome. The ER retains mutant proteins in many diseases. Loss of function can manifest as intracellular accumulation of abnormal protein that should have been delivered to the cell surface. This has been documented in ADTKD.

Until recently, a variety of disease names and overlapping phenotypes caused confusion among clinicians and geneticists concerning these disorders. The relevant genes are *UMOD, MUC1, REN,* and *HNF1b*. *REN*-associated disease is the rarest. A 2015 KDIGO conference stated "Multiple names have been proposed for these disorders, including Medullary Cystic Kidney Disease (MCKD) type 2, Familial Juvenile Hyperuricemic Nephropathy (FJHN), or Uromodulin-Associated Kidney Disease (UAKD) for *UMOD*-related diseases, and MCKD type 1 for the disease caused by *MUC1* mutations.[78] The multiplicity of these terms, and the fact that cysts are not pathognomonic, creates confusion. [We] propose adoption of a new terminology for this group of diseases using the term 'Autosomal Dominant Tubulointerstitial Kidney Disease' (ADTKD) appended by a gene-based sub-classification, and suggest diagnostic criteria. Implementation of these recommendations is anticipated to facilitate recognition and characterization of these monogenic diseases."

Typically, ADTKD presents with early-onset renal impairment and relentless progressive renal shrinkage due to fibrosis. Hyperuricemia is usually (but not always) present, gout is seen in about 67%, diabetes mellitus may be present, and sometimes impaired urinary concentrating capacity is detected.[79] Urinalysis reveals bland sediment and only modest proteinuria. It was thought that reduced urate excretion was a defining feature, but it is not always present.[80] Some forms of ADTKD are associated with medullary cysts, and this led to misdiagnosis as nephronophthisis. The hallmark of these disorders is interstitial fibrosis on biopsy, out of proportion with the degree of renal impairment and often with secondary glomerulosclerosis.

A family history should be sought but is often unclear. From the genotype–phenotype perspective, *REN* mutations are particularly associated with anemia, *HNF1β* with hypomagnesemia, and *HNF1β* and *MUC1* with prominence of cysts. In patients with *UMOD* mutations, radiographic evidence of renal cysts is only found in approximately 33%.[81] Although none of the causative genes encode uric acid transporters, anecdotes suggest that allopurinol therapy may delay ESRD. However, there is no proven disease-modifying therapy beyond blood pressure control.[79]

UMOD encodes uromodulin (UMOD, Tamm–Horsfall protein), the most abundant protein in normal human urine and the major component of urinary casts. Uromodulin is secreted into the urine solely by cells of the thick ascending limb, is heavily glycosylated, and has a variety of proposed functions including protecting epithelial integrity in the loop of Henle and bladder, modulating inflammatory responses *via* cytokine binding, inhibiting calcium oxalate crystal aggregation (although it is notable that ADTKD is *not* associated with stone formation), and preventing urinary infections. Its primary function remains under debate.[82]

All known *UMOD* mutations alter protein structure, as its sequence is rich in highly conserved cysteine residues, particularly in exons 4/5 leading to a high degree of intramolecular cross-linkage. The majority of *UMOD* mutations are missense involving exon 4, with others in exons 3/5/7/8, most involving a cysteine residue. One recurrent insertion–deletion mutation replaces five amino acids with four novel ones.[83] Some mutations correlate with age at ESRD onset.[84]

Mutated UMOD polymerizes within the ER, leading to cellular stress and apoptosis.[85] The mechanism of interstitial fibrosis is not well understood but could potentially include mis-secretion basolaterally or triggering of local inflammatory responses.[86] As with other dominantly inherited disorders, knocking out *UMOD* in

TABLE 25.3 Tubulointerstitial Nephropathies

	Inheritance	Gene(s)	Chronic Kidney Disease	OMIM	Usual Consequence of Mutation[a]
PROXIMAL TUBULE					
Dent disease	XR	*CLCN5* *OCRL1*	Yes	300009 300555	Defective endosomal acidification/recycling Defective endosomal acidification/recycling
Lowe syndrome	XR	*OCRL1*	Yes	309000	
Cystinuria	AR,AD	*SLC3A1* *SLC7A9*	(Yes) (Yes)	220100	Intracellular retention Mistargeting
Primary renal Fanconi syndrome	AD	Unknown *EHHADH*	No No	134600 615605	Mistargeting
Hypophosphatemic nephrolithiasis	AD	*SLC34A1*	No	612286	Intracellular retention
Hereditary hypophosphatemic rickets	AR	*SLC9A3R1* *SLC34A3*	No No	612287 241530	
Infantile hypercalcemia	AR	*SLC34A1*	No	616963	
LOOP OF HENLE					
ADTKD	AD	*UMOD* *MUC1* *REN*	Yes Yes Yes	603860 174000 613092	Intracellular retention Intracellular retention
Bartter syndromes	AR	*SLC12A1* *KCNJ1* *CLCNKB* *BSND*	(Yes) (Yes) (Yes) (Yes)	601678 241200 607364 602522	Intracellular retention Intracellular retention Intracellular retention Intracellular retention
DISTAL CONVOLUTED TUBULE					
Gitelman syndrome	AR	*SLC12A3*	No	263800	Intracellular retention/glycosylation defect
Primary hypomagnesemia	AD AR	*FXYD2* *EGF*	No No	154020 611718	Intracellular retention Impaired basolateral sorting
Familial hypomagnesemia–hypercalciuria syndrome	AR	*CLDN16* *CLDN19*	Yes Yes	248250 248190	Intracellular retention/mistargeting Intracellular retention/mistargeting
Gordon syndrome	AD	*WNK1* *WNK4* *CUL3* *KLHL3*	No	145260	Overexpression Loss of kinase activity Impaired ligand binding
COLLECTING DUCT					
Liddle syndrome	AD	*SCNN1B* *SCNN1G*	(Yes) (Yes)		Retention at plasma membrane Retention at plasma membrane
Distal renal tubular acidosis	AD AR	*SLC4A1* *ATP6V1B1* *ATP6V0A4*	Yes (Yes) (Yes)	179800 267300 602722	Inappropriate plasma membrane targeting Uncoupling of ATPase and H^+ pumping
Nephrogenic diabetes insipidus	AR XR	*AQP2* *AVPR2*	No	125800 304800	Inappropriate plasma membrane targeting Intracellular retention

Continued

TABLE 25.3 Tubulointerstitial Nephropathies—cont'd

	Inheritance	Gene(s)	Chronic Kidney Disease	OMIM	Usual Consequence of Mutation[a]
GENERALIZED RENAL EXPRESSION/EXTRA-RENAL ORIGIN					
Zellweger syndrome	AR	*PEX1*	No	214100	Mistargeting
Dominant hypocalcemia	AD	*CASR*	No	601198	Inappropriate activation
Hypercalciuric hypocalcemia	AD	*GNA11*	No	615361	Increased CASR sensitivity
Hypocalciuric hypercalcemia	AD	*CASR*	No	145980	Reduced sensitivity
		GNA11	No	145981	Reduced CASR sensitivity
Cystinosis	AR	*CTNS*	Yes	219800	Mistargeting
Primary hyperoxaluria (liver)	AR	*AGXT*	Yes	259900	Mistargeting
		GRHPR	Yes	260000	
		HOGA1	No	613616	

[a]*other than loss of transcription/translation; (Yes) = CKD if untreated.*

mice does not reproduce the human phenotype. Rather, evidence from transgenic models supports that misfolding delays intracellular trafficking of wild-type protein, i.e., a dominant-negative effect of heterozygous mutations.[87]

In *MUC1*-associated ADTKD, mutations involve insertion of a single cytosine in the terminal portion of a canonical 60-mer repeat in the encoded protein Mucin-1.[88] This produces a frameshift leading to the protein lacking several important domains. For technical reasons, these mutations are often impossible to identify, but immunohistological methods for diagnosis have recently been developed.[89]

Mucin-1 differs from UMOD in being a transmembrane glycoprotein expressed more broadly, including in the distal convoluted tubule. It is thought to play a role in cell adhesion, recognition, and/or cytoprotection.[90] As with UMOD, mutant MUC1 is improperly processed, and intracellular trafficking is delayed. Knockout mice have an essentially normal phenotype, again consistent with a dominant-negative mechanism.

Positional cloning identified the renin gene *REN* as mutated and segregating with disease in three families with AD progressive renal failure and a phenotype consistent with MCKD, including hyperuricemia.[91] Anemia in affected children is erythropoietin-responsive, and hyperkalemia may be present, both consistent with impaired renin activity. *REN* mutations are either deletion or substitution of a single leucine residue in the signal sequence for renin, which leads to failure of secretion, with evidence of activated ER stress. It is hypothesized that this produces accelerated apoptosis in juxtaglomerular apparatus cells, with impaired development and nephron loss.

Finally, some families with an apparent *UMOD/MUC1* phenotype harbor mutations in the HNF1β gene.[92] HNF1β is a transcription factor with a wide variety of target genes. A recent study showed ablation of *HNF1β* in renal epithelial cells led to epithelial–mesenchymal transition and aberrant TGF-*β* signaling with resultant renal fibrosis.[93]

Abnormalities of membrane transporter disposal also result in disease. Liddle syndrome is an autosomal dominant form of secondary hypertension, in which elevated blood pressure may be evident from childhood.[94] Hypertensive end-organ damage is frequent if untreated. Its genetic basis and physiology were revealed after one of Liddle's original kindred developed ESRD. A strong family history of premature death from cardiovascular or kidney disease is typical.[95] Liddle's patients behaved as if they had primary hyperaldosteronism with volume expansion, high-normal sodium, and hypokalemic metabolic alkalosis. Measured aldosterone and plasma renin activity, however, were markedly suppressed.

Liddle's syndrome is associated with mutations of either the beta or gamma subunit of the epithelial sodium channel (ENaC), which mainly affect the C-terminus, and lead to high constitutive levels of ENaC activity.[96] The normal C-termini of ENaC subunits contain motifs recognized by the ubiquitylation machinery responsible for internalizing the protein and targeting it for disposal. Compromised integrity of this domain leads to an apparent gain of function because too many ENaC trimers become stuck in the apical collecting duct plasma membrane.[97] This accounts for increased sodium absorption in the cortical collecting duct and hypertension with physiologically appropriate reductions in renin and aldosterone. Blood pressure reduction and normalization of plasma potassium levels can be achieved using amiloride or triamterene, but not spironolactone. An important cofactor is concomitant restriction of dietary sodium, because the drugs compete with sodium for binding to ENaC.

Disorders of intracellular protein misrouting include Dent disease (DD) and Lowe syndrome. DD and the

oculocerebrorenal syndrome of Lowe (LS) are X-linked recessive disorders with closely overlapping renal phenotypes, characterized by proximal tubulopathy with low molecular weight proteinuria and aminoaciduria, albuminuria, variable urinary losses of glucose and phosphate, hypercalciuria, renal stones, nephrocalcinosis, and progressive CKD.[98] They differ in LS having additional severely disabling extra-renal features (cataracts, other eye disorders leading to blindness, mental retardation, muscular hypotonia, and other neurologic disturbances) and renal tubular acidosis.

About 60% of cases of DD are associated with mutations in the *CLCN5* gene encoding a voltage-gated chloride transporter (CLC5) expressed in the proximal tubule, medullary thick ascending limb, and intercalated cells of the collecting tubule. LS is consistently associated with *OCRL1* mutations encoding phosphatidylinositol-4,5-bisphosphate-5-phosphatase. Approximately 15% of patients with clinical DD have mutations in the Lowe *OCRL1* gene, and some have mild extra-renal abnormalities. Both proteins participate in pathways affecting trafficking of membrane proteins. Both are found on endosomes and OCRL1 in the *trans*-Golgi network (TGN). Loss of function results in defective endosomal recycling and/or abnormal TGN function, particularly in the proximal tubule.[99]

Cystinosis resides in the lysosomal storage disorder family. It is characterized by an accumulation of cystine within all organs, as a result of a deletion or mutation in *CTNS*, which encodes the widely expressed lysosomal cystine transporter, cystinosin.[100] Although there are milder forms, children with infantile cystinosis appear normal at birth, but demonstrate failure to thrive at less than 1 year, with proximal tubular dysfunction followed by rickets. Renal insufficiency is inevitable before teenage years, if untreated, and at a median 20 years when therapy with cysteamine is initiated early. Deposition of cystine crystals in the cornea occurs early, causing photophobia and painful corneal erosions. In the second to third decades, hypothyroidism, hypogonadism, diabetes, myopathy, and central nervous system deterioration are often observed.

Cystinosin is required to clear cystine (released from the hydrolytic cleavage of peptides) from lysosomes into the cytosol. Cystinosin contains a classic tyrosine-based lysosomal targeting signal (GYDQL) in its C-terminal tail. Unusually, mutation analysis revealed a novel second signal, the core of which is YFPQA situated in the fifth loop of the protein. Alterations within either domain result in misdirection of cystinosin to the plasma membrane.[100] Thus, cystinosis may arise either because cystinosin is absent or nonfunctional (e.g., with truncation mutations) or because it cannot traffic normally to the lysosome, as reported in missense mutations in the fifth loop or C-terminal truncations.[101,102]

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis is a very rare autosomal recessive condition characterized by progressive renal failure often evident in childhood, with nephrocalcinosis, hypomagnesemia with renal magnesium wasting, kidney stones, UTI, and in some cases ophthalmologic abnormalities such as severe myopia, macular colobomas, horizontal nystagmus, and chorioretinitis.[103] Positional cloning led to the identification of the paracellin-1 (claudin 16) gene on chromosome 3q as causative.[104] Subsequently, another family member, claudin 19, was found to be mutated in patients with ocular abnormalities.[105] Claudins are expressed at the tight junction between cells of the medullary thick ascending limb and are important in maintaining selectivity of paracellular cation transport, facilitating the reabsorptive movement of magnesium and calcium driven by positive luminal potential. Mutations drive the protein away from tight junctions, in one case to lysosomes[106] and in another transiently to the plasma membrane until internalized.[107]

Distal renal tubular acidosis (dRTA) is a disease of defective urinary acidification, caused by dysfunction of intercalated cells (α-IC) in the collecting system. It is characterized by hyperchloremic hypokalemic metabolic acidosis with reduced urinary citrate excretion, metabolic bone disease, hypercalciuria, and nephrocalcinosis and/or nephrolithiasis, often with progressive CKD. Of the inherited forms (much rarer than acquired), autosomal dominant dRTA (ddRTA) generally presents later, and less severely than the recessive form.[108] Recessive dRTA is often associated with progressive and irreversible sensorineural hearing loss. Treatment for all forms of dRTA is alkali replacement, which corrects most biochemical abnormalities but does not improve hearing.

In the α-IC, protons are secreted into the urine by apical H^+ATPases, coupled to the reclamation of bicarbonate across the basolateral plasma membrane *via* the Cl-bicarbonate exchanger, AE1. Although recessive disease is heterogeneous, and accounted for by loss-of-function mutations in one of the apical H^+ATPase subunits, mutations in *SLC4A1* encoding AE1 are the only genetic cause of ddRTA reported to date.

Autosomal ddRTA is unlikely to result from simple haploinsufficiency, because AE1 mutations causing the autosomal dominant erythrocyte diseases hereditary spherocytosis and ovalocytosis (the red cell being the other site of expression of AE1) are not associated with defects in urine acidification. Second, dRTA-associated AE1 mutations demonstrate near-normal anion exchange function when expressed in *Xenopus* oocytes. Examination of missense mutations and an 11-amino acid truncation at the C-terminus, R901X, have demonstrated that while some mutants are retained intracellularly, others lose their normal basolateral localization

and end up partly or wholly at the apical surface by acquiring a novel targeting motif.[109,110] Mislocalization is predicted to disturb voltage locally and disrupt vectorial proton and bicarbonate transport. Further studies have shown that loss of C-terminal interactions with GAPDH and the sodium pump cause loss of AE1 retention at the cell surface.[111,112]

Type I primary hyperoxaluria (PH) is a rare autosomal recessive disorder characterized by high urinary oxalate excretion, progressive bilateral calcium oxalate stone formation, nephrocalcinosis, and progressive CKD by adulthood.[113] PH is primarily a liver disease, caused by functional defects of the liver enzyme alanine–glyoxylate aminotransferase (AGT). Catabolism of glyoxylate to glycine fails, leading to overuse of the alternate pathway by which oxalate is produced. The kidney is the only excretory pathway for oxalate, which cannot be further metabolized. Therapy with pyridoxine, phosphates, magnesium, and citrate has proven helpful.[113] Extra-renal oxalate deposits occur in later stages, including in cardiovascular tissues, bone, and retinae. AGT normally resides in peroxisomes. In some patients, mutations in the *AGT* gene on chromosome 2 do not cause loss of the protein, but instead result in mistargeting to the mitochondria, a highly unusual mechanism of disease.[114]

Approaches to diagnosis and therapy include careful phenotypic and biochemical assessments. These are important in narrowing the likely differential diagnosis in tubule–interstitial nephropathies. Clinical mutation analysis is increasingly available for many of the affected genes.

Unless noted, no specific therapy exists for many of these disorders. Treatment is conservative, focusing on control of hypertension and hyperuricemia, repletion of vitamin D, limiting salt (other than in salt-wasting disorders), and supplementing electrolyte deficiencies. Apart from hyperoxaluria (where combined liver–kidney transplantation is required), they do not recur in renal transplants, because they are inherent to the recipient kidneys.

DIABETIC KIDNEY DISEASE

DKD is a common microvascular complication of type 1 (T1D) and type 2 diabetes (T2D), leading to increased morbidity and premature mortality. The etiology of DKD is multifactorial, including an inherent genetic component supported by the familial aggregation of DKD and related intermediate phenotypes across European American, African American, Asian, and Pima Indian populations. In addition, there is a markedly higher risk for developing disease among certain racial and ethnic groups. These observations suggest the presence of genetic variation underlying the etiology of DKD.

Early reports attempting to decipher the genetic architecture of DKD focused on candidate gene studies and the assessment of SNPs, typically coding mutations which have an increased likelihood of being functionally implicated in disease, residing in genes with a plausible physiological role in disease. Among loci evaluated, the angiotensin-converting enzyme (*ACE*), aldo-keto reductase family 1 member B (*AKR1B1*), and ectonucleotide pyrophosphatase/phosphodiesterase one genes (*ENPP1*) have been implicated in DKD in individuals with T1D and T2D. ACE is part of the renin–angiotensin system and regulates blood pressure and hemodynamics. The genetic association observed resides with an insertion/deletion of a 287 base pair *alu* repeat sequence,[115] with the deletion associated with higher ACE activity thus hypothesized to alter renal hemodynamics.[116] AKR1B1 is part of the aldose reductase pathway. Among variants associated with DKD, a dinucleotide repeat upstream of the transcription start site has been shown to impact expression of AKR1B1, leading to its association with disease.[117] ENPP1, also referred to as plasma cell membrane glycoprotein (PC-1), plays a role in insulin resistance, through blockade of the tyrosine kinase activity of the insulin receptor with a substitution at amino acid 121 influencing protein–protein interactions and providing biological plausibility for involvement.[118] The apolipoprotein E (*APOE*) and peroxisome proliferator-activated receptor gamma genes (*PPARG*) have been associated with DKD in those with T2D. APOE plays a central role in lipid and lipoprotein metabolism, although the mechanism conferring risk of DKD remains controversial. PPARG affects renal hemodynamics and water and sodium transport. Although numerous candidate gene studies have been published, results have been largely inconsistent.[119] Among the limitations of this approach are a relatively naïve understanding of the pathophysiology, selection of a modest number of genetic variants which fail to comprehensively capture variation at the locus, and relatively small numbers of cases and controls which adversely impacts study power. Despite these limitations, individual candidate gene studies can contribute to larger, well-powered meta-analyses in an effort to identify and validate loci which contribute to DKD. The major advantage of the meta-analysis approach is an increase in sample size, thereby increasing study power to detect genetic associations of more nominal effect. This approach has been applied to DKD.[120] In a comprehensive review of the literature, 671 studies investigating DKD were identified with a subsequent meta-analysis identifying 21 variants significantly associated with DKD. Among the most significant findings, *ACE* was associated with disease among

patients with T1D and T2D and was the most intensively studied gene for DKD. Specific to T1D, the findings also highlighted *AKR1B1*, erythropoietin (*EPO*), and heparan sulfate proteoglycan 2 genes (*HSPG2*). Specific to T2D, additional loci included the *APOE* and carnosine dipeptidase 1 genes (*CNDP1*). Despite new insights, this methodological advance has the same limitations as candidate gene studies. In addition, these studies are negatively impacted by publication bias, which may overestimate the effect size and may also yield false negative associations owing to phenotypic heterogeneity as a result of imprecise phenotypic characterization among study participants.

In an effort to provide more comprehensive coverage of the genome in a pathophysiology agnostic manner, linkage studies of DKD have been explored. Linkage studies rely on clustering of affected individuals within families to examine cosegregation of the phenotype with regions of the genome. Through interrogation of genetic variation, typically microsatellite markers evenly spaced across the genome, regions of the genome which are coinherited with disease across generations can be identified. The first linkage analysis for DKD was performed among Pima Indian sibling pairs, where DKD was defined as the presence of overt proteinuria and/or macroalbuminuria in the setting of T2D.[121] The strongest linkage signal observed was at 7q32.3−33 with significant linkage at two microsatellite markers, log of the odds (LOD) score of 2.04, spanning 4.9 cM (approximately, 4.9 Mb). Among the genes with a plausible biological role were aldose reductase (*ALDR1*), T-cell receptor β-chain (*TCRBC*), and constitutive endothelial nitric oxide synthase genes (*NOS*). More contemporary linkage studies have extended the evaluation of linkage peaks and identified positional candidate genes for evaluation. The most notable example is a linkage analysis in Turkish kindred and Pima Indian families which identified a linkage peak on 18q22.3−23 with a LOD score of 6.6 spanning 8.5 cM (approximately, 2.9 Mb).[122] Among the positional candidate genes, the carnosinase genes, *CNDP1* and *CNDP2*, were identified as positional candidates related to their role in inhibition of oxidative stress and advanced glycation end products, thus, protecting against the adverse effects of hyperglycemia.[123] Among variants analyzed, a trinucleotide repeat in exon 2 of *CNDP1* was significantly associated with DKD and replicated in European Americans.[124] The allelic form containing five leucine repeats, referred to as CNDP1 Mannheim, was observed with increased frequency among controls and associated with lower serum carnosinase concentration, which is hypothesized to result in higher levels of carnosine.

More recent linkage scans for DKD have focused on quantitative intermediate phenotypes, e.g., eGFR and albuminuria, in an attempt to dissect the heterogeneous phenotype of DKD.[125−127] Results from linkage analysis require further investigation as they often span on the order of megabases. In such cases, positional candidate gene studies are required. The utility and significance of linkage analysis for DKD remains unclear, with identification of relatively few genetic determinants. The major advantage of family-based approaches such as linkage analysis is minimization of population stratification or systematic differences in allele frequencies among subpopulations. Thus, as an alternative application, family-based studies may be well-suited for the study of rare genetic variation derived from next generation sequencing studies, as the family-based design will enrich these variants beyond frequencies observed in the general population.

GWAS comprehensively interrogate the entire genome, with less reliance on family-based recruitment. These studies can be extended through imputation, a statistical methodology which estimates ungenotyped variation through the use of reference populations with extensive genetic data. The search for genetic susceptibility loci for DKD using the GWAS approach was first performed in a Japanese patient population with T2D.[128] Through the gene-based analysis of 80,000 SNPs, a variant in intron 18 of the engulfment and cell motility 1 gene (*ELMO1*) was identified for association with DKD. Interestingly, although ELMO1 plays a role in promotion of phagocytosis and cell migration, there was no prior evidence for a role in DKD. Among the pathophysiological phenotypes, expression of *ELMO1* was increased under hyperglycemic conditions, which may result in excess accumulation of extracellular matrix proteins and lead to development and progression of DKD.

An early GWAS for T1D-associated DKD was performed in the Genetics of Kidneys in Diabetes (GoKinD) cohort.[129] Although not meeting strict evidence for statistical significance, this analysis in 820 cases and 885 controls genotyped for 360,000 SNPs identified the 4.1 protein ezrin, radixin, moesin (FERM) domain containing 3 (*FRMD3*) and cysteinyl-tRNA synthetase genes (*CARS*) as putative DKD susceptibility genes with replication in an independent cohort. The cohort was subsequently leveraged for a large-scale meta-analysis composed of three existing collections with 6691 participants as part of the GEnetics of Nephropathy: an International Effort (GENIE) consortium.[130] Using GWAS with imputation, GENIE evaluated ∼2.4 million SNPs and identified two variants associated with ESRD: a SNP in the AF4/FMR2 family, member 3 gene (*AFF3*) and an intergenic SNP on 15q26 located between RGM domain family, member A (*RGMA*), and multiple C2 domains, transmembrane 2 genes (*MCTP2*). Extension of this work under the auspices of the SUrrogate markers for Micro- and Macrovascular hard endpoints

for Innovative diabetes Tools (SUMMIT) Consortium amassed 12,540 individuals with GWAS and imputation, but failed to identify genetic variants reaching stringent levels of statistical significance despite adequate study power, i.e., 80% power to detect a variant with a MAF>10% and an allelic odds ratio (OR) $\geq$1.55.[131] However, investigators did establish the narrow-sense heritability, i.e. phenotypic variance explained by genome-wide SNPs, of DKD in the setting of T1D at 35%. The genetic similarity calculated from array-based data used to estimate this narrow-sense heritability is broadly similar to earlier estimates from family-based studies.[132]

In an effort to further expand sample size, researchers investigating the genetic architecture of DKD in the setting of T2D have undertaken meta-analyses combining DKD in T1D and T2D to identify similar and distinct genetic features of these diseases. Using data from 6335 individuals with T2D, researchers established the narrow-sense heritability of DKD at 8%. In comparison to estimates derived from DKD in patients with T1D, these estimates strongly parallel the genetic basis of the diabetes phenotype. To investigate the genetic basis of DKD and related phenotypes, analysis included up to 40,340 subjects with diabetes (18,582 with DKD) for association of greater than nine million variants from GWAS with imputation. Although this study represents the largest study of the genetic basis of DKD for patients with T2D, there were no significant genetic associations for DKD following replication analysis. However, a novel locus, the gamma-aminobutyric acid receptor subunit rho-1 gene (*GABRR1*), was associated with microalbuminuria. *GABRR1* gene expression is upregulated in kidney biopsies from DKD subjects supporting a role in disease. This locus was not associated with DKD in subjects with T1D. With its focus on European and Asian populations, a potential limitation of this study was failure to include ethnic minority samples with increased incidence and prevalence of T2D, such as African Americans. Relative to European Americans, African Americans are more often affected by T2D and proteinuric kidney diseases such as FSGS. Although inclusion of these populations may increase study size and ultimately power to detect more modest genetic effects, improved phenotypic precision coupled with ascertainment of controls that lack clinical symptoms at advanced age would still be required.

Progress in identifying the genetic architecture underlying DKD has been arduous, with the realization that a single locus of large effect does not exist. A general consensus is that DKD is a polygenic disorder with multiple genetic loci, each contributing a modest effect. Beyond statistical implication of genetic variation for susceptibility to DKD, further work will be needed to identify the causal variant as comprehensive approaches relying on linkage analysis identify broad genomic regions, and array-based technologies capture only common variation representative of the regional genetic landscape. Thus, there is an increasing need for next generation sequence analysis of participants coupled with detailed phenotypic evaluation. To better dissect the heterogeneous disorder DKD, clinicians and researchers need to identify novel disease biomarkers beyond clinically used measures such as eGFR, albuminuria, blood urea nitrogen, uric acid, and S[Cr] to facilitate earlier diagnosis and establish novel therapeutic interventions.

A relatively new area of exploration to identify putative biomarkers is metabolomics. Metabolites are small molecule intermediates produced by metabolic processes within the cell. For research targeted to identify predictive biomarkers, metabolomic assessment of serum or urine represent appropriate, easily obtainable biologically relevant samples. For DKD in the setting of T1D[133] and T2D,[134] these types of studies are still in the early stages. Coupling these findings with existing genetic linkage and association approaches will provide a systematic approach to gain insight into the genetic modulation of relevant pathways and identify genetic susceptibility markers.

CONCLUSIONS

This chapter highlights recent breakthroughs in the genetic underpinning of rare Mendelian nephropathies and more common forms of kidney disease. Advances have been made in nondiabetic kidney disease, particularly FSGS, nonspecific forms of glomerulosclerosis, and tubulointerstitial kidney diseases. In comparison, genetic developments in DKD have lagged. Large meta-analyses reveal that kidney disease in patients with diabetes is polygenic. Although DKD associates with multiple genes, each appears to have a relatively small effect. Environmental factors including hyperglycemia play important roles in susceptibility to DKD.

These laboratory discoveries have led to advances in patient care. Select genetic forms of FSGS have been shown to respond to medical therapy, and *APOL1* genotyping may improve outcomes in kidney transplantation. Finally, novel therapies targeting the *APOL1* gene are under development to prevent kidney disease in populations with recent African ancestry. The genetics revolution has been of great benefit to the field of nephrology. It will help patients with and at risk for CKD.

References

1. Lovric S, Ashraf S, Tan W, Hildebrandt F. Genetic testing in steroid-resistant nephrotic syndrome: when and how? *Nephrol Dial Transplant* 2016;**31**(11):1802–13.
2. Kestila M, Lenkkeri U, Mannikko M, et al. Positionally cloned gene for a novel glomerular protein–nephrin–is mutated in congenital nephrotic syndrome. *Mol Cell* 1998;**1**(4):575–82.
3. Tory K, Menyhard DK, Woerner S, et al. Mutation-dependent recessive inheritance of NPHS2-associated steroid-resistant nephrotic syndrome. *Nat Genet* 2014;**46**(3):299–304.
4. Braun DA, Sadowski CE, Kohl S, et al. Mutations in nuclear pore genes NUP93, NUP205 and XPO5 cause steroid-resistant nephrotic syndrome. *Nat Genet* 2016;**48**(4):457–65.
5. Ashraf S, Kudo H, Rao J, et al. Mutations in six nephrosis genes delineate a pathogenic pathway amenable to treatment. *Nat Commun* 2018;**9**(1):1960.
6. Wan X, Chen Z, Choi WI, Gee HY, Hildebrandt F, Zhou W. Loss of epithelial membrane protein 2 aggravates podocyte injury via upregulation of caveolin-1. *J Am Soc Nephrol* 2016;**27**(4):1066–75.
7. Warejko JK, Tan W, Daga A, et al. Whole exome sequencing of patients with steroid-resistant nephrotic syndrome. *Clin J Am Soc Nephrol* 2018;**13**(1):53–62.
8. Holmberg C, Jalanko H. Congenital nephrotic syndrome and recurrence of proteinuria after renal transplantation. *Pediatr Nephrol* 2014;**29**(12):2309–17.
9. Fox CS, Yang Q, Cupples LA, et al. Genomewide linkage analysis to serum creatinine, GFR, and creatinine clearance in a community-based population: the Framingham Heart Study. *J Am Soc Nephrol* 2004;**15**(9):2457–61.
10. Kottgen A, Glazer NL, Dehghan A, et al. Multiple loci associated with indices of renal function and chronic kidney disease. *Nat Genet* 2009;**41**(6):712–7.
11. Kottgen A, Pattaro C, Boger CA, et al. New loci associated with kidney function and chronic kidney disease. *Nat Genet* 2010; **42**(5):376–84.
12. Wuttke M, Kottgen A. Insights into kidney diseases from genome-wide association studies. *Nat Rev Nephrol* 2016;**12**(9):549–62.
13. Liu CT, Garnaas MK, Tin A, et al. Genetic association for renal traits among participants of African ancestry reveals new loci for renal function. *PLoS Genet* 2011;**7**(9):e1002264.
14. Pattaro C, Teumer A, Gorski M, et al. Genetic associations at 53 loci highlight cell types and biological pathways relevant for kidney function. *Nat Commun* 2016;**7**:10023.
15. Ko YA, Yi H, Qiu C, et al. Genetic-variation-driven gene-expression changes highlight genes with important functions for kidney disease. *Am J Hum Genet* 2017;**100**(6):940–53.
16. Boger CA, Chen MH, Tin A, et al. CUBN is a gene locus for albuminuria. *J Am Soc Nephrol* 2011;**22**(3):555–70.
17. Kottgen A, Raffler J, Sekula P, Kastenmuller G. Genome-wide association studies of metabolite concentrations (mGWAS): relevance for nephrology. *Semin Nephrol* 2018;**38**(2):151–74.
18. Trudu M, Janas S, Lanzani C, et al. Common noncoding UMOD gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. *Nat Med* 2013;**19**(12): 1655–60.
19. Devuyst O, Pattaro C. The UMOD locus: insights into the pathogenesis and prognosis of kidney disease. *J Am Soc Nephrol* 2018; **29**(3):713–26.
20. Sjaarda J, Gerstein HC, Yusuf S, et al. Blood HER2 and uromodulin as causal mediators of CKD. *J Am Soc Nephrol* 2018;**29**(4): 1326–35.
21. Yeo NC, O'Meara CC, Bonomo JA, et al. Shroom3 contributes to the maintenance of the glomerular filtration barrier integrity. *Genome Research* 2015;**25**(1):57–65.
22. Khalili H, Sull A, Sarin S, et al. Developmental origins for kidney disease due to Shroom3 deficiency. *J Am Soc Nephrol* 2016;**27**(10): 2965–73.
23. Menon MC, Chuang PY, Li Z, et al. Intronic locus determines SHROOM3 expression and potentiates renal allograft fibrosis. *J Clin Invest* 2015;**125**(1):208–21.
24. Prokop JW, Yeo NC, Ottmann C, et al. Characterization of coding/noncoding variants for SHROOM3 in patients with CKD. *J Am Soc Nephrol* 2018;**29**(5):1525–35.
25. Gorski M, Tin A, Garnaas M, et al. Genome-wide association study of kidney function decline in individuals of European descent. *Kidney Int* 2015;**87**(5):1017–29.
26. Li M, Li Y, Weeks O, et al. SOS2 and ACP1 loci identified through large-scale exome chip analysis regulate kidney development and function. *J Am Soc Nephrol* 2017;**28**(3):981–94.
27. Stanescu HC, Arcos-Burgos M, Medlar A, et al. Risk HLA-DQA1 and PLA(2)R1 alleles in idiopathic membranous nephropathy. *N Engl J Med* 2011;**364**(7):616–26.
28. Cui Z, Xie LJ, Chen FJ, et al. MHC class II risk alleles and amino acid residues in idiopathic membranous nephropathy. *J Am Soc Nephrol* 2017;**28**(5):1651–64.
29. Gbadegesin RA, Adeyemo A, Webb NJ, et al. HLA-DQA1 and PLCG2 are candidate risk loci for childhood-onset steroid-sensitive nephrotic syndrome. *J Am Soc Nephrol* 2015;**26**(7): 1701–10.
30. Debiec H, Dossier C, Letouze E, et al. Transethnic, genome-wide analysis reveals immune-related risk alleles and phenotypic correlates in pediatric steroid-sensitive nephrotic syndrome. *J Am Soc Nephrol* 2018;**29**(7):2000–13.
31. Kiryluk K, Novak J, Gharavi AG. Pathogenesis of immunoglobulin A nephropathy: recent insight from genetic studies. *Annu Rev Med* 2013;**64**:339–56.
32. Kiryluk K, Li Y, Scolari F, et al. Discovery of new risk loci for IgA nephropathy implicates genes involved in immunity against intestinal pathogens. *Nat Genet* 2014;**46**(11):1187–96.
33. Li M, Foo JN, Wang JQ, et al. Identification of new susceptibility loci for IgA nephropathy in Han Chinese. *Nat Commun* 2015;**6**:7270.
34. Gorski M, van der Most PJ, Teumer A, et al. 1000 Genomes-based meta-analysis identifies 10 novel loci for kidney function. *Sci Rep* 2017;**7**:45040.
35. U.S. Renal Data System. *USRDS 2012 Annual Data Report, vol 1: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases*. 2012. 2012.
36. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010;**329**(5993):841–5.
37. Tzur S, Rosset S, Shemer R, et al. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. *Hum Genet* 2010; **128**(3):345–50.
38. Kruzel-Davila E, Wasser WG, Aviram S, Skorecki K. APOL1 nephropathy: from gene to mechanisms of kidney injury. *Nephrol Dial Transplant* 2016;**31**(3):349–58.
39. Freedman BI, Iskandar SS, Appel RG. The link between hypertension and nephrosclerosis. *Am J Kidney Dis* 1995;**25**(2):207–21.
40. Freedman BI, Volkova NV, Satko SG, et al. Population-based screening for family history of end-stage renal disease among incident dialysis patients. *Am J Nephrol* 2005;**25**(6):529–35.
41. Thomson R, Genovese G, Canon C, et al. Evolution of the primate trypanolytic factor APOL1. *Proc Natl Acad Sci U S A* 2014;**111**(20): E2130–9.
42. Reeves-Daniel AM, Depalma JA, Bleyer AJ, et al. The APOL1 gene and allograft survival after kidney transplantation. *Am J Transplant* 2011;**11**(5):1025–30.

43. Perez-Morga D, Vanhollebeke B, Paturiaux-Hanocq F, et al. Apolipoprotein L-I promotes trypanosome lysis by forming pores in lysosomal membranes. *Science* 2005;**309**(5733):469–72.
44. Bruno J, Pozzi N, Oliva J, Edwards JC. Apolipoprotein L1 confers pH-switchable ion permeability to phospholipid vesicles. *J Biol Chem* 2017;**292**(44):18344–53.
45. Olabisi OA, Zhang JY, VerPlank L, et al. APOL1 kidney disease risk variants cause cytotoxicity by depleting cellular potassium and inducing stress-activated protein kinases. *Proc. Natl. Acad. Sci. U.S.A* 2016;**113**(4):830–7.
46. Ma L, Chou JW, Snipes JA, et al. APOL1 renal-risk variants induce mitochondrial dysfunction. *J Am Soc Nephrol* 2017;**28**(4): 1093–105.
47. Granado D, Muller D, Krausel V, et al. Intracellular APOL1 risk variants cause cytotoxicity accompanied by energy depletion. *J Am Soc Nephrol* 2017;**28**(11):3227–38.
48. Beckerman P, Bi-Karchin J, Park AS, et al. Transgenic expression of human APOL1 risk variants in podocytes induces kidney disease in mice. *Nat Med* 2017;**23**(4):429–38.
49. Lan X, Jhaveri A, Cheng K, et al. APOL1 risk variants enhance podocyte necrosis through compromising lysosomal membrane permeability. *Am J Physiol Renal Physiol* 2014;**307**(3):F326–36.
50. Kruzel-Davila E, Shemer R, Ofir A, et al. APOL1-Mediated cell injury involves disruption of conserved trafficking processes. *J Am Soc Nephrol* 2017;**28**(4):1117–30.
51. Cheng D, Weckerle A, Yu Y, et al. Biogenesis and cytotoxicity of APOL1 renal risk variant proteins in hepatocytes and hepatoma cells. *J Lipid Res* 2015;**56**(8):1583–93.
52. Bruggeman LA, Wu Z, Luo L, et al. APOL1-G0 or APOL1-G2 transgenic models develop preeclampsia but not kidney disease. *J Am Soc Nephrol* 2016;**27**(12):3600–10.
53. Bruggeman LA, O'Toole JF, Ross MD, et al. Plasma apolipoprotein L1 levels do not correlate with CKD. *J Am Soc Nephrol* 2014;**25**(3): 634–44.
54. Weckerle A, Snipes JA, Cheng D, et al. Characterization of circulating APOL1 protein complexes in African Americans. *J Lipid Res* 2016;**57**(1):120–30.
55. Freedman BI, Pastan SO, Israni AK, et al. APOL1 genotype and kidney transplantation outcomes from deceased african American donors. *Transplantation* 2016;**100**(1):194–202.
56. Friedman DJ, Kozlitina J, Genovese G, Jog P, Pollak MR. Population-based risk assessment of APOL1 on renal disease. *J Am Soc Nephrol* 2011;**22**(11):2098–105.
57. Divers J, Palmer ND, Lu L, et al. Gene-gene interactions in APOL1-associated nephropathy. *Nephrol Dial Transplant* 2014; **29**(3):587–94.
58. Lipkowitz MS, Freedman BI, Langefeld CD, et al. Apolipoprotein L1 gene variants associate with hypertension-attributed nephropathy and the rate of kidney function decline in African Americans. *Kidney Int* 2013;**83**(1):114–20.
59. Kopp JB, Nelson GW, Sampath K, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol* 2011;**22**(11):2129–37.
60. Cohen SD, Kopp JB, Kimmel PL. Kidney diseases associated with human immunodeficiency virus infection. *N Engl J Med* 2017; **377**(24):2363–74.
61. Freedman BI, Cohen AH. Hypertension-attributed nephropathy: what's in a name? *Nat Rev Nephrol* 2016;**12**(1):27–36.
62. Appel LJ, Wright Jr JT, Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010;**363**(10):918–29.
63. Divers J, Nunez M, High KP, et al. JC polyoma virus interacts with APOL1 in African Americans with nondiabetic nephropathy. *Kidney Int* 2013;**84**(6):1207–13.
64. Freedman BI, Kistler AL, Skewes-Cox P, et al. JC polyoma viruria associates with protection from chronic kidney disease independently from apolipoprotein L1 genotype in African Americans. *Nephrol Dial Transplant* 2018;**33**(11):1960–7.
65. Hayek SS, Koh KH, Grams ME, et al. A tripartite complex of suPAR, APOL1 risk variants and alphavbeta3 integrin on podocytes mediates chronic kidney disease. *Nat Med* 2017;**23**(8):945–53.
66. Bodonyi-Kovacs G, Ma JZ, Chang J, et al. Combined effects of GSTM1 null allele and APOL1 renal risk alleles in CKD progression in the african American study of kidney disease and hypertension trial. *J Am Soc Nephrol* 2016;**27**(10):3140–52.
67. Zhang JY, Wang M, Tian L, et al. UBD modifies APOL1-induced kidney disease risk. *Proc. Natl. Acad. Sci. U.S.A* 2018;**115**(13):3446–51.
68. Langefeld CD, Comeau ME, Ng MCY, et al. Genome-wide association studies suggest that APOL1-environment interactions more likely trigger kidney disease in African Americans with nondiabetic nephropathy than strong APOL1-second gene interactions. *Kidney Int* 2018;**94**(3):599–607.
69. Foster MC, Coresh J, Fornage M, et al. APOL1 variants associate with increased risk of CKD among African Americans. *J Am Soc Nephrol* 2013;**24**(9):1484–91.
70. Freedman BI, Langefeld CD, Turner J, et al. Association of APOL1 variants with mild kidney disease in the first-degree relatives of African American patients with non-diabetic end-stage renal disease. *Kidney Int* 2012;**82**(7):805–11.
71. Parsa A, Kao WH, Xie D, et al. APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med* 2013; **369**(23):2183–96.
72. Peralta CA, Bibbins-Domingo K, Vittinghoff E, et al. APOL1 genotype and race differences in incident albuminuria and renal function decline. *J Am Soc Nephrol* 2016;**27**(3):887–93.
73. Freedman BI, Julian BA, Pastan SO, et al. Apolipoprotein L1 gene variants in deceased organ donors are associated with renal allograft failure. *Am J Transplant* 2015;**15**(6):1615–22.
74. Doshi MD, Ortigosa-Goggins M, Garg AX, et al. APOL1 genotype and renal function of black living donors. *J Am Soc Nephrol* 2018; **29**(4):1309–16.
75. Julian BA, Gaston RS, Brown WM, et al. Effect of replacing race with apolipoprotein L1 genotype in calculation of kidney donor risk index. *Am J Transplant* 2017;**17**(6):1540–8.
76. Freedman BI, Moxey-Mims M. The APOL1 long-term kidney transplantation outcomes network-APOLLO. *Clin J Am Soc Nephrol* 2018;**13**(6):940–2.
77. Braakman I, Bulleid NJ. Protein folding and modification in the mammalian endoplasmic reticulum. *Annu Rev Biochem* 2011;**80**: 71–99.
78. Eckardt KU, Alper SL, Antignac C, et al. Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management–A KDIGO consensus report. *Kidney Int* 2015;**88**(4): 676–83.
79. Venkat-Raman G, Gast C, Marinaki A, Fairbanks L. From juvenile hyperuricaemia to dysfunctional uromodulin: an ongoing metamorphosis. *Pediatr Nephrol* 2016;**31**(11):2035–42.
80. Bleyer AJ, Hart TC, Shihabi Z, Robins V, Hoyer JR. Mutations in the uromodulin gene decrease urinary excretion of Tamm-Horsfall protein. *Kidney Int* 2004;**66**(3):974–7.
81. Bollee G, Dahan K, Flamant M, et al. Phenotype and outcome in hereditary tubulointerstitial nephritis secondary to UMOD mutations. *Clin J Am Soc Nephrol* 2011;**6**(10):2429–38.
82. Devuyst O, Bochud M. Uromodulin, kidney function, cardiovascular disease, and mortality. *Kidney Int* 2015;**88**(5):944–6.
83. Smith GD, Robinson C, Stewart AP, et al. Characterization of a recurrent in-frame UMOD indel mutation causing late-onset autosomal dominant end-stage renal failure. *Clin J Am Soc Nephrol* 2011;**6**(12):2766–74.
84. Moskowitz JL, Piret SE, Lhotta K, et al. Association between genotype and phenotype in uromodulin-associated kidney disease. *Clin J Am Soc Nephrol* 2013;**8**(8):1349–57.

85. Stewart AP, Sandford RN, Karet Frankl FE, Edwardson JM. Pathogenic uromodulin mutations result in premature intracellular polymerization. *FEBS Lett* 2015;**589**(1):89−93.
86. Trudu M, Schaeffer C, Riba M, et al. Early involvement of cellular stress and inflammatory signals in the pathogenesis of tubulointerstitial kidney disease due to UMOD mutations. *Sci Rep* 2017; **7**(1):7383.
87. Bernascone I, Janas S, Ikehata M, et al. A transgenic mouse model for uromodulin-associated kidney diseases shows specific tubulointerstitial damage, urinary concentrating defect and renal failure. *Hum Mol Genet* 2010;**19**(15):2998−3010.
88. Kirby A, Gnirke A, Jaffe DB, et al. Mutations causing medullary cystic kidney disease type 1 lie in a large VNTR in MUC1 missed by massively parallel sequencing. *Nat Genet* 2013;**45**(3):299−303.
89. Gale DP, Kleta R. MUC1 makes me miserable. *J Am Soc Nephrol* 2018;**29**(9):2257−8.
90. Pemberton LF, Rughetti A, Taylor-Papadimitriou J, Gendler SJ. The epithelial mucin MUC1 contains at least two discrete signals specifying membrane localization in cells. *J Biol Chem* 1996;**271**(4): 2332−40.
91. Zivna M, Hulkova H, Matignon M, et al. Dominant renin gene mutations associated with early-onset hyperuricemia, anemia, and chronic kidney failure. *Am J Hum Genet* 2009;**85**(2):204−13.
92. Bingham C, Ellard S, van't Hoff WG, et al. Atypical familial juvenile hyperuricemic nephropathy associated with a hepatocyte nuclear factor-1beta gene mutation. *Kidney Int* 2003;**63**(5):1645−51.
93. Chan SC, Zhang Y, Shao A, et al. Mechanism of fibrosis in HNF1B-related autosomal dominant tubulointerstitial kidney disease. *J Am Soc Nephrol* 2018;**29**(10):2493−509.
94. Liddle GW, Bledsoe T, Coppage WSJ. A familial renal disorder simulating primary aldosteronism but with negligible aldosterone secretion. *Trans Assoc Am Phys* 1963;**76**:199−213.
95. Botero-Velez M, Curtis JJ, Warnock DG. Brief report: liddle's syndrome revisited–a disorder of sodium reabsorption in the distal tubule. *N Engl J Med* 1994;**330**(3):178−81.
96. Yang KQ, Xiao Y, Tian T, Gao LG, Zhou XL. Molecular genetics of Liddle's syndrome. *Clin Chim Acta* 2014;**436**:202−6.
97. Rotin D, Staub O. Role of the ubiquitin system in regulating ion transport. *Pflügers Archiv* 2011;**461**(1):1−21.
98. Lowe M. Structure and function of the Lowe syndrome protein OCRL1. *Traffic* 2005;**6**(9):711−9.
99. Devonald MA, Karet FE. Renal epithelial traffic jams and one-way streets. *J Am Soc Nephrol* 2004;**15**(6):1370−81.
100. Cherqui S, Courtoy PJ. The renal Fanconi syndrome in cystinosis: pathogenic insights and therapeutic perspectives. *Nat Rev Nephrol* 2017;**13**(2):115−31.
101. Shotelersuk V, Larson D, Anikster Y, et al. CTNS mutations in an American-based population of cystinosis patients. *Am J Hum Genet* 1998;**63**(5):1352−62.
102. Kalatzis V, Cohen-Solal L, Cordier B, et al. Identification of 14 novel CTNS mutations and characterization of seven splice site mutations associated with cystinosis. *Hum Mutat* 2002;**20**(6):439−46.
103. Claverie-Martin F. Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis: clinical and molecular characteristics. *Clin Kidney J* 2015;**8**(6):656−64.
104. Simon DB, Lu Y, Choate KA, et al. Paracellin-1, a renal tight junction protein required for paracellular $Mg2^{+}$ resorption. *Science* 1999;**285**(5424):103−6.
105. Konrad M, Schaller A, Seelow D, et al. Mutations in the tight-junction gene claudin 19 (CLDN19) are associated with renal magnesium wasting, renal failure, and severe ocular involvement. *Am J Hum Genet* 2006;**79**(5):949−57.
106. Muller D, Kausalya PJ, Claverie-Martin F, et al. A novel claudin 16 mutation associated with childhood hypercalciuria abolishes binding to ZO-1 and results in lysosomal mistargeting. *Am J Hum Genet* 2003;**73**(6):1293−301.
107. Muller D, Kausalya PJ, Bockenhauer D, et al. Unusual clinical presentation and possible rescue of a novel claudin-16 mutation. *J Clin Endocrinol Metab* 2006;**91**(8):3076−9.
108. Karet FE. Inherited distal renal tubular acidosis. *J Am Soc Nephrol* 2002;**13**(8):2178−84.
109. Fry AC, Su Y, Yiu V, Cuthbert AW, Trachtman H, Karet Frankl FE. Mutation conferring apical-targeting motif on AE1 exchanger causes autosomal dominant distal RTA. *J Am Soc Nephrol* 2012; **23**(7):1238−49.
110. Toye AM, Banting G, Tanner MJ. Regions of human kidney anion exchanger 1 (kAE1) required for basolateral targeting of kAE1 in polarised kidney cells: mis-targeting explains dominant renal tubular acidosis (dRTA). *J Cell Sci* 2004;**117**(Pt 8):1399−410.
111. Su Y, Al-Lamki RS, Blake-Palmer KG, et al. Physical and functional links between anion exchanger-1 and sodium pump. *J Am Soc Nephrol* 2015;**26**(2):400−9.
112. Su Y, Hiemstra TF, Yan Y, et al. PDLIM5 links kidney anion exchanger 1 (kAE1) to ILK and is required for membrane targeting of kAE1. *Sci Rep* 2017;**7**:39701.
113. Leumann E, Hoppe B. The primary hyperoxalurias. *J Am Soc Nephrol* 2001;**12**(9):1986−93.
114. Danpure CJ, Lumb MJ, Birdsey GM, Zhang X. Alanine:glyoxylate aminotransferase peroxisome-to-mitochondrion mistargeting in human hereditary kidney stone disease. *Biochim Biophys Acta* 2003;**1647**(1−2):70−5.
115. Wang F, Fang Q, Yu N, et al. Association between genetic polymorphism of the angiotensin-converting enzyme and diabetic nephropathy: a meta-analysis comprising 26,580 subjects. *J Renin-Angiotensin-Aldosterone Syst JRAAS* 2012;**13**(1):161−74.
116. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest* 1990;**86**(4):1343−6.
117. Donaghue KC, Margan SH, Chan AK, et al. The association of aldose reductase gene (AKR1B1) polymorphisms with diabetic neuropathy in adolescents. *Diabet Med* 2005;**22**(10):1315−20.
118. Sortica DA, Buffon MP, Souza BM, et al. Association between the ENPP1 K121Q polymorphism and risk of diabetic kidney disease: a systematic review and meta-analysis. *PLoS One* 2015;**10**(3): e0118416.
119. Williams WW, Salem RM, McKnight AJ, et al. Association testing of previously reported variants in a large case-control meta-analysis of diabetic nephropathy. *Diabetes* 2012;**61**(8):2187−94.
120. Mooyaart AL, Valk EJ, van Es LA, et al. Genetic associations in diabetic nephropathy: a meta-analysis. *Diabetologia* 2011;**54**(3): 544−53.
121. Imperatore G, Hanson RL, Pettitt DJ, Kobes S, Bennett PH, Knowler WC. Sib-pair linkage analysis for susceptibility genes for microvascular complications among Pima Indians with type 2 diabetes. Pima Diabetes Genes Group. *Diabetes* 1998;**47**(5): 821−30.
122. Vardarli I, Baier LJ, Hanson RL, et al. Gene for susceptibility to diabetic nephropathy in type 2 diabetes maps to 18q22.3-23. *Kidney Int* 2002;**62**(6):2176−83.
123. Janssen B, Hohenadel D, Brinkkoetter P, et al. Carnosine as a protective factor in diabetic nephropathy: association with a leucine repeat of the carnosinase gene CNDP1. *Diabetes* 2005;**54**(8): 2320−7.
124. Freedman BI, Hicks PJ, Sale MM, et al. A leucine repeat in the carnosinase gene CNDP1 is associated with diabetic end-stage renal disease in European Americans. *Nephrol Dial Transplant* 2007; **22**(4):1131−5.
125. Iyengar SK, Abboud HE, Goddard KA, et al. Genome-wide scans for diabetic nephropathy and albuminuria in multiethnic populations: the family investigation of nephropathy and diabetes (FIND). *Diabetes* 2007;**56**(6):1577−85.

126. Schelling JR, Abboud HE, Nicholas SB, et al. Genome-wide scan for estimated glomerular filtration rate in multi-ethnic diabetic populations: the Family Investigation of Nephropathy and Diabetes (FIND). *Diabetes* 2008;**57**(1):235–43.
127. Igo Jr RP, Iyengar SK, Nicholas SB, et al. Genomewide linkage scan for diabetic renal failure and albuminuria: the FIND study. *Am J Nephrol* 2011;**33**(5):381–9.
128. Shimazaki A, Kawamura Y, Kanazawa A, et al. Genetic variations in the gene encoding ELMO1 are associated with susceptibility to diabetic nephropathy. *Diabetes* 2005;**54**(4):1171–8.
129. Pezzolesi MG, Poznik GD, Mychaleckyj JC, et al. Genome-wide association scan for diabetic nephropathy susceptibility genes in type 1 diabetes. *Diabetes* 2009;**58**(6):1403–10.
130. Sandholm N, Salem RM, McKnight AJ, et al. New susceptibility loci associated with kidney disease in type 1 diabetes. *PLoS Genet* 2012;**8**(9):e1002921.
131. Sandholm N, Van Zuydam N, Ahlqvist E, et al. The genetic landscape of renal complications in type 1 diabetes. *J Am Soc Nephrol* 2017;**28**(2):557–74.
132. Ma RC. Genetics of cardiovascular and renal complications in diabetes. *J Diabetes Investig* 2016;**7**(2):139–54.
133. Klein RL, Hammad SM, Baker NL, et al. Decreased plasma levels of select very long chain ceramide species are associated with the development of nephropathy in type 1 diabetes. *Metabolism* 2014;**63**(10):1287–95.
134. Hirayama A, Nakashima E, Sugimoto M, et al. Metabolic profiling reveals new serum biomarkers for differentiating diabetic nephropathy. *Anal Bioanal Chem* 2012;**404**(10):3101–9.
135. Santin S, et al. Clinical utility of genetic testing in children and adults adolescents with steroid-resistant nephrotic syndrome. *Clin J Am Soc Nephrol* 2013;**6**:1139–48. https://doi.org/10.2215/CJN.05260610.
136. Rood IM, et al. Genetic causes of focal segmental glomerulosclerosis: implications for clinical practice. *Nephrol Dial Transplant* 2012;**27**:882–90.
137. Fuchsberger C, et al. Genetic architecture of type 2 diabetes. *Nature* 2016;**536**(7614):41–7.

QUESTIONS AND ANSWERS

Question 1

A 32-year-old European man presents with subacute onset of NS with hypertension. His S[Cr] is 1.05 mg/dL (preserved kidney function), and he denies a family history of kidney disease. Physical exam reveals a blood pressure of 150/98 mm Hg and is otherwise unremarkable except for 2 + ankle edema bilaterally. He receives a statin and ACE inhibitor. A kidney biopsy displays FSGS with "not otherwise specified" lesion. Which of the following is the most appropriate approach to evaluation and treatment?

A. Consider immunosuppressive therapy because screening for mutations in adults with sporadic FSGS is not indicated
B. Test for mutations in the *INF2* (inverted formin-2) gene
C. Test for mutations in the *NPHS2* (podocin) gene, especially its p.R229Q variant
D. Test for mutations in the *APOL1*
E. Test for mutations in the *TRPC6* (transient receptor potential cation channel, subfamily 6) gene

Answer: A

Adults with European ancestry who have sporadic or nonfamilial forms of FSGS are highly unlikely to have causative mutations detected. Although screening for the p.R229Q variant in the *NPHS2* (podocin) gene can be considered for family planning purposes, few such mutations will be detected in settings such as this. Podocin mutations are common causes of childhood SRNS with autosomal recessive inheritance. The specific *NPHS2* variant p.R229Q variant is permissive, allowing adults to develop disease with only one *NPHS2* disease-associated variant. Although mutations in *INF2* and *TRPC6* cause adult FSGS, this is relevant in autosomal dominant forms of disease, and this patient lacked a family history of nephropathy. *APOL1* mutations are common causes of idiopathic FSGS in individuals of African ancestry.[135]

Question 2

Which of the following gene mutations is the most common cause of nonsyndromic (renal-limited) steroid resistant nephrotic syndrome (SRNS) in children less than 5 years of age?

A. Nephrin gene (*NPHS1*)
B. Inverted formin-2 gene (*INF2*) gene
C. Podocin (*NPHS2*) gene
D. Phospholipase C, epsilon 1 gene (*PLCE1*)
E. Wilms tumor 1 gene (*WT1*)

Answer C

Autosomal recessive mutations in the podocin (*NPHS2*) gene are the most common cause of autosomal recessive SRNS in infants and children and can be identified in sporadic and familial cases of SRNS. Based on this, *NPHS2* should be the first gene assessed in these cases. Autosomal recessive mutations in the *PLCE1* and *NPHS1* genes are less often detected—but can be assessed if risk variants in *NPHS2* are absent. *WT1* mutations typically cause syndromic (nonrenal limited) kidney diseases such as Denys–Drash and Frasier syndrome, and they are inherited in an autosomal dominant pattern.[136]

Question 3

Which statement regarding chronic kidney disease in hypertensive African Americans who lack diabetes mellitus and have less than 1 gm proteinuria per day is true?

A. The most common lesion on a kidney biopsy is FSGS, collapsing variant
B. Aggressive treatment of hypertension to <120/80 mm Hg using ACE inhibitors reliably halts the progression of nephropathy
C. Progression of kidney disease commonly relates to possessing two renal-risk variants in the *APOL1* inherited in an autosomal recessive inheritance pattern
D. Renal arteriolar narrowing and hyalinosis are rarely present

Answer: C

Kidney biopsies in hypertensive, nondiabetic African Americans with low level proteinuria reveal FGGS with interstitial fibrosis and small vessel arteriolar changes. The arteriolar lesions do not correlate with systemic blood pressure. Subnephrotic forms of FSGS may also be observed; however, collapsing lesions are uncommon. Results of the NIH AASK study revealed that nearly 60% of participants treated with ACE inhibitors to low blood pressure targets still reached the composite endpoint of ESRD, doubling of S[Cr], or death after 10-year follow-up. In contrast to blood pressure target or class of antihypertensive medication, presence of two *APOL1* renal-risk variants predicted progression of kidney failure. This study demonstrates that this type of kidney disease in African Americans is not likely caused

by high blood pressure but resides in the spectrum of *APOL1*-associated nephropathy.[58]

Question 4

Mutations in which of the following genes does not cause ADTKD?

A. Uromodulin (*UMOD*)
B. Mucin-1 (*MUC1*)
C. Claudin 16 (*CLDN16*)
D. Renin (*REN*)
E. HNF1 Homeobox B (*HNF1β*)

Answer: C

Mutations in the claudin 16 gene (also called paracellin-1) lead to the rare syndrome "familial hypomagnesemia and nephrocalcinosis". In contrast, mutations in *UMOD*, *MUC1*, *REN*, and *HNF1β* associate with ADTKD. Many patients have hyperuricemia and gout; anemia can be seen with *REN* mutations and hypomagnesemia with *HNF1β* mutations.[78]

Question 5

Liddle's syndrome is caused by mutations in the beta or gamma subunits of the *ENaC* gene. Affected patients display all of the following except:

A. Hypertension with plasma volume expansion
B. Loss-of-function mutations in ENaC with urinary sodium wasting
C. Gain-of-function mutations in ENaC with sodium retention
D. Low or undetectable plasma renin and aldosterone levels
E. Improvement in hypertension with amiloride or triamterene

Answer: B

Liddle's syndrome is associated with mutations of either the beta or gamma subunit of the ENaC; these produce high constitutive levels of ENaC activity. This leads to an apparent gain of function and accounts for increased sodium absorption in the cortical collecting duct and hypertension with physiologically appropriate reductions in renin and aldosterone. Effective blood pressure reduction and normalization of plasma potassium in patients with this syndrome can be achieved using amiloride or triamterene (not spironolactone) with concomitant dietary sodium restriction. Salt restriction is critical because these drugs compete with sodium for binding to ENaC.[96]

Question 6

Which of the following statements is true regarding genetic factors in DKD?

A. Polymorphisms in the *ACE* gene contribute to the majority of cases
B. Family-based linkage studies reveal that a trinucleotide repeat sequence in the carnosinase 1 gene (*CNDP1*) cause most cases of kidney disease in patients with type 2 diabetes mellitus
C. A single locus of large effect has not been identified
D. DKD is a polygenic disorder (multiple genes contribute to risk), whereas environmental factors including hyperglycemia play a minor role

Answer: C

Progress in identifying the genetic architecture underlying DKD has been difficult with realization that one locus of large effect does not exist. DKD is a polygenic disorder with multiple genetic loci, each contributing modest effect. To better dissect the heterogeneous disorder DKD, clinicians and researchers need to identify novel disease biomarkers beyond clinically used measures such as eGFR, albuminuria, blood urea nitrogen, uric acid, and S[Cr] to facilitate earlier diagnosis and establish novel therapeutic interventions.[137]

CHAPTER

26

Acute Kidney Injury and Chronic Kidney Disease

Matthew T. James[a], *Lakhmir S. Chawla*[b,c,d], *Paul L. Kimmel*[c]

[a]Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; [b]Department of Anesthesiology and Critical Care Medicine, George Washington University Medical Center, Washington, DC, United States; [c]Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States; [d]University California of San Diego, San Diego, CA, United States

Abstract

Previous conventional wisdom suggested patients who survived an episode of acute kidney injury (AKI) fully recovered renal function. AKI and chronic kidney disease (CKD) have been traditionally approached as separate clinical syndromes, mainly distinguished by criteria based on timing and duration of reduced kidney function. However, recent research demonstrates that AKI and CKD are closely related. CKD is an important risk factor for the development of AKI. In turn, AKI is associated with the development of CKD and progression of preexisting CKD in significant numbers of patients. Both AKI and CKD are associated with increased morbidity and mortality, particularly when they are seen in combination, including increased risks of major adverse cardiovascular events.

AKI and CKD may be better considered as interconnected syndromes, rather than two disparate entities. This knowledge has implications for the longitudinal care of survivors of AKI and patients with CKD. Interventions that target the AKI to CKD continuum may improve outcomes of patients with kidney disease, although strong evidence identifying strategies that improve outcomes remains lacking. Improved strategies for identification of patients at risk could inform the design of clinical trials, but well-designed RCTs are needed to determine effective interventions and best care practices to mitigate the pathways of AKI to CKD and to ameliorate its progression.

INTRODUCTION

Medical teaching has traditionally divided pathophysiology of disease into organ systems, and within these, into syndromic approaches.[1,2] For more than a half century, nephrologists have taught limited and separate modules pertaining to acute renal failure (ARF) and chronic renal disease to medical students. Over the last 15 years, in part to facilitate clinical recognition and research, conceptual definitions of chronic kidney disease (CKD)[3] and acute kidney injury (AKI)[4,5] have been developed and refined, categorizing disease states and stages according to measures based on long-term level and acute changes in S[Cr]. AKI is currently defined by decline in kidney function over one week or less, whereas CKD is defined as alterations of kidney function and structure for more than 3 months.[6,7]

Previous conventional wisdom suggested favorable long-term outcomes of patients with ARF, and acute tubular necrosis (ATN) in particular, if recovery occurred during hospitalization. In 1952, Lowe reported creatinine clearances ranging from 65.3 to 99 mL/min in a subset of 14 of 40 patients with oliguria or anuria and a diagnosis of ATN when followed 228 days to 2.9 years.[8] Most of the values for creatinine clearance one to three years after the ATN episode remained below normal. Premorbid levels of renal function were not recorded. Lowe concluded "… once recovery has been made from the acute episode of ATN, a favorable prognosis can be given… the levels of renal function attained are compatible with normal expectation of life, although the renal reserve is diminished." Finkenstaedt and Merrill described long-term outcomes of 16 patients with ARF who did not have cardiovascular disease (CVD) or kidney disease before the acute episode.[9] In these patients as well, "clearance values obtained for the majority of the patients fell below the lower limit of normal." Inulin clearances ranged from 35 to 120 mL/min/1.73 m^2 at 1 to 76 months after the episode of ARF. Three

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00026-7

of the patients had long-term values of inulin clearance less than or equal to 63 mL/min/1.73 m^2. The lessons of these small seminal papers published in the Lancet and the New England Journal of Medicine regarding long-term outcomes of ATN more than a half century ago have been forgotten or misinterpreted.[1]

Recent evidence, however, from large well-designed observational studies shows a substantial proportion of patients with AKI, even those without a history of previous renal disease, progress to high stage CKD,[1,2,10] and that AKI is an independent prognostic factor for the progressive loss of renal function in patients with CKD.[1,10–12] Although the antecedents and clinical correlates of ARF have been known for many years, in the era of CKD and AKI classifications, CKD has emerged as the preeminent risk factor for AKI.[1,2,13,14] Since 2007, the concept of AKI has been generally accepted by the kidney research and clinical communities.[3,5] Several observational studies have documented ominous outcomes associated with small increases in S[Cr] in populations. Concepts and definitions of AKI (Table 26.1) demonstrate numerous similarities to those of CKD.[1,3,7,15,16]

The public health impact of the long-term outcomes of AKI is significant. AKI is associated with significant morbidity and mortality, and the incidence of AKI has nearly doubled over the past two decades.[17,18] AKI is common, morbid, deadly, and costly.[4] AKI has been linked with the development of subsequent CVD, CKD, and end-stage renal disease (ESRD) and is associated with high costs of care.[1,2,10,18–20] Secular trends suggest that while the incidence of AKI has increased, early mortality from AKI has diminished in high-income countries. As a result, the number of survivors who may live with sequelae of CKD has increased over time.[20–22]

The annual incidence of AKI has been estimated as approximately 2100 per million population.[23,24] Given the population of the developed world, there are projected to be over 2 million cases of AKI yearly, with an expected 1.5 million AKI survivors.[24,25] Of these patients, more than 15% of those without preexisting CKD will progress to advanced stage CKD within 24 months, resulting in an incidence of more than 300,000 cases of advanced CKD a year.[24,25] Furthermore, episodes of AKI that are superimposed on CKD may hasten the progression to ESRD of additional patients with established CKD.[20] These estimates demonstrate the significant population attributable risk of CKD associated with AKI. Given the higher incidence of AKI in older populations, the projected incidence of CKD and ESRD related to AKI is expected to increase.[15,18,24,26]

Observational studies show a large proportion of patients with AKI, even in the absence of concurrent or preexisting CKD, progress to advanced stages of CKD, even if not treated with RRT during the index hospitalization.

Given the relationships between AKI and incident CKD, progression of preexisting CKD, increased risk of entry into ESRD programs, and higher mortality,[1,2,20,27,28] AKI and CKD can be considered parts of an interdigitated syndrome (Figure 26.1). The individual components, AKI and CKD, differ in presentation both temporally and clinically. AKI involves rapid changes in glomerular filtration rate (GFR), while CKD is usually characterized by slowly progressive decline in GFR. Patients with AKI are at high risk of developing CKD, even when GFR recovers after the initial episode. Patients with CKD remain at risk for developing episodes of AKI, which may further contribute to progression toward kidney failure.[1,2,14] The individual components of the syndrome and their combination are common and associated with adverse long-term outcomes. This syndrome can be expanded to include patients with acute kidney diseases and disorders when alterations in kidney function or structure are present for less than 3 months, which includes patients who do and do not strictly meet AKI criteria but also have similar relationships with increased risks of CKD and ESRD.[7,29] CKD, however, is the obverse face of the AKI coin. For patients with reduced GFR, AKI and CKD are the twin prognostic profiles of Janus, the two-faced Roman god of doorways, beginnings and endings.

TABLE 26.1 Putative Factors Associated with Progressive Loss of Renal Function in CKD and AKI

Systemic and intrarenal hypertension
Hyperfiltration
Tubular hypertrophy and atrophy
Tubulointerstitial fibrosis
Progressive glomerular sclerosis
Arteriosclerosis
Disordered physiologic, humoral, and biochemical responses associated with CKD
PTH, FGF-23, inflammation, hyperphosphatemia, uremic toxins
Endothelial injury and vascular dropout
Interstitial infiltration
Specific populations of immune cells including subpopulations of macrophages and T cells
Dietary sodium and protein intake

FGF-23, fibroblast growth factor 23; *PTH*, parathyroid hormone.

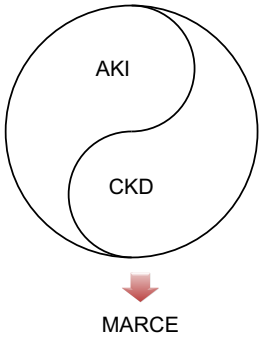


FIGURE 26.1 AKI and CKD are interconnected syndromes. AKI patients are at risk for developing long-term decrements in GFR, even if full recovery occurs after an episode. CKD patients are at the highest risk of developing AKI. Patients with AKI and CKD are at risk for developing major adverse renal and cardiovascular events (MARCE). *AKI*, acute kidney injury; *CKD*, chronic kidney disease; *MARCE*, major adverse renal and cardiovascular events.

AKI AND DEVELOPMENT OF CKD, END-STAGE RENAL DISEASE, AND CARDIOVASCULAR EVENTS

Several retrospective studies have characterized the relationship between AKI and development of CKD. In an important early study, Vikse and colleagues showed the rate of entry into ESRD programs was 3.7 per 100,000 women per year, but women with a diagnosis of preeclampsia had a relative risk of ESRD that was 3.2- to 15-fold higher.[30] Ishani et al. showed, in a retrospective, observational study of Medicare patients, with follow-up of two years, that a coded diagnosis of ARF was associated with a 13-fold increase in the risk of development of ESRD compared with hospitalized patients without such a diagnosis. Patients who had a diagnosis of both ARF and CKD had a 40-fold increased risk of entering the ESRD program compared with patients without either diagnosis, and their ESRD risk was almost five times as great as those with a diagnosis of CKD in the absence of AKI.[20] The mortality rate for patients with a diagnosis of ARF was 57.7%, twice as high as that of comparable patients without a diagnosis of ARF. Patients who had diagnostic coding related both to ARF and CKD had a mortality rate 18% higher than those with only an ARF diagnosis, 70% higher than those with CKD alone, and 2.4-fold higher than those without either diagnosis. Newsome et al. showed similar increases in both ESRD and mortality among patients with acute myocardial infarction (MI) who sustained small increases in S[Cr].[31] Lo et al. found, after controlling for potential confounders such as presence of diabetes mellitus and baseline level of estimated GFR (eGFR), that AKI necessitating dialysis was independently associated with an almost 30-fold increase in the risk of developing subsequent stage 4 or 5 CKD, and a more than doubled risk of death.[28] Bucaloiu et al.[11] showed, using propensity score matching techniques, an approximately 50% increased risk in mortality of patients with AKI, but without concomitant CKD, as well as an almost doubled risk of developing incident CKD in the Geisinger Health System in Pennsylvania. A strength of the study was the ability to ascertain information regarding urinary protein excretion, when present in the medical record. Of note, almost three quarters of the AKI patients only had stage 1 disease, by Acute Kidney Injury Network criteria, and the duration of AKI was less than 24 hours. Hsu et al. showed AKI had an incrementally adverse effect on patients with preexisting CKD in a cohort of patients from the Kaiser Permanente dataset. Compared with patients who had CKD and did not experience AKI, those who had AKI superimposed on CKD had a 30% higher long-term risk of death or ESRD.[32] Wald et al. showed, in an administrative database study of a Canadian population of patients who required dialysis during hospitalization, but survived free of dialysis for at least a month after hospital discharge, that the group had a threefold increased risk of ESRD compared with the control group.[27] In a cohort of Canadian patients identified from a prospective cardiac catheterization registration, patients who exhibited laboratory evidence of AKI following coronary angiography were at particular risk for subsequent loss of renal function and ESRD.[14]

Amdur and colleagues examined the long-term risk of patients diagnosed with ATN, as well as ARF, in the US Veterans Administration health system.[24] Progression of loss of renal function in patients with ATN who did not have preexisting, concomitant CKD to stage 4 CKD or higher was similar to those who were diagnosed with CKD at study baseline. CKD and ATN patients had similar mortality, which was higher than that of the control group, which was comprised of patients with the serious hospital diagnoses of MI or pneumonia, acutely ill patients with a substantial burden of CVD and cardiovascular risk factors. Patients with ATN had approximately six times the risk of developing CKD compared with the control group, whereas those with ARF had a fourfold increase in risk. Approximately 20% of patients with a diagnosis of ATN, without preexisting CKD, entered stage 4 CKD after a follow-up of more than six years. More than 13% of patients with a diagnosis of ARF, without preexisting CKD, developed stage 4 CKD during the study observation period. The risk of developing stage 4 CKD in patients with a diagnosis of ATN or ARF was 5.6 and more than 3-fold greater, respectively, than that of a control group of hospitalized patients with MI or pneumonia.

Nineteen retrospective cohort studies have characterized the relationships between AKI, based on the KDIGO criteria, and the risks of CKD and ESRD. Based

on meta-analyses of these data, AKI carries an over twofold increased risk of new or progressive CKD (17.8 vs. 7.6 cases per 100 person-years for those with vs. without AKI) and an over fourfold increased risk of ESRD (0.47 vs. 0.08 cases per 100 person-years for those with vs. without AKI). More severe AKI stages are consistently associated with higher risks for both outcomes. These findings have recently been confirmed in a multicenter prospective study from the US. The Assessment Serial Evaluation and Subsequent Sequelae (ASSESS) AKI study compared outcomes following discharge of patients with AKI and matched hospitalized patients without AKI. Importantly, this study employed protocolized follow-up measurements of eGFR and proteinuria to ascertain CKD in a consistent manner during follow-up.[33,34] The ASSESS AKI study reported that AKI was associated with an over threefold higher adjusted rate of development of CKD incidence and an over twofold higher adjusted rate of CKD progression.

The risk of development of CKD and progression of CKD to and development of ESRD is enhanced after AKI, but is also negatively affected by the increased severity of and number of episodes of AKI.[10,35,36] Risk factors that have been identified for developing CKD following AKI include older age, presence of a diagnosis of diabetes mellitus, heart failure, the magnitude of increase in S[Cr], provision of dialysis, lower baseline eGFR, level of RIFLE score, albuminuria, and hypoalbuminemia (Table 26.2).[36,37] These findings have been confirmed in a systematic review, demonstrating an almost ninefold increased risk of developing CKD for patients with AKI, a threefold increased risk of developing ESRD, and a doubled risk of death.[10] The study suggested increased risks of developing CKD and ESRD associated with severity of AKI as well.[10] Table 26.2 outlines factors which may be associated with long-term outcomes in patients after an episode of AKI.

TABLE 26.2 Clinical Factors Thought to be Associated with Long-Term Outcomes of AKI

Age
Level of initial renal function
Extent and severity of injury
Albuminuria
Diabetes mellitus
Ethnicity
Degree of early recovery of kidney function
Lack of follow-up by physicians
Genetic susceptibility

Several large observational cohort studies show patients who survive an AKI episode are at high risk for both progression to CKD and increased cardiovascular events.[14,19,38] In a cohort of patients who received coronary angiography in Alberta Canada, AKI was independently associated with subsequent hospitalizations for heart failure and MI.[14] In an analysis of the Veterans Administration hospital database, after a median follow-up of 1.4 years (interquartile range 0.5–3.4 years), patients with a diagnosis of ARF or with AKI had a cumulative incidence of major renal and cardiovascular events 37% higher than that of a comparison group of patients with a diagnosis of MI.[19] More than 60% of patients with AKI had a major cardiovascular or kidney event during follow-up (Figure 26.1). The highest risk of death, kidney, and cardiovascular events was observed in patients with AKI and MI. In a meta-analysis of six studies with a minimum follow-up of 6 months, Odutayo et al. found AKI was associated with an approximately 86% higher risk of cardiovascular mortality, and 38% higher risk of a major cardiovascular event.[39] Go et al. found that, among hospitalized patients from Kaiser Permanente in California, 20% of patients with AKI experienced a cardiovascular event in the year after hospital discharge, and that individuals with AKI were at 18% higher adjusted risk of developing acute coronary syndrome, peripheral arterial disease, ischemic stroke, or heart failure.[40] However, AKI was most strongly and significantly associated with a 44% increased risk of heart failure, without significantly increased risks of atherosclerotic disease following adjustment. The prospective ASSESS AKI study showed similar findings when cardiovascular events following hospitalization were clinically adjudicated, with significantly higher adjusted risks of heart failure, but not major atherosclerotic events identified among those with AKI.[33,34]

AKI AS A SYNERGISTIC COMPLICATION OF PROGRESSION OF CKD

Patients with AKI superimposed on preexisting CKD present special challenges to clinicians and researchers.[41] Analyses of repeated measures of kidney function suggest trajectories of CKD progression may include AKI episodes, but in a complex manner which makes analyses of the data problematic, and the formulation of definitive conclusions challenging.[2,42,43] O'Hare and colleagues identified four distinct trajectories of eGFR in patients with CKD during the two years before onset of ESRD. The trajectories included relatively stable courses, progressive loss of renal function, and both aggressive and catastrophic decreases in GFR. Patients with more aggressive progression to ESRD were more likely to have been hospitalized and to have had a diagnosis of AKI.[43]

CKD is the most important risk factor for the development of AKI, and patients with CKD appear uniquely susceptible to the development of AKI.[1,2,14,16] This was illustrated in a large cohort study from Alberta, Canada, that included almost 1 million participants with outpatient eGFR and albuminuria measurements to characterize their CKD stage. The risk of hospitalization with AKI was shown to increase progressively with both lower eGFR and greater albuminuria.[44] The importance of CKD as a predictor of AKI is also apparent from the development of clinical risk scores for AKI after cardiac surgery and cardiac catheterization.[45–47] Most risk scores for AKI include a history of CKD or baseline eGFR among the strongest predictors. More recently, some have also identified albuminuria as an additional independent predictor of AKI in multivariable models.

Mechanisms by which patients with CKD may be at risk for developing transient decreases of renal function include failure of autoregulation, abnormal vasodilatation, lack of renal reserve, failure of adequate renal tubular mechanisms to reabsorb water and sodium, frequent hospitalizations with the potential for iatrogenic mishaps or exposure to nephrotoxins, treatment to achieve diuresis leading to volume depletion, susceptibility to effects of antihypertensives, overvigorous medication, the use of RAAS blockers, nephrotoxins, and age-related physiologic changes.[1,2,14,16,26,48] Patients with congestive heart failure or those with cardiorenal syndrome would seem to be intrinsically at increased risk because of their decreased renal function, even in the absence of laboratory evaluations which suggest the presence of CKD.[49–51] Some data suggest, however, the uremic milieu might be associated with protective factors, such as antiinflammatory responses that modify factors associated with progression of kidney disease.[52]

Of note, the data linking small changes in S[Cr] with adverse outcomes may have potential significance apart from traditional notions of disease states such as ATN, acute interstitial nephritis (AIN), acute glomerulonephritis, or renal vascular disease.[15] If such findings are confirmed in prospective studies, the implication is that patients who experience changes in cardiac hemodynamics, such as those with congestive heart failure or one of the cardiorenal syndromes, may represent a population at risk, but not necessarily from kidney dysfunction as a prime determinant. In addition, commonly employed therapeutic maneuvers, theoretically applied by extrapolating from findings from RCTs conducted in patients with CKD, such as diuretic therapy, interventions to control level of blood pressure, salt restriction, and intervention with agents which affect the RAAS may have unintended adverse consequences in patients with AKI and CKD. The ramifications, especially regarding patients with prerenal hemodynamics, are wide-ranging. Although the clinical paradigm of "acute on chronic" kidney disease has been well-appreciated, it is only recently that observational data (frequently from administrative sources) have been effectively used to study such patients. The nephrology community's therapeutic approach to patients with simultaneous AKI and CKD is limited to anecdotal approaches. In addition, whether temporal sequence (such as whether AKI preceded CKD or CKD was complicated by AKI) is associated with outcomes in patients with coexisting CKD and AKI is unknown.

Although the large number of observational studies linking episodes of AKI to the development and progression of CKD has established consistent relationships, causal links cannot be inferred by these study designs. Observational studies, particularly those using administrative databases or conducted retrospectively, are subject to errors associated with confounding and selection bias.[1,2,12,14,53] Findings linking small changes in S[Cr] to adverse outcomes may be affected by the clinical circumstances associated with receiving multiple laboratory tests, such as site of care, and linkages may be missed in those patients who do not have systematic or frequent ascertainment of S[Cr]. The assessment of renal disease using administrative data often does not have the granularity necessary to assess specific laboratory findings. The prospect of underestimation of the scope of the clinical problem is magnified when mild abnormalities, such as failure to maximally concentrate or acidify urine, in the presence or absence of a specific stressor, are considered as measures of CKD or tubular dysfunction.

Only an RCT designed to test whether an intervention decreases the incidence of CKD or progressive loss of renal function after an episode of AKI can achieve a definitive conclusion regarding causality. In one of the few studies to explore this question, a randomized clinical trial testing off-pump vs. on-pump coronary artery bypass grafting surgery showed off-pump surgery reduced the incidence of AKI by 17%. There was no difference detected between the treatment groups in the risk of a 20% decline in renal function one year later in this trial.[54] A lack of other effective early interventions for prevention and treatment of AKI has limited opportunities to further test causal pathways between AKI and long-term outcomes, and inferences continue to be drawn from several sets of extant data.[2,53,55]

Children usually do not have underlying comorbidities associated with risk for AKI or CKD, such as diabetes mellitus or hypertension. Several studies show children who sustain an episode of AKI develop signs of CKD, such as hypertension, decreased GFR, and urinary abnormalities, in the absence of comorbidities characterizing the adult population.[56–58] In analyses in adult populations, when variation in the presence of

comorbidities is considered, AKI emerges as an independent risk factor for the development of CKD, progressive loss of renal function, and development of ESRD. The severity of AKI has been associated with the development of adverse outcomes.[10,36,59] Finally, the number and severity of episodes of AKI has been linked to adverse outcomes.[35]

MECHANISMS ASSOCIATED WITH PROGRESSIVE RENAL INJURY

The long-term course after an episode of AKI is presumably determined by the extent of the decrement in GFR, the reversibility of the injury, and the temporal balance between effective and maladaptive repair mechanisms (Figure 26.2, Table 26.3).[1,16] Although the mechanisms underlying progression of renal dysfunction in humans are incompletely understood, and are primarily derived from studies in animals and model systems, rather than from individual level clinical findings, data from animal studies delineate a number of possible mechanisms.

Neugarten and Baldwin and colleagues first proposed that progression of chronic disease might occur by processes independent of the original pathology or injury, originally in glomerular diseases.[60] The group showed evidence of renal dysfunction, consisting of incident hypertension, proteinuria, and hematuria, in addition to change in renal function characterized the long-term course of patients who recovered from an episode of poststreptococcal glomerulonephritis.[61] They subsequently expanded these notions to patients with other glomerular diseases, and with decrements in renal function nonspecifically.[62] These metrics are used today in analyses of CKD in children.

A variety of mechanisms associated with progressive injury in AKI patients is similar to that proposed for progression in CKD (Table 26.1, Table 26.3).[1,2,16] These include the effects of systemic and intrarenal hypertension and hyperfiltration, tubular hypertrophy and atrophy, tubulointerstitial fibrosis, progressive glomerular sclerosis, arteriosclerosis, and disordered physiologic, humoral, and biochemical responses associated with CKD (such as PTH, FGF-23, inflammation, and hyperphosphatemia [Table 26.1]). In addition, endothelial injury, as part of tubular interstitial injury, and vascular dropout may set up vicious cycles of hypoxia and ischemia, in turn affecting renal cellular function (Table 26.3).[63] The state of the interstitium has been known to be associated with long-term outcomes in many glomerular and tubular diseases for many years.[64]

AKI has been associated with interstitial infiltration, mediated by chemokines, resulting in an influx of macrophages, T cells, and neutrophils (Table 26.1).[65,66] Such cellular responses can culminate in facilitation of repair and regenerative mechanisms, or might be associated with maladaptive responses such as enhancing fibrosis, or interfering with cellular responses. Studies have assessed the roles of arrest of the normal cell cycle, and epigenetic changes within renal epithelial and interstitial cells. These processes might be exacerbated by diets rich in sodium and protein (Table 26.3).[2,67,68]

A balance of injury and restorative factors underlies outcomes for the kidneys in patients with AKI and

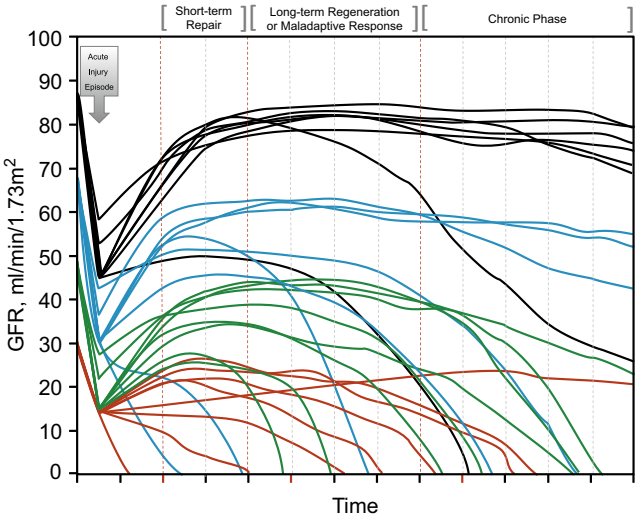


FIGURE 26.2 Renal functional changes after AKI. Previous investigators have outlined possible courses of AKI over time: complete resolution of renal functional decline, rapid, irreversible progression to ESRD, and intermediate long-term courses with progressive decline or maintenance of renal function. Findings from the African-American Study of Kidney Disease and Hypertension (AASK study) suggest the individual trajectories of renal functional changes over time in CKD patients are not simple linear slope relationships interrupted by the steep, rapid sloped declines of AKI, but are rather complicated higher order curves which render modeling difficult. The severity of injury and, most importantly, the baseline level of function at the beginning of the AKI episode, likely determine the long-term course. The Y axis depicts the range of GFR, and the X axis time, in months and years. Different colors indicate different individual patients, with similar GFR before the beginning of an episode of AKI. The time frame for the AKI episode is illustrated with an arrow. The individual lines indicate distinct patients, with varying changes in GFR over time after an episode of AKI. Dotted lines indicate repair and long-term regenerative phases. The scope of outcomes however theoretically includes the entire range of the GFR (right margin, Y axis). Responses after AKI and during the subsequent course of disease may vary over several phases, which may differ between patients in timing: repair and regeneration and chronic maladaptive periods. Individual factors such as age, genetic susceptibilities, the robust nature of repair and regenerative processes compared to those associated with fibrosis, and prescribed therapy may change the slope of decline differentially during the phases. Repetitive episodes of AKI during the course of illness in patients with diminished GFR will make analyses more difficult.

TABLE 26.3 Selected Putative AKI-Specific Factors Related to Progressive Loss of Renal Function

Arrest of normal cell cycle
p21
Epigenetic changes within renal epithelial and interstitial cells
Hypoxia-inducible factors
Heme oxygenase
Angiogenic factors
Repetitive injury
Failed differentiation and sustained proinflammatory profibrotic signaling
Progressive capillary loss
Specific populations of immune cells including subpopulations of macrophages and T cells

CKD, or the combination of the two entities (Table 26.3).[2] It may also be that repetitive insults play meaningful roles.[16,69] Various mediators (such as p21) have been outlined as protective factors in AKI, but may be contributors to ongoing fibrosis, inflammation, and CKD, depending on temporal regulation and expression.[1,2,16] Other factors associated with long-term outcomes after an episode of AKI include failed differentiation, and sustained proinflammatory profibrotic signaling, progressive capillary loss, and endothelial−mesenchymal transformation, G2 M cell cycle block, and epigenetic changes.[1,2,16] Hypoxia-inducible factor-1-α (HIF-1-α) has been outlined as a protective factor in AKI but may be a contributor to CKD.[16] Heme oxygenase-1 protects against acute insults, but also suppresses inflammation. Complex interactions between heme oxygenase and TGF-β1, over time, in specific cell subsets, may have ameliorative or maladaptive consequences.[16,69,70] The lack of kidney tissue from patients with AKI and suitable controls has been identified as a barrier to enhancing our understanding of factors associated with outcomes in patients with AKI.[2,71] The National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) supports the Assessment, Serial Evaluation and Subsequent Sequelae of AKI (ASSESS AKI) study, which prospectively evaluated long-term outcomes of hospitalized patients, with and without CKD, after an episode of AKI, to determine the natural history of AKI and delineate risk factors for progression and development of complications, including CVD. This study also prospectively collected biological samples that will aid future evaluation of associations between selected biomarkers and long-term outcomes.[33]

CLINICAL CONSIDERATIONS

Few patients with AKI receive follow-up after hospital discharge, by generalists, cardiologists, or nephrologists.[1,72,73] Siew et al. demonstrated a low rate of referral of patients with AKI to nephrologists after hospital discharge in the Veterans Administration system.[73] Severity of renal disease did not affect referral rates. A survey study of Canadian nephrologists suggested a substantial gap between the opinions of nephrologists regarding patients who should receive follow-up and actual processes of nephrology care after hospitalization with AKI.[74] Both patients and healthcare providers have described important challenges to care after a hospitalization with AKI, which may affect health outcomes.[75,76]

Despite the relationships between AKI and CKD, not all survivors of AKI go on to develop CKD. However, identification of patients at high risk of CKD following AKI could be used to target specialized care to individuals at greater risk. A predictive model for progression of AKI to stage 4 or 5 CKD was developed in over 14,000 survivors of an AKI hospitalization with a baseline eGFR >45 mL/min/1.73 m^2 from Alberta, Canada. The model was validated in over 2700 patients from Ontario, Canada.[37] Six independent variables associated with advanced CKD following AKI hospitalization were combined in the model: older age, female sex, higher baseline S[Cr], albuminuria, greater severity of AKI, and higher S[Cr] at the time of discharge. A multivariable model based on these predictors was well-calibrated and achieved good discrimination for predicting advanced CKD in the external validation cohort. This model could be used at the time of hospital discharge to identify patients at high risk warranting specialized follow-up after AKI.

We suggest patients with AKI at risk of developing CKD following discharge from the hospital should have periodic assessment of renal function and urinary albumin:creatinine ratio (UACR), to assess prognosis and outcome. Patients at high risk or who sustain severe or persistent decrements in renal function should have follow-up with a nephrologist.[2]

How to treat patients who have survived an AKI episode whether or not they have CKD is unclear.[1,2] Care for patients without preexisting CKD, who sustained an episode of AKI, should include avoidance of nephrotoxic medications, which may include nonsteroidal antiinflammatory drugs (NSAIDs) and contrast agents.[2] However, because of lack of appropriate studies, we do not know whether current practices employed in CKD care slow or worsen the progression of renal disease in patients, with or without CKD, who

survive an episode of AKI.[1,2] Addressing factors associated with poor outcomes in CKD patients, by treating hypertension, and optimizing diabetes care would seem to be useful, but the efficacy and safety of these interventions in patients after an episode of AKI is unknown.[2] For example, more intensive blood pressure lowering resulted in more frequent episodes of AKI in the Systolic Blood Pressure Intervention (SPRINT) Trial,[77] and patients with diabetes who develop AKI have been reported to be at higher subsequent risk of hypoglycemia, particularly when they experienced partial or no recovery of kidney function.[78] Use of RAAS blockers has been associated with lower mortality after AKI but may carry an increased risk of renal complications, including hospitalization for hyperkalemia or recurrence of AKI, suggesting cautious monitoring is warranted in this setting.[79] Low sodium diets and other dietary interventions should be evaluated in such patients. Patients who have had an episode of AKI superimposed on CKD, a common clinical occurrence, should be followed by nephrologists to ensure optimal care.

FUTURE DIRECTIONS

Although recent studies have focused on outcomes based on KDIGO AKI definitions, and changes in S [Cr], several areas need emphasis in future research. Little is known from prospective observational data regarding the long-term course of ATN. It is important that the long-term consequences of AKI be delineated in patients with specific renal diseases, such as ATN, or AIN, as well as prerenal azotemia, and renal vascular disease. The setting in which AKI occurs may be critical to outcome. We know little specifically about AKI which occurs in intensive care unit settings.[80] Although sepsis is understood to be an important common etiologic factor in the development of AKI, relatively little is known about patients who develop AKI after sepsis.[2,16,80–82] In addition, the elderly are particularly susceptible to the development of AKI.[1,26,80]

Finally, only recently have we begun to investigate the long-term sequelae of pediatric and neonatal AKI as well as AKI in low- and middle-income countries.[57,71,83] Studies in children with AKI are particularly important regarding the scope of the problem of CKD in the US and worldwide. If AKI is associated with even small changes in renal function, and the development of chronic disease is dependent, at least in part on time, perinatal status, developmental stage, early nutritional experiences, and absence of diagnostic and therapeutic services, the potential for children with serious illness in the neonatal period or in early life to develop CKD, which is unnoticed until adulthood, perhaps first during a physical examination for the military, an occupational-associated insurance evaluation or a medical encounter for acute illness or traumatic episode, is enormous. If AKI is fundamentally associated with the development of CKD, it is imperative that we understand the course of events in children who survive AKI and come to medical attention in adolescence or young adulthood.

Biomarkers have been sought to predict the susceptibility to AKI, the course of the disease, and progression of CKD.[84–86] It will be important to validate fit-for-purpose biomarkers to predict long-term outcomes of patients with AKI, in the presence or absence of CKD, to determine both prognosis, and therapeutic response to interventions.

Nephrologists caring for patients with AKI, and with AKI superimposed on CKD, urgently need evidence from well-designed, controlled clinical trials to guide the therapy of their patients.[2,82,87] However, initial evaluations suggest therapeutic trials will need to be large and costly, and prevention trials must include very large numbers of participants.[87] The NIDDK has held workshops to facilitate design of clinical trials for AKI patients.[87] Designs considered included prevention trials, trials in specific patient populations, such as those with sepsis, or hospitalized in an intensive care setting, and evaluation of the challenges encountered in developing new therapeutics. The most recent workshop discussed mechanisms that drive susceptibility to future CKD and cardiovascular events and characterized key knowledge gaps to facilitate new strategies to improve clinical outcomes of patients with AKI after hospitalization.[88]

The NIDDK has also sought suggestions regarding research in the field through an electronic medium, the Kidney Research National Dialogue.[71] Responses encompassed developing clinical trial tools, including refining proteomic and metabolomic approaches to diagnosis and prognosis, improving AKI patient phenotyping, including complex clinical, environmental and pharmacologic interactions, determining genetic links with disease susceptibility and outcomes, assessing, characterizing, and validating fit-for-purpose biomarkers in observational and clinical trial settings, focusing on the interplay between repair and regenerative processes in association with mechanisms engendering fibrotic responses, developing better and more clinically relevant animal models, enhancing the evaluation of human renal tissue samples, building public/private partnerships, including academia, regulatory agencies and industry, and performing longitudinal studies.[71] Attention to the AKI stage, setting, and characteristics of the patient population will be critical for research resulting in the improvement of outcomes for patients with AKI in the presence and absence of CKD due to a variety of causes.

CONCLUSIONS

AKI and CKD are interconnected syndromes. To care for patients, nephrologists, pediatricians, internists, critical care specialists, and public health professionals, as well as policy makers, must appreciate the individual components of the syndrome, as well as their combined nature. Identification and implementation of effective interventions and models of care for patients with AKI, CKD, and AKI superimposed on CKD will be necessary to decrease the progression of CKD, and the incidence of ESRD, as well as the incidence and progression of CVD. More knowledge is needed regarding the interplay of AKI and CKD in distinct populations, in particular clinical settings. Like Janus, the two-profiled Roman god, we must evaluate AKI and CKD simultaneously in research, as well as in past and present studies, to advance the care and outcomes of patients with this complex interdigitated syndrome of decrement in renal function.

References

1. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. *Kidney Int* 2012;**82**(5): 516–24.
2. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med* 2014;**371**(1):58–66. https://doi.org/10.1056/NEJMra1214243.
3. Levey AS, Coresh J. Chronic kidney disease. *Lancet (London, England)* 2012;**379**(9811):165–80.
4. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet (London, England)* 2012;**380**(9843):756–66.
5. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;**11**(2):R31.
6. Levin A, Stevens PE, Bilous RW, Coresh J, De Francisco AL, De Jong PE, et al. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**(1):1–150.
7. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int* 2012;**2**(Suppl. 1):1–141.
8. Lowe KG. The late prognosis in acute tubular necrosis; an interim follow-up report on 14 patients. *Lancet (London, England)* 1952: 1086–8.
9. Finkenstaedt JT, Merrill JP. Renal function after recovery from acute renal failure. *N Engl J Med* 1956;**254**:1023–6.
10. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int* 2012;**81**(5):442–8.
11. Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle 2nd JE, Perkins RM. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. *Kidney Int* 2012;**81**(5): 477–85.
12. Leung KC, Tonelli M, James MT. Chronic kidney disease following acute kidney injury-risk and outcomes. *Nat Rev Nephrol* 2013;**9**(2): 77–85.
13. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. *J Am Soc Nephrol* 2005;**16**(1):162–8.
14. James MT, Ghali WA, Knudtson ML, Ravani P, Tonelli M, Faris P, et al. Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography. *Circulation* 2011; **123**(4):409–16.
15. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005;**16**(11):3365–70.
16. Venkatachalam MA, Griffin KA, Lan R, Geng H, Saikumar P, Bidani AK. Acute kidney injury: a springboard for progression in chronic kidney disease. *Am J Physiol Renal Physiol* 2010;**298**(5): F1078–94. https://doi.org/10.1152/ajprenal.00017.2010. Epub 2010 Mar 3.
17. Hsu RK, McCulloch CE, Dudley RA, Lo LJ, Hsu CY. Temporal changes in incidence of dialysis-requiring AKI. *J Am Soc Nephrol* 2013;**24**(1):37–42.
18. Xue JL, Daniels F, Star RA, Kimmel PL, Eggers PW, Molitoris BA, et al. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. *J Am Soc Nephrol* 2006;**17**(4):1135–42.
19. Chawla LS, Amdur RL, Shaw AD, Faselis C, Palant CE, Kimmel PL. Association between AKI and long-term renal and cardiovascular outcomes in United States veterans. *Clin J Am Soc Nephrol* 2014; **9**(3):448–56. https://doi.org/10.2215/CJN.02440213. Epub 2013 Dec 5.
20. Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, et al. Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol* 2009;**20**(1):223–8.
21. Waikar SS, Curhan GC, Wald R, McCarthy EP, Chertow GM. Declining mortality in patients with acute renal failure, 1988 to 2002. *J Am Soc Nephrol* 2006;**17**(4):1143–50.
22. Sanoff S, Okusa MD. Impact of acute kidney injury on chronic kidney disease and its progression. *Contrib Nephrol* 2011;**171**: 213–7.
23. Ali T, Khan I, Simpson W, Prescott G, Townend J, Smith W, et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. *J Am Soc Nephrol* 2007;**18**(4): 1292–8.
24. Amdur RL, Chawla LS, Amodeo S, Kimmel PL, Palant CE. Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. *Kidney Int* 2009;**76**(10):1089–97.
25. Goldstein SL, Jaber BL, Faubel S, Chawla LS. AKI transition of care: a potential opportunity to detect and prevent CKD. *Clin J Am Soc Nephrol* 2013;**8**(3):476–83.
26. Anderson S, Eldadah B, Halter JB, Hazzard WR, Himmelfarb J, Horne FM, et al. Acute kidney injury in older adults. *J Am Soc Nephrol* 2011;**22**(1):28–38.
27. Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM, et al. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. *JAMA* 2009;**302**(11):1179–85.
28. Lo LJ, Go AS, Chertow GM, McCulloch CE, Fan D, Ordonez JD, et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. *Kidney Int* 2009;**76**(8):893–9.
29. James MT, Levey AS, Tonelli M, Tan Z, Barry R, Pannu N, et al. Incidence and prognosis of acute kidney diseases and disorders using an integrated approach to laboratory measurements in a universal health care system. *JAMA Netw Open* 2019;**2**(4):e191795.
30. Vikse BE, Irgens LM, Leivestad T, Skjaerven R, Iversen BM. Preeclampsia and the risk of end-stage renal disease. *N Engl J Med* 2008;**359**(8):800–9.
31. Newsome BB, Warnock DG, McClellan WM, Herzog CA, Kiefe CI, Eggers PW, et al. Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction. *Arch Intern Med* 2008;**168**(6):609–16.

32. Hsu CY, Chertow GM, McCulloch CE, Fan D, Ordonez JD, Go AS. Nonrecovery of kidney function and death after acute on chronic renal failure. *Clin J Am Soc Nephrol* 2009;**4**(5):891–8.
33. Go AS, Parikh CR, Ikizler TA, Coca S, Siew ED, Chinchilli VM, et al. The assessment, serial evaluation, and subsequent sequelae of acute kidney injury (ASSESS-AKI) study: design and methods. *BMC Nephrol* 2010;**11**:22.
34. Go AS, Chinchilli VM, Himmelfarb J, Kimmel PL, Parikh C, et al. *Prospective evaluation of AKI and risk of heart failure: the ASSESS-AKI study. ABSTRACT: SA-OR103 American Society of Nephrology Kidney Week, New Orleans*. ASN Kidney Week, New Orleans, Louisiana. 2017.
35. Thakar CV, Christianson A, Himmelfarb J, Leonard AC. Acute kidney injury episodes and chronic kidney disease risk in diabetes mellitus. *Clin J Am Soc Nephrol* 2011;**6**(11):2567–72.
36. Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. *Kidney Int* 2011;**79**(12):1361–9.
37. James MT, Pannu N, Hemmelgarn BR, Austin PC, Tan Z, McArthur E, et al. Derivation and external validation of prediction models for advanced chronic kidney disease following acute kidney injury. *JAMA* 2017;**318**(18):1787–97.
38. Choi AI, Li Y, Parikh C, Volberding PA, Shlipak MG. Long-term clinical consequences of acute kidney injury in the HIV-infected. *Kidney Int* 2010;**78**(5):478–85.
39. Odutayo A, Wong CX, Farkouh M, Altman DG, Hopewell S, Emdin CA, et al. AKI and long-term risk for cardiovascular events and mortality. *J Am Soc Nephrol* 2017;**28**(1):377–87.
40. Go AS, Hsu CY, Yang J, Tan TC, Zheng S, Ordonez JD, et al. Acute kidney injury and risk of heart failure and atherosclerotic events. *Clin J Am Soc Nephrol* 2018;**13**(6):833–41.
41. Palevsky PM. Chronic-on-acute kidney injury. *Kidney Int* 2012; **81**(5):430–1.
42. Li L, Astor BC, Lewis J, Hu B, Appel LJ, Lipkowitz MS, et al. Longitudinal progression trajectory of GFR among patients with CKD. *Am J Kidney Dis* 2012;**59**(4):504–12.
43. O'Hare AM, Batten A, Burrows NR, Pavkov ME, Taylor L, Gupta I, et al. Trajectories of kidney function decline in the 2 years before initiation of long-term dialysis. *Am J Kidney Dis* 2012;**59**(4): 513–22.
44. James MT, Hemmelgarn BR, Wiebe N, Pannu N, Manns BJ, Klarenbach SW, et al. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. *Lancet (London, England)* 2010;**376**(9758):2096–103.
45. Huen SC, Parikh CR. Predicting acute kidney injury after cardiac surgery: a systematic review. *Ann Thorac Surg* 2012;**93**(1):337–47.
46. Allen DW, Ma B, Leung KC, Graham MM, Pannu N, Traboulsi M, et al. Risk prediction models for contrast-induced acute kidney injury accompanying cardiac catheterization: systematic review and meta-analysis. *Can J Cardiol* 2017;**33**(6):724–36.
47. Pannu N, Graham M, Klarenbach S, Meyer S, Kieser T, Hemmelgarn B, et al. A new model to predict acute kidney injury requiring renal replacement therapy after cardiac surgery. *CMAJ* 2016;**188**(15):1076–83.
48. Palmer BF. Renal dysfunction complicating the treatment of hypertension. *N Engl J Med* 2002;**347**(16):1256–61.
49. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008;**52**(19):1527–39.
50. Raj DS, D'Mello S, Somiah S, Sheeba SD, Mani K. Left ventricular morphology in chronic renal failure by echocardiography. *Ren Fail* 1997;**19**(6):799–806.
51. Collins AJ, Foley RN, Herzog C, Chavers B, Gilbertson D, Herzog C, et al. US Renal Data System 2012 annual data report. *Am J Kidney Dis* 2013;**61**(1):E1–459.
52. Zager RA. Biologic memory in response to acute kidney injury: cytoresistance, toll-like receptor hyper-responsiveness and the onset of progressive renal disease. *Nephrol Dial Transplant* 2013; **28**(8):1985–93.
53. Rifkin DE, Coca SG, Kalantar-Zadeh K. Does AKI truly lead to CKD? *J Am Soc Nephrol* 2012;**23**(6):979–84.
54. Garg AX, Devereaux PJ, Yusuf S, Cuerden MS, Parikh CR, Coca SG, et al. Kidney function after off-pump or on-pump coronary artery bypass graft surgery: a randomized clinical trial. *JAMA* 2014; **311**(21):2191–8.
55. Hsu CY. Yes, AKI truly leads to CKD. *J Am Soc Nephrol* 2012;**23**(6): 967–9.
56. Garg AX, Suri RS, Barrowman N, Rehman F, Matsell D, Rosas-Arellano MP, et al. Long-term renal prognosis of diarrhea-associated hemolytic uremic syndrome: a systematic review, meta-analysis, and meta-regression. *J Am Med Assoc* 2003;**290**(10): 1360–70.
57. Askenazi DJ, Feig DI, Graham NM, Hui-Stickle S, Goldstein SL. 3-5 year longitudinal follow-up of pediatric patients after acute renal failure. *Kidney Int* 2006;**69**(1):184–9.
58. Mammen C, Al Abbas A, Skippen P, Nadel H, Levine D, Collet JP, et al. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. *Am J Kidney Dis* 2012;**59**(4):523–30.
59. Ishani A, Nelson D, Clothier B, Schult T, Nugent S, Greer N, et al. The magnitude of acute serum creatinine increase after cardiac surgery and the risk of chronic kidney disease, progression of kidney disease, and death. *Arch Intern Med* 2011;**171**(3): 226–33.
60. Baldwin DS, Neugarten J, Feiner HD, Gluck M, Spinowitz B. The existence of a protracted course in crescentic glomerulonephritis. *Kidney Int* 1987;**31**(3):790–4.
61. Baldwin DS. Poststreptococcal glomerulonephritis. A progressive disease? *Am J Med* 1977;**62**(1):1–11.
62. Baldwin DS. Chronic glomerulonephritis: nonimmunologic mechanisms of progressive glomerular damage. *Kidney Int* 1982;**21**(1): 109–20.
63. Basile DP. The endothelial cell in ischemic acute kidney injury: implications for acute and chronic function. *Kidney Int* 2007;**72**(2): 151–6.
64. Bohle A, Strutz F, Muller GA. On the pathogenesis of chronic renal failure in primary glomerulopathies: a view from the interstitium. *Exp Nephrol* 1994;**2**(4):205–10.
65. Duffield JS. Macrophages and immunologic inflammation of the kidney. *Semin Nephrol* 2010;**30**(3):234–54.
66. Kinsey GR, Sharma R, Okusa MD. Regulatory T cells in AKI. *J Am Soc Nephrol* 2013;**24**(11):1720–6.
67. Spurgeon-Pechman KR, Donohoe DL, Mattson DL, Lund H, James L, Basile DP. Recovery from acute renal failure predisposes hypertension and secondary renal disease in response to elevated sodium. *Am J Physiol Renal Physiol* 2007;**293**(1): F269–78.
68. Kaushal GP, Shah SV. Challenges and advances in the treatment of AKI. *J Am Soc Nephrol* 2014;**25**(5):877–83.
69. Nath KA, Croatt AJ, Haggard JJ, Grande JP. Renal response to repetitive exposure to heme proteins: chronic injury induced by an acute insult. *Kidney Int* 2000;**57**(6):2423–33.
70. Zager RA, Johnson AC. Progressive histone alterations and proinflammatory gene activation: consequences of heme protein/iron-mediated proximal tubule injury. *Am J Physiol Renal Physiol* 2010; **298**(3):F827–37.
71. Bonventre JV, Basile D, Liu KD, McKay D, Molitoris BA, Nath KA, et al. AKI: a path forward. *Clin J Am Soc Nephrol* 2013;**8**(9):1606–8.

72. USRDS Annual Report 2007. Department of Health and Human Services, NIDDK, United States Renal Data System (USRDS) (NIH Publication No 07-3176). 2007;**1**:240-241.
73. Siew ED, Peterson JF, Eden SK, Hung AM, Speroff T, Ikizler TA, et al. Outpatient nephrology referral rates after acute kidney injury. *J Am Soc Nephrol* 2012;**23**(2):305–12.
74. Karsanji DJ, Pannu N, Manns BJ, Hemmelgarn BR, Tan Z, Jindal K, et al. Disparity between nephrologists' opinions and contemporary practices for community follow-up after AKI hospitalization. *Clin J Am Soc Nephrol* 2017;**12**(11):1753–61.
75. Silver SA, Saragosa M, Adhikari NK, Bell CM, Harel Z, Harvey A, et al. What insights do patients and caregivers have on acute kidney injury and posthospitalisation care? A single-centre qualitative study from Toronto, Canada. *BMJ Open* 2018;**8**(6): e021418.
76. Phipps DL, Morris RL, Blakeman T, Ashcroft DM. What is involved in medicines management across care boundaries? A qualitative study of healthcare practitioners' experiences in the case of acute kidney injury. *BMJ Open* 2017;**7**(1):e011765.
77. Rocco MV, Sink KM, Lovato LC, Wolfgram DF, Wiegmann TB, Wall BM, et al. Effects of intensive blood pressure treatment on acute kidney injury events in the systolic blood pressure intervention trial (SPRINT). *Am J Kidney Dis* 2018;**71**(3):352–61.
78. Hung AM, Siew ED, Wilson OD, Perkins AM, Greevy Jr RA, Horner J, et al. Risk of hypoglycemia following hospital discharge in patients with diabetes and acute kidney injury. *Diabetes Care* 2018;**41**(3):503–12.
79. Brar S, Ye F, James MT, Hemmelgarn B, Klarenbach S, Pannu N. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with outcomes after acute kidney injury. *JAMA Intern Med* 2018;**178**(12):1681–90.
80. Cohen SD, Kimmel PL. Long-term sequelae of acute kidney injury in the ICU. *Curr Opin Crit Care* 2012;**18**(6):623–8.
81. Bonventre JV, Basile D, Liu KD, McKay D, Molitoris BA, Nath KA, Nickolas TL, Okusa MD, Palevsky PM, Schnellmann R, Rys-Sikora K, Kimmel PL, Star RA. Kidney Research National Dialogue (KRND) AKI: a path forward. *Clin J Am Soc Nephrol* 2013; **8**(9):1606–8. https://doi.org/10.2215/CJN.06040613. Epub 2013 Jul 18.
82. Star R. Design issues for clinical trials in acute renal failure. *Blood Purif* 2001;**19**(2):233–7.
83. Abitbol CL, Rodriguez MM. The long-term renal and cardiovascular consequences of prematurity. *Nat Rev Nephrol* 2012;**8**(5):265–74.
84. Liu KD, Glidden DV, Eisner MD, Parsons PE, Ware LB, Wheeler A, et al. Predictive and pathogenetic value of plasma biomarkers for acute kidney injury in patients with acute lung injury. *Crit Care Med* 2007;**35**(12):2755–61.
85. Chawla LS, Seneff MG, Nelson DR, Williams M, Levy H, Kimmel PL, et al. Elevated plasma concentrations of IL-6 and elevated Apache II score predict acute kidney injury in patients with severe sepsis. *Clin J Am Soc Nephrol* 2007;**2**(1):22–30.
86. Liu KD, Yang W, Anderson AH, Feldman HI, Demirjian S, Hamano T, et al. Urine neutrophil gelatinase-associated lipocalin levels do not improve risk prediction of progressive chronic kidney disease. *Kidney Int* 2013;**83**(5):909–14.
87. Molitoris BA, Okusa MD, Palevsky PM, Chawla LS, Kaufman JS, Devarajan P, et al. Design of clinical trials in AKI: a report from an NIDDK workshop. Trials of patients with sepsis and in selected hospital settings. *Clin J Am Soc Nephrol* 2012;**7**(5): 856–60.
88. *NIDDK workshop: improving care for patients after hospitalization with AKI*. Bethesda, MD: Natcher Conference Center; 2019. Available from: https://www.niddk.nih.gov/news/meetings-workshops/2019/improving-care-patients-hospitalization-aki.

QUESTIONS AND ANSWERS

Question 1

A 58-year-old man underwent coronary artery bypass surgery. Postoperatively he developed AKI. He was treated with HD over a two week period. S[Cr] on discharge was 1.2 mg/dL.

Which ONE of the following statements in NOT TRUE regarding his future risk?

A. He is at higher risk of developing CVD
B. He is at higher risk of developing ESRD
C. He is at higher risk of developing advanced stage CKD
D. He is at higher risk of developing a malignancy

Answer: D

There is no evidence that he is at higher risk of developing a malignancy making Answer D not true and the correct answer to this question. AKI has been linked with the development of subsequent CVD, CKD, and ESRD making Answers A, B, and C true.[1,10,18–20]

Question 2

A 63-year-old woman with normal kidney function is admitted with sepsis secondary to a urinary tract infection. She developed AKI during the hospitalization but recovered kidney function and did not require treatment with HD.

Which ONE of the following is true regarding her subsequent hospital course?

A. She is NOT at higher risk of developing advanced stage CKD because there was no preexisting CKD before her episode of AKI
B. She is NOT at higher risk of developing advanced stage CKD because her AKI episode did not require dialysis
C. She has a higher mortality risk secondary to developing AKI
D. She is NOT at higher risk of developing CVD

Answer: C

Answer C is true and the correct answer to this question. AKI leads to new CKD, progression of preexisting CKD, increased risk of entry into ESRD programs, and worsened mortality.[1,20,27,28] Observational studies show a large proportion of patients with AKI, even in the absence of concurrent or preexisting CKD, progress to advanced stages of CKD, even if not treated with RRT during the index hospitalization, therefore Answers A and B are not true.[1,10,24,28,32] Several large observational cohorts show patients who survive an AKI episode are at risk for both progression to CKD and increased cardiovascular events making Answer D not true.[14,25,38]

Question 3

Which of the following clinical factors are associated with poor long-term outcomes of AKI?

A. Level of initial kidney function
B. Extent and severity of AKI
C. Older age
D. Lack of follow-up by physicians
E. All of the above

Answer: E

All of these factors are associated with poor renal outcomes following an episode of AKI. See Table 26.3 for a more comprehensive list.

Question 4

Which of the following factors places CKD patients at higher risk for developing AKI?

A. Failure of autoregulation
B. Abnormal vasodilatory responses
C. Lack of renal reserve
D. Failure of renal tubular mechanisms to reabsorb sodium and water
E. All of the above

Answer: E

All of these factors place CKD patients at higher risk for developing AKI. In addition, frequent hospitalizations with the potential for iatrogenic mishaps or exposure to nephrotoxins, treatment to achieve volume depletion, susceptibility to the use of antihypertensives, overvigorous medication, the use of RAAS blockers, the use of nephrotoxins, and age-related physiologic changes also increase the risk of developing AKI.[1,16,26,48]

Question 5

Which of the following factors have been proposed as factors associated with progressive loss of renal function following AKI?

A. Tubulointerstitial fibrosis
B. Progressive glomerular sclerosis
C. Endothelial injury and vascular dropout
D. Tubular hypertrophy and atrophy
E. All of the above

Answer: E

All of these factors have been associated with progressive loss of renal function following AKI. See Table 26.1 for a comprehensive list of factors.

Question 6

A 47-year-old man is discharged after a prolonged hospitalization for sepsis following an episode of severe pancreatitis. Baseline S[Cr] was 1.1 mg/dL. He required three weeks of treatment with HD and eventually recovered kidney function. Discharge S[Cr] was 2.1 mg/dL.

Which ONE of the following should be part of his post discharge management?

A. No renal follow-up is necessary because he is recovering from his episode of AKI and no longer requires dialysis
B. Renal follow-up is needed to monitor his renal recovery
C. The patient should be seen one year following discharge to recheck S[Cr]
D. It is safe to use NSAIDs because he has recovered renal function

Answer: B

Answer B is correct. We suggest patients discharged from the hospital should have periodic assessment of renal function and UACR, to assess prognosis and outcome. Patients with severe decrement in renal function should have follow-up by a nephrologist, therefore Answer A is incorrect. Answer C is incorrect because one year follow-up is too late to assess his course. Answer D is incorrect as he has not fully recovered kidney function and is at higher risk for rehospitalization with recurrent AKI, which could result from NSAID use.

CHAPTER

27

Psychosocial Issues in Chronic Kidney Disease Patients

Daniel Cukor[a], *Nisha Ver Halen*[b], *Paul L. Kimmel*[c]

[a]Behavioral Health, The Rogosin Institute, New York, NY, United States; [b]Center for Integrative Health and Wellbeing, Weil Cornell Medicine, New York, NY, United States; [c]Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States

Abstract

The mental health needs of patients with chronic kidney disease (CKD) are reviewed with particular emphasis on the roles of depression, quality of life, and adherence. We also review the likely precipitating factors and effects of each of these psychological phenomena, including a discussion of some of the health disparities in the psychological presentations of CKD patients. Identification of depression in patients with renal disease is improving, but intervention strategies and research are greatly needed. Biopsychosocial formulation and intervention would provide better overall medical care to patients with CKD.

INTRODUCTION

The psychological response to the diagnosis and continued demands of chronic kidney disease (CKD) are variable but largely understudied. The course, prognosis, and symptom burden of a medical illness alter patients' responses. Beyond medical and illness factors, the psychological landscape of individuals also shapes the patient's perception of his or her ability to cope with the disease. Past psychiatric history, level of social support, understanding of the disease, and characteristics of relationships with physicians all play roles in determining how the CKD patient will adjust. Research on psychological influences on CKD course is still underdeveloped. We review the existing scientific literature regarding psychosocial challenges in CKD patients, concentrating on the roles of comorbid psychopathology, adherence to medical prescription, and perception of quality of life (QOL).

PSYCHOPATHOLOGY

Psychosocial functioning can affect medical outcomes. We propose a general heuristic of the path from CKD to consequent negative health outcomes (Figure 27.1). In the model, the CKD patient can enter a cycle of increased symptom burden, depression, and social strain, which can lead to a second cycle of decreased compliance, increased illness activity, and feeling worse. This second cycle can cause further complications and contribute to continuing decline in kidney function.

Depression

Both depression and poor QOL have been associated with increased morbidity and mortality in patients with end-stage renal disease (ESRD).[1–3] However, the prevalence and long-term effects of psychological comorbidities that develop in earlier stages of CKD have been understudied.

Depression Measurement

The identification of depression in patients with CKD is complicated by the substantial overlap between the symptoms of the affective disorder and those of uremia.[4–6] Careful attention to the etiology, nature, and timing of the presentation is required. There is similarity between the uremic symptoms of encephalopathy, anorexia, sleep apnea, and neuropathic pain and the psychomotor changes, weight and appetite changes, sleep difficulties, and aches and pains associated with depression.

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00027-9

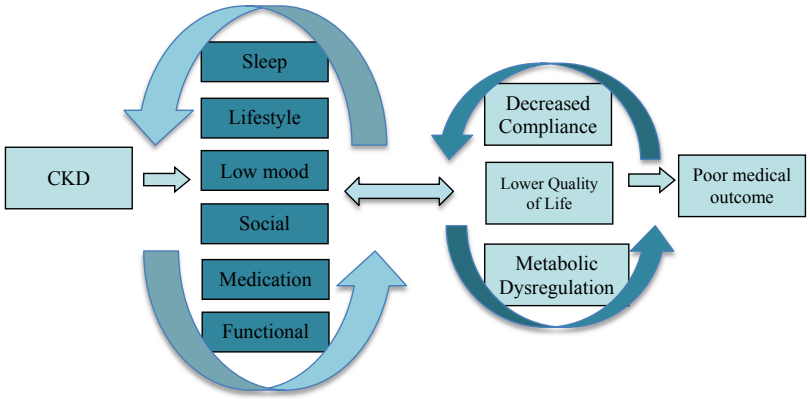


FIGURE 27.1 Suggested pathways of psychosocial variables leading chronic kidney disease (CKD) to increased negative medical outcomes. The vicious cycle between symptoms of illness, depression, and social strain lead to a second cycle of decreased compliance, increased illness activity, and feeling worse. These cycles then lead to worsened health outcomes.

Another challenge to the identification of depression in patients with medical illness is the lack of a standard measurement tool. A variety of psychological measures have been used to measure depression in CKD patients, but the validity and reliability of these measures in this population are not well studied. The field still needs to arrive at a consensus regarding the appropriate screening and diagnostic tools for the broad population of patients with kidney disease. Evaluation of the appropriate cutoff scores for these measures is warranted, as the prognostic value of these measures has yet to be determined in CKD samples. Furthermore, the sensitivity of these measures to track depression over time or illness course is still unclear.[7]

Prevalence of Depression in CKD

Depression has been identified as a prominent psychological issue facing patients with ESRD, with studies reporting prevalence rates of approximately 20%.[5–15] Far less is known about rates of depressive affect and major depressive disorder in patients with CKD prior to starting renal replacement therapy (RRT). Early stages of CKD are often not associated with symptoms. Only after a severe decrease in GFR does the symptom burden of CKD increase, at which point symptoms of depression may be more likely to emerge. In a study of male Veterans, Hedayati et al.[15] reported that 21% of the sample had a lifetime history of a major depressive episode, using the Mini International Neuropsychiatric Interview (MINI). The prevalence of depression did not vary according to stage of CKD. In a large multicenter cohort of African Americans with hypertensive CKD, 26% of participants were found to have elevated depressive affect, measured by the Beck Depression Inventory (BDI)-II using a threshold score of >14.[16] In our study of 70 Black CKD patients, we found the rate of depression to be 30%, using the BDI self-report scale.[17]

Effects of Depression in CKD

CKD patients who are also depressed are at risk for consequences that may affect the course of disease progression. We found that baseline depression scores predicted eGFR at 6 months in a study of CKD patients.[17] These results were confirmed using a regression model, even after controlling for baseline eGFR and presence of hypertension and diabetes. Another longitudinal study examined depression as a predictor of adverse outcomes in patients with CKD.[18] Patients with a major depressive episode were 1.86 times more likely to experience an adverse outcome within 1 year. Although this study highlights the important predictive role of depression, it was limited to psychiatric diagnosis in a select population of Veterans, for a limited duration (1 year). Kellerman et al.[19] found that depressive affect predicted mortality in CKD patients over a 7-year follow-up, as measured in a population of predominantly White males, but like all the studies mentioned, it was limited to a single psychological variable. In a large cohort of Veterans, depression in late-stage CKD was associated with a 6% increase in mortality after transition to ESRD.[20] Depression has also been found to be associated with other physical health outcomes, such as prevalence of pain, sexual dysfunction, and sleep disturbance in patients with CKD.[21]

The impact of the treatment of depression on other outcome variables has not been well studied. In fact, a recent randomized controlled trial did not demonstrate improved depression response to sertraline vs. placebo in patients with CKD.[22]

Investigators have examined the association between depression and health outcomes in ethnic minority groups.[16,23] In a large multicenter cohort of African Americans with hypertensive CKD, Fischer et al. found elevated depressive affect was associated with greater incidence of cardiovascular death or hospitalization.[16]

A second study, a cross-sectional analysis of 3853 Hispanic and non-Hispanic patients with CKD, revealed elevated depressive affect was associated with lower eGFR and higher levels of proteinuria.[23]

The relationship between depression, CKD, and cognitive decline requires further investigation. Kurella et al.[24] assessed cognitive functioning in a sample of 80 CKD patients not requiring dialysis and 80 ESRD patients receiving maintenance hemodialysis. An association between stage of CKD and degree of cognitive impairment was found on measures of mental status, executive functioning, and verbal memory. Similarly, Elias et al.[25] found an association between CKD severity and cognitive impairment. CKD patients with lower renal function as well as those with higher S [Cr] demonstrated decreased performance on visual spatial processing, attention, and planning abilities. In examining 2800 SPRINT-MIND participants, an association was detected between both lower eGFR and higher urine albumin:creatinine ratio and poorer global cognitive functioning. Cerebrovascular disease may be a key link between CKD and extent of cognitive impairment.[26]

Other Psychopathology

A number of other psychiatric disorders can either develop or manifest during the course of CKD. Nephrologists are increasingly called on to serve their patients' mental health needs or coordinate psychiatric consultation. There is little research on the effect an anxiety disorder, personality disorder, or substance abuse disorder might have on CKD course or treatment.

There is a small but developing literature on anxiety disorders and their effect in CKD patients. A review of 55 studies that examined anxiety symptoms in ESRD patients revealed an average prevalence rate of 38% with levels for individual studies ranging from 12% to 52%.[27] Anxiety in CKD and ESRD patients has been associated with decreased QOL, with specific reductions in ratings of emotional wellbeing, burden of kidney disease, quality of social interaction, and even general health.[28–33] There are few treatment studies of anxiety disorders in nondialysis CKD patients.

Treatment options for CKD patients with psychiatric disorders include psychotherapy, particularly cognitive behavioral therapy, and pharmacologic agents similar to those used in the general patient population. However, treatment of psychological disease in the ESRD population presents unique challenges. Careful consideration of medication dose adjustments for level of GFR must be addressed each time pharmacologic therapy is considered in a CKD patient. The challenges of treating anxiety in CKD patients should not limit use of appropriate therapy.

There is increasing evidence in the ESRD literature that psychiatric disorders should be evaluated and followed, as they may have a significant impact on outcome.[34,35] This emerging evidence is leading to an acceptance that a focus on the emotional needs of the patient should be included in the provision of comprehensive medical care to the CKD patient.

QUALITY OF LIFE

Treatment of CKD has evolved to entail more than mere survival and extension of life, and includes maintenance of wellbeing.[36,37] Though prolonging life remains an essential goal of treatment, physicians are additionally examining how CKD impacts patients' daily living and functioning. Preserving the patients' sense of wellbeing, or their QOL, is an essential component of medical treatment for CKD.

Quality of Life Definitions

The World Health Organization defines QOL as an "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns."[38] Essentially, QOL is an expansive, multidimensional concept that includes one's subjective appraisal of the "goodness" of various aspects of life.[39] Measuring this construct of subjective wellbeing requires an assessment of pleasant and unpleasant affect, general life satisfaction, and satisfaction in various domains including work, family, leisure, health, and finances.[39]

Health-related quality of life (HRQOL) is a somewhat narrower construct, often looked at within the chronic disease literature, that focuses on health concerns and demands.[40] HRQOL refers to quality of life issues that are related to health or illness. The concept of HRQOL has evolved from the World Health Organization's definition of health as more than the lack of disease or sickness, including total physical, mental, and social wellbeing.[41] HRQOL is defined as one's perception of the effect of disease and its treatment across physical, psychological, and social areas of functioning and wellbeing.[40] HRQOL is measured using both general multidimensional assessments, which allow comparison across diseases, and disease-specific multidimensional assessments, which allow specific examination of characteristics common to specific diseases or populations.[40] The SF-36 is a commonly used generic survey that has been deployed in a variety of disease populations.[42,43] This assessment examines health status over the past 4 weeks within eight domains including physical function, role limitations caused by physical problems,

pain, general health, vitality/energy, social function, mental health, and role limitations caused by mental health. The Kidney Disease Quality of Life Instrument (KDQOL) is a commonly used disease-specific self-administered survey designed specifically for patients with kidney disease.[44–47]

Threats to Quality of Life

A substantial amount of research indicates ESRD patients experience impaired QOL.[1,42,48–53] Generally, it appears the HRQOL of ESRD patients treated with dialysis is worse than the general population and patients with kidney transplants.[37,42,45] Although few studies have examined HRQOL in CKD patients in earlier stages not on RRT, age, frailty, symptom burden, and treatment frequency may all be important predictors of diminished QOL. Some findings suggest that even in early stages of CKD, impairments in QOL are exhibited across stages and over time.

There are conflicting results concerning whether QOL impairments occur progressively across CKD stages. Although one study showed progressive impairments in all dimensions of HRQOL across renal function levels and CKD stages, another study did not demonstrate such a progressive decrease in HRQOL throughout CKD stages.[40,50] Other studies show a relationship of HRQOL to mortality, but not disease progression.[53] Nevertheless, studies clearly demonstrate a significant drop in QOL within CKD stages 1–3 in both physical and mental health dimensions. Patients in CKD stages 2 and 3 exhibited significantly lower scores on HRQOL dimensions compared to matched controls.[40] It appears the HRQOL of CKD patients can be affected by a variety of different factors across multiple domains.

Medical Factors

Several medical factors specific to CKD, and CKD-related comorbidities and risk factors, have been implicated as negatively affecting QOL. A recent study found C-reactive protein (CRP) and cardiovascular disease (CVD) were the most important predictors of poor QOL in 535 patients with CKD stages 2–5, followed by reduced GFR and diabetes.[40] One study of 155 predialysis patients (CKD stages 1 through 5) and 36 dialysis patients found the presence of three or more comorbidities had a negative impact on the physical functioning, physical role functioning, and the physical component summary scores of the SF-36.[40] Numerous studies have also found anemia is a central predictor of QOL and that treatment of anemia for CKD patients can lead to positive changes in perception of QOL.[36,42,47] A study of 81 CKD patients not on dialysis found that improvements in hemoglobin were associated with statistically significant and clinically meaningful HRQOL increases in physical activity, vitality, and fatigue.[54] Hypertension, which commonly occurs with CKD, may also reduce HRQOL.[55]

Psychological and Subjective Factors

Renal functional decrements and medical factors are not the sole determinants of perception of impaired QOL in CKD patients. Several studies delineate a relationship between pain, physical activity, sleep, and perception of QOL in the CKD population.[21] Ninety-two predialysis patients with CKD exhibited a significant association between poor sleep and poor QOL and between pain and lower QOL. There were no significant differences in perception of pain or sleep disturbance between these CKD patients and a comparison group of 61 general medical outpatients without renal disease.[21] Regardless of whether the amount of pain and sleep disturbance in patients with CKD is unique or similar to individuals suffering from other chronic illnesses, it is important to assess such factors when evaluating QOL in this patient population.[56] Another study found that in 79 predialysis patients with stages 3 and 4 CKD and 19 dialysis patients, higher emotionally defensive coping was associated with a lower score on the mental component summary of the SF-36 and with the physical component summary, indicating coping strategies can have varying effects on the different dimensions of HRQOL.[57] Though research specifically examining the effect of depression on QOL in early stage CKD patients is lacking, one cross-sectional study of advanced CKD (stages 4 and 5) and ESRD patients revealed depression was strongly correlated with the mental component summary of the SF-36.[58] Coping and illness perception are important ways of measuring people's response to their illness and may well lead to targeted psychological interventions in the future.[59]

Sociodemographic Factors

A cross-sectional study of 155 predialysis patients and 36 dialysis patients noted that more sociodemographic factors, such as age, ethnicity, gender, professional activity, education, and income, were associated with decreased perception of QOL compared to physical factors.[56] One large-scale, longitudinal study revealed early-stage CKD patients who were female and/or over the age of 65 had worse perception of QOL.[36]

ADHERENCE

Treatment for CKD requires adherence to a complex medical prescription including dietary, medication, and behavioral regimens. To slow the progression of

kidney disease, patients must work with their physicians to develop a treatment plan. Diabetes and high blood pressure are the two most common causes of CKD. Hypertension and diabetes are responsible for approximately two-thirds of all cases of ESRD and a substantial proportion of patients with CKD.[60] For patients with diabetes and/or hypertension, treatment involves taking prescribed medication, as well as making significant lifestyle changes, including substantive changes in diet. CKD patients should also attend appointments with nephrologists and in some cases follow recommendations for surgical procedures.

Medical Prescription

Treatment of diabetes mellitus and/or hypertension often involves taking medication, and the medication regimen may be complex, including multiple drugs. There are three ways in which a patient may be nonadherent to medication.[61] The first is through nonfulfillment, whereby the patient may accept a prescription from the physician but then fail to fill it in a timely manner, or at all. In a second form of nonadherence, nonpersistence, patients may initially comply with the prescription but over time cease to take the medication for various reasons. Finally, patients may have difficulty taking medication at the correct dosage or time, known as nonconforming.

Dietary changes are prescribed with the goal of preserving existing kidney function and delaying onset of later stages of CKD. Dietary changes include limiting protein intake to reduce kidney burden, decreasing sodium intake to control high blood pressure, decreasing phosphate intake, and managing blood glucose levels in diabetic patients. Exercise recommendations for the CKD patient typically involve increasing aerobic activity. CKD patients who regularly exercise show improvements in physical fitness, walking capacity, cardiovascular health, and perception of QOL.[62]

CKD patients must attend regular follow-up visits with a nephrologist to monitor progression of the disease. Given that many CKD patients manage multiple comorbid illnesses, these appointments may add to the perceived burden of illness. In the later stages of CKD, the patient and physician must begin to prepare for RRT. Access placement represents a time of increased stress for patients with CKD.[63,64] One study found that this stage of illness was associated with the highest levels of depression, measured by the BDI.[64] Increased stress burden coupled with elevated depressive affect could affect adherence to prescription for access placement.

Evidence of Nonadherence

Research on adherence in CKD has largely been limited to the study of ESRD patients. More recently, studies have begun to examine medication nonadherence in patients with earlier stages of CKD. Data from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study indicated that in a sample of approximately 4000 patients with CKD using antihypertensive medications, 27.7% of participants indicated that they had forgotten to take their medication, 4.4% reported being careless about taking medication, 5.7% reported not taking medication when they felt better, and 4.2% missed taking medications when feeling sick. In this study CKD and non-CKD patients reported similarly poor adherence to antihypertensive medication.[65] In a longitudinal study of medication adherence, researchers in Brazil used self-reported pill counts and questionnaires to assess adherence in 149 patients with CKD for 1 year. At baseline 17.4% of patients were found to be nonadherent, and this number increased to 26.8% at 1-year follow-up.[66]

Another study examined a large cohort of patients who presented at the Cincinnati Veterans Administration Medical Center for ambulatory care.[67] Researchers examined patterns and effects of antihypertensive medication adherence in 7227 patients with CKD (GFR less than 60 mL/min/1.73 m^2 during the 2-year study period). Unlike studies that used self-report to measure adherence, this study calculated medication adherence using the Medication Possession Ratio (MPR), derived from prescription information included in the Veteran's Administration medical database. MPR was defined as actual treatment days divided by total possible treatment days (truncated for the study period or death). An MPR of less than 0.80 constituted poor medication adherence. Approximately one-third of patients with CKD had poor medication adherence. MPR declined along with renal function and with increase in number of medications.[67] Vupputuri et al.[68] also assessed MPR in patients with CKD taking antihypertensive medication. In a sample of 3077 patients, 22.6% and 8.9%, respectively, had low and very low medication adherence.

Barriers to Adherence

There are numerous factors that make adhering to the medication, dietary, and behavioral treatments for CKD challenging. Polypharmacy and regimen complexity are two significant obstacles to medication adherence in patients managing chronic illnesses including CKD.[66,67] Polypharmacy and regimen

complexity may present particular challenges for elderly patients who may have concurrent cognitive decline.

Barriers to adherence have been separated into three categories: patient factors, physician factors, and system factors. Patient factors are individual-level variables that may affect a patient's thoughts and behaviors associated with treatment adherence. Depression and medical illness can interfere with adherence by reducing motivation and energy to engage in healthy behaviors, obtain social support, take medications, attend appointments, and plan for future treatment.[11,17,34] Difficulties with memory and concentration can present a significant obstacle to compliance with drug therapy. Health beliefs regarding the prioritization of illnesses and effectiveness of treatment can also affect adherence behaviors, particularly for patients taking many medications with side effects. In a qualitative study of older adults with CKD, interviews revealed that patients prioritize medications based on perceptions of the salience of a particular condition and revealed a discordance between patients' beliefs about medication and conventional medical opinion.[69] Cultural associations with particular foods may make it difficult for some CKD patients to abstain from meals high in protein or sodium.

Physicians play an important role in determining patient adherence to treatment. The physician–patient relationship has been identified as an important predictor of treatment adherence across various chronic illnesses.[70] Patients dealing with other illnesses as well as CKD must learn about each of these conditions to successfully manage their health. The nephrology team is responsible for providing education about course of illness, treatment options, and effects of nonadherence. The team should be sensitive to the impact that the information and recommendations may have on patients' lifestyles. Ethnic differences between patient and physician can serve as a barrier to participation and effective communication.[71–73] Open and culturally sensitive communication with the patient will inform the physician about relevant individual-level factors that may interfere with adherence. Physicians should be cognizant of these factors when developing a treatment plan with the patient.

Systemic factors are variables that are typically outside the control of both the patient and the physician, and present potential obstacles to treatment adherence. Of primary importance for many is the issue of cost of medications, hospitalizations, and physician visits. Pharmacotherapy for psychiatric as well as medical illness may be costly and can influence patient prioritization of medications. Access to care can also be a challenge for disabled patients or those living in particular geographic regions.

Effects of Nonadherence

Poor adherence to medication regimens accounts for substantial worsening of disease, death, and increased healthcare costs in the US.[74–77] Although there is limited literature about the specific effects of treatment nonadherence on CKD outcomes, there is overwhelming evidence that uncontrolled diabetes and hypertension are associated with progression of CKD. Schmitt et al.[67] found patients with poor adherence were 23% more likely to remain hypertensive over a 2-year observation period, controlling for age, renal function, and comorbid illness. Vupputuri et al.[68] showed poor medication adherence was consistently associated with uncontrolled hypertension. Tangkiatkumjai[75] showed that nonadherence to antihypertensive medication in patients with CKD was associated with more rapid disease progression.

MENTAL HEALTH DISPARITIES

In the general population the prevalence, persistence, and impact of depression appear to vary by race. Williams et al.[78] conducted a national survey of 6082 African American, Caribbean Black, and non-Hispanic White participants and found that lifetime prevalence of major depressive disorder was highest for Whites. Chronicity and severity of depression, however, were greater for both Black groups. Furthermore, depression was more likely to be untreated in African Americans and Caribbean Blacks.[78,79] In two studies, the impact of elevated depressive affect in hypertensive CKD in the African–American Study of Kidney Disease and Hypertension (AASK) Cohort Study was investigated. In the first study,[16] baseline data were analyzed. Among 628 subjects, 166 had scores over 14 on the BDI, but only 34 were prescribed antidepressant medication. Although there was no direct relationship between depression scores and GFR, a relationship was found with unemployment, lower income, and lower QOL and satisfaction with life scales. In a further analysis that included a 5-year observation period, Cox regression analyses were used to relate cardiovascular and renal outcomes to baseline BDI scores.[56] Forty-two percent of the sample ($n = 628$) had BDI-II scores of 11 or more, and 26% had a score above 14. During a 5-year follow-up, the cumulative incidence of cardiovascular death/hospitalization was significantly greater for participants with baseline BDI-II scores of 11 or more compared with those with scores less than 11.

Fischer et al.[23] examined data from the Chronic Renal Insufficiency Cohort (CRIC) and Hispanic-CRIC (H-CRIC) studies. CRIC enrolled Hispanics and non-Hispanics at seven centers, and H-CRIC enrolled

Hispanics at the University of Illinois. Twenty-seven percent of participants (n = 3853) had evidence of elevated depressive symptoms (greater than 11 on BDI). Only 31% of those with elevated depressive symptoms were taking antidepressants. They found a relationship between the prevalence of elevated depressive symptoms and level of kidney function. Decreased eGFR was associated with a greater risk for elevated depressive affect. In regression analyses, BDI score, Hispanic ethnicity, non-Hispanic Black race, and higher urine albumin levels were each associated with decreased odds of antidepressant use. Women had greater odds of antidepressant use.

Although more research on the mental health disparities within CKD are urgently needed, certain points are clear.[80] Elevated depressive symptoms are common in individuals with CKD. Individuals of racial and ethnic minority background and CKD have a substantial burden of elevated depressive symptoms. In general, depression treatment utilization is low and appears to be lower for men, Hispanics and Blacks.

CONCLUSIONS

CKD by definition is a chronic and often progressive disease. Patients' psychological functioning, ability to cope, perception of social support, and resources may well predict their reaction to the diagnosis and acceptance of the illness. Depression is the most common psychiatric disorder in patients with CKD. Although the identification of depression can be complicated by overlapping CKD symptoms, screening may be warranted. Untreated depression is a risk factor for progressive CKD and possibly mortality. Depression is also associated with decreased QOL. Beyond depression, QOL for CKD patients can be negatively affected by several medical and psychological factors, some of which may be modifiable.

As physicians' treatment goals increasingly embrace a biopsychosocial perspective, more intervention trials aimed at improving mental health and QOL of CKD patients will be needed. As treatment for CKD requires dietary, medication, and behavioral adherence, the factors that predict and explain patient nonadherence warrant further investigation.

There may be meaningful mental health disparities in CKD patients, with rates of psychopathology being higher in some minority groups. As minority populations are overrepresented among CKD patients, they form an important group for assessment and treatment. The formal study of the psychosocial needs of CKD patients is still in its early stage of development, and there are many important questions still unanswered. What is clear, however, is that the psychosocial needs of the CKD patient can be substantial, and quality medical care should attempt to identify and address those needs.

References

1. Kimmel PL, Peterson R, Weihs K, Simmens SJ, Alleyne S, Cruz I. Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. *Kidney Int* 2000; **57**:2093–8.
2. Revuelta KL, López FJG, de Álvaro Moreno F, Alonso J. Perceived mental health at the start of dialysis as a predictor of morbidity and mortality in patients with end-stage renal disease (CALVIDIA Study). *Nephrol Dial Transplant* 2004;**19**:2347–53.
3. Hedayati SS, Bosworth HB, Briley L, Sloane RJ, Pieper CF, Kimmel PL. Death or hospitalization of patients on chronic hemodialysis is associated with a physician-based diagnosis of depression. *Kidney Int* 2008;**74**:930–6.
4. Kimmel PL, Cukor D, Cohen SO, Peterson RA. Depression in end-stage renal disease patients: a critical review. *Adv Chron Kidney Dis* 2007;**14**:328–34.
5. Kimmel PL. Depression in patients with chronic renal disease: what we know and what we need to know. *J Psychosom Res* 2002; **53**:951–6.
6. Kimmel PL, Peterson RA. Depression in end-stage renal disease patients treated with hemodialysis: tools, correlates, outcomes, and needs. *Semin Dial* 2005;**18**:91–7.
7. Toups M, Carmody T, Trivedi MH, Rush AJ, Hedayati SS. Performance of depression rating scales in patients with chronic kidney disease: an item response theory-based analysis. *Gen Hosp Psychiatry* 2016;**42**:60–6.
8. Kimmel PL. Psychosocial factors in dialysis patients. *Kidney Int* 2001;**59**:1599–613.
9. Kimmel PL, Peterson RA. Depression in patients with end-stage renal disease treated with dialysis: has the time to treat arrived? *Clin J Am Soc Nephrol* 2006;**1**:349–52.
10. Hedayati SS, Bosworth HB, Kuchibhatia M, Kimmel PL, Szczech LA. The predictive value of self-reported questionnaires compared to physician diagnosis of depression in end stage renal disease patients receiving chronic hemodialysis. *Kidney Int* 2006; **69**:1662–8.
11. Cukor D, Peterson RA, Cohen SD, Kimmel PL. Depression in end-stage renal disease hemodialysis patients. *Nat Clin Pract Nephrol* 2006;**2**:678–87.
12. Cukor D, Coplan J, Brown C, Friedman S, Cromwell-Smith A, Peterson RA. Depression and anxiety in urban hemodialysis patients. *Clin J Am Soc Nephrol* 2007;**2**:484–90.
13. Kimmel PL, Thamer M, Richard CM, Ray NF. Psychiatric illness in patients with end-stage renal disease. *Am J Med* 1998;**105**:214–21.
14. Watnick S, Kirwin P, Mahnensmith R, Concato J. The prevalence and treatment of depression among patients starting dialysis. *Am J Kidney Dis* 2003;**41**:105–10.
15. Hedayati SS, Minhajuddin AT, Toto RD, Morris DW, Rush AJ. Prevalence of major depressive episode in CKD. *Am J Kidney Dis* 2009; **54**:424–32.
16. Fischer MJ, Kimmel PL, Greene T, Gassman JJ, Wang X, Brooks DH. Elevated depressive affect is associated with adverse cardiovascular outcomes among African Americans with chronic kidney disease. *Kidney Int* 2011;**80**(6):670–8.
17. Cukor D, Fruchter Y, Ver Halen N, Naidoo S, Patel A, Saggi SJ. A preliminary investigation of depression and kidney functioning in patients with chronic kidney disease. *Nephron Clin Pract* 2012; **122**:139–45.
18. Hedayati SS, Minhajuddin AT, Afshar M, Toto RD, Trivedi MH, Rush AJ. Association between major depressive episodes in

patients with chronic kidney disease and initiation of dialysis, hospitalization, or death. *J Am Med Assoc* 2010;**303**:1946–53.
19. Kellerman QD, Christensen AJ, Baldwin AS, Lawton WJ. Association between depressive symptoms and mortality risk in chronic kidney disease. *Health Psychol* 2010;**29**:594–600.
20. Molnar MZ, Streja E, Sumida K, Soohoo M, Ravel VA, Gaipov A, Potukuchi PK, Thomas F, Rhee CM, Lu JL, Kalantar-Zadeh K. Pre-ESRD depression and post-ESRD mortality in patients with advanced CKD transitioning to dialysis. *Clin J Am Soc Nephrol* 2017;**12**(9):1428–37.
21. Cohen SD, Patel SS, Khetpal P, Peterson RA, Kimmel PL. Pain, sleep disturbance, and quality of life in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2007;**2**(5):919–25.
22. Hedayati SS, Gregg LP, Carmody T, Jain N, Toups M, John Rush A, Toto RD, Trivedi MH. Effect of sertraline on depressive symptoms in patients with chronic kidney disease without dialysis dependence: the CAST randomized clinical trial. *J Am Med Assoc* 2017; **318**(19):1876–90.
23. Fischer MJ, Xie D, Jordan N, Kop WJ, Krousel-Wood M, Kurella Tamura M. Factors associated with depressive symptoms and use of antidepressant medications among participants in the Chronic Renal Insufficiency Cohort (CRIC) and Hispanic-CRIC studies. *Am J Kidney Dis* 2012;**60**(1):27–38.
24. Kurella M, Chertow GM, Luan J, Yaffe K. Cognitive impairment in chronic kidney disease. *J Am Geriatr Soc* 2004;**52**(11):1863–9.
25. Elias MF, Elias PK, Seliger SL, Narsipur SS, Dore GA, Robbins MA. Chronic kidney disease, creatinine and cognitive functioning. *Nephrol Dial Transplant* 2009;**24**(8):2446–52.
26. DE Weiner, Gaussoin SA, Nord J, Auchus AP, Chelune GJ, Chonchol M, Coker L, Haley WE, Killeen AA, Kimmel PL, Lerner AJ. Cognitive function and kidney disease: baseline data from the systolic blood pressure intervention trial (SPRINT). *Am J Kidney Dis* 2017;**70**(3):357–67.
27. Murtagh FE, Addington-Hall J, Higginson IJ. The prevalence of symptoms in end-stage renal disease: a systematic review. *Adv Chron Kidney Dis* 2007;**14**:82–99.
28. Martin C, Thompson D. Prediction of quality of life in patients with end-stage renal disease. *Br J Health Psychol* 2000;**5**:41–55.
29. Feroze U, Martin D, Kalanter-Zadeh K, Kim J, Reina-Patton A, Kopple JD. Anxiety and depression in maintenance dialysis patients: preliminary data of a cross-sectional study and brief literature review. *J Ren Nutr* 2012;**22**:207–10.
30. Çelik G, Annagür BB, Yılmaz M, Kara F. Findings of multidimensional instruments for determining psychopathology in diabetic and non-diabetic hemodialysis patients. *Int J Clin Exp Med* 2012; **5**:346–54.
31. Birmele B, Le Gall A, Sautenet B, Aguerre C, Camus V. Clinical, sociodemographic, and psychological correlates of health-related quality of life in chronic hemodialysis patients. *Psychosomatics* 2012;**53**:30–7.
32. Vasquez I, Vaderrabano F, Fort J, Jofre R, Lopez-Gomez JM, Moreno F. Psychosocial factors and health-related quality of life in hemodialysis patients. *Qual Life Res* 2005;**1**:179–90.
33. Kallay E, Pop R, Balazsi R. Emotional profile and quality of life in chronic renal failure and renal transplant patients. *Cogn Brain Behav* 2009;**13**:313–28.
34. Cukor D, Cohen SD, Peterson RA, Kimmel PL. Psychosocial aspects of chronic disease: ESRD as a paradigmatic illness. *J Am Soc Nephrol* 2007;**18**(12):3042–55.
35. Wuerth D, Finkelstein SH, Ciarcia J, Peterson R, Kliger AS, Finkelstein FO. Identification and treatment of depression in a cohort of patients maintained on chronic peritoneal dialysis. *Am J Kidney Dis* 2001;**37**(5):1011–7.
36. Soni RK, Weisbord SD, Unruh ML. Health-related quality of life outcomes in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2012;**19**(2):153.
37. Unruh ML, Hess R. Assessment of health-related quality of life among patients with chronic kidney disease. *Adv Chron Kidney Dis* 2007;**14**(4):345–52.
38. WHOQOL group. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med* 1995;**41**:1403–9.
39. Theofilou P. Quality of life: definition and measurement. *Eur J Psychol* 2013;**9**(1):150–62.
40. Pagels AA, Söderkvist BK, Medin C, Hylander B, Heiwe S. Health-related quality of life in different stages of chronic kidney disease and at initiation of dialysis treatment. *Health Qual Life Outcomes* 2012;**10**(1):71.
41. *Preamble to the constitution of the World Health Organization as adopted by the international health conference, New York, 19–22 June 1946; signed on 22 July 1946 by the representatives of 61 states (Official records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948. World Health Organization: the first ten years of the World Health Organization*. Geneva: World Health Organization; 1958.
42. Kimmel PL. Just whose quality of life is it anyway? Controversies and consistencies in measurements of quality of life. *Kidney Int* 2000;**57**:S113–20.
43. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;**30**(6):473–83.
44. Hays RD, Kallich JD, Mapes DL, Coons SJ, Carter WB. Development of the kidney disease quality of life (KDQOL) instrument. *Qual Life Res* 1994;**3**:329–38.
45. Patel SS, Peterson RA, Kimmel PL. Psychosocial factors in patients with chronic kidney disease: the impact of social support on end-stage renal disease. *Semin Dial* 2005;**18**:98–102.
46. Finkelstein FO, Wuerth D, Finkelstein SH. Health related quality of life and the CKD patient: challenges for the nephrology community. *Kidney Int* 2009;**76**(9):946–52.
47. Weisbord SD, Kimmel PL. Health-related quality of life in the era of erythropoietin. *Hemodial Int* 2008;**12**:6–15.
48. Mapes DL, Lopes AA, Satayathum S, Mccullough KP, Goodkin DA, Locatelli F. Health-related quality of life as a predictor of mortality and hospitalization: the dialysis outcomes and practice patterns study (DOPPS). *Kidney Int* 2003;**64**(1):339–49.
49. Kang GW, Lee IH, Ahn KS, Lee J, Ji Y, Woo J. Clinical and psychosocial factors predicting health-related quality of life in hemodialysis patients. *Hemodial Int* 2015;**19**(3):439–46.
50. Cruz MC, Andrade C, Urrutia M, Draibe S, Nogueira-Martins LA, Sesso Rde C. Quality of life in patients with chronic kidney disease. *Clinics* 2011;**66**(6):991–5.
51. Voskamp PW, van Diepen M, Evans M, Caskey FJ, Torino C, Postorino M, Szymczak M, Klinger M, Wallquist C, van de Luijtgaarden MW, Chesnaye NC. The impact of symptoms on health-related quality of life in elderly pre-dialysis patients: effect and importance in the EQUAL study. *Nephrol Dial Transplant* 2018:1–9. https://doi.org/10.1093/ndt/gfy167.
52. Garg AX, Suri RS, Eggers P, Finkelstein FO, Greene T, Kimmel PL, Kliger AS, Larive B, Lindsay RM, Pierratos A, Unruh M. Patients receiving frequent hemodialysis have better health-related quality of life compared to patients receiving conventional hemodialysis. *Kidney Int* 2017;**91**(3):746–54.
53. Porter AC, Lash JP, Xie D, Pan Q, DeLuca J, Kanthety R, Kusek JW, Lora CM, Nessel L, Ricardo AC, Nunes JW. Predictors and outcomes of health–related quality of life in adults with CKD. *Clin J Am Soc Nephrol* 2016;**11**(7):1154–62.
54. Alexander M, Kewalramani R, Agodoa L, Globe D. Association of anemia correction with health related quality of life in patients not on dialysis. *Curr Med Res Opin* 2007;**23**(12):2997–3008.
55. Gusmão JLD, Mion D, Pierin AM. Health-related quality of life and blood pressure control in hypertensive patients with and without complications. *Clinics* 2009;**64**(7):619–28.

56. Fischer MJ, Kimmel PL, Greene T, Gassman JJ, Wang X, Brooks DH. Sociodemographic factors contribute to the depressive affect among African Americans with chronic kidney disease. *Kidney Int* 2010;**77**:1010–9.
57. Kaltsouda A, Skapinakis P, Damigos D, Ikonomou M, Kalaitzidis R, Mavreas V. Defensive coping and health-related quality of life in chronic kidney disease: a cross-sectional study. *BMC Nephrol* 2011;**12**:28.
58. Abdel-Kader K, Unruh ML, Weisbord SD. Symptom burden, depression, and quality of life in chronic and end-stage kidney disease. *Clin J Am Soc Nephrol* 2009;**4**:1057–64.
59. Meuleman Y, Chilcot J, Dekker FW, Halbesma N, van Dijk S. Health-related quality of life trajectories during predialysis care and associated illness perceptions. *Health Psychol* 2017;**36**(11): 1083.
60. Levey AS, Coresh J. Chronic kidney disease. *Lancet* 2012;**379**: 165–80.
61. Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. *Am J Geriatr Pharmacother* 2011;**9**:11–23.
62. Heiwe S, Jacobson SH. Exercise training for adults with chronic kidney disease. *Cochrane Database Syst Rev* 2011;(10).
63. National Kidney Foundation. *NKF-K/DOQI clinical practice guidelines for vascular access*. 2006.
64. Sacks CR, Peterson RA, Kimmel PL. Perception of illness and depression in chronic renal disease. *Am J Kidney Dis* 1990;**15**:31–9.
65. Muntner P, Judd SE, Krousel-Wood M, McClellan WM, Safford MM. Low medication adherence and hypertension control among adults with CKD: data from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) Study. *Am J Kidney Dis* 2010;**56**(3):447–57.
66. Magacho EJC, Ribeiro LC, Chaoubah A, Bastos MG. Adherence to drug therapy in kidney disease. *Braz J Med Biol Res* 2011;**44**(3): 258–62.
67. Schmitt KE, Edie CF, Laflam P, Simbartl LA, Thakar CV. Adherence to antihypertensive agents and blood pressure control in chronic kidney disease. *Am J Nephrol* 2010;**32**(6):541–8.
68. Vupputuri S, Muntner P, Winkelmayer WC, Smith DH, Nichols GA. Low medication adherence is related to poor hypertension control among patients with chronic kidney disease. *Circulation* 2012;**125**:AP097.
69. Rifkin DE, Laws MB, Rao M, Balakrishnan VS, Sarnak MJ, Wilson IB. Medication adherence behavior and priorities among older adults with CKD: a semistructured interview study. *Am J Kidney Dis* 2010;**56**(3):439–46.
70. Zolnierek KBH, DiMatteo MR. Physician communication and patient adherence to treatment: a meta-analysis. *Med Care* 2009; **47**(8):826–34.
71. Lure N, Yergan J. Teaching residents to care for vulnerable populations in the outpatient setting. *J Gen Intern Med* 1990;**5**:S27–234.
72. Mull JD. Cross Cultural communication in the physician's office. *West J Med* 1993;**159**:609–13.
73. Cooper-Patrick L, Gallo JJ, Gonzales JJ, Vu HT, Powe NR, Nelson C. Race, gender and partnership in the patient-physician relationship. *J Am Med Assoc* 1999;**282**(6):583–9.
74. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;**353**:5.
75. Tangkiatkumjai M, Walker D-M, Praditpornsilpa K, Boardman H. Association between medication adherence and clinical outcomes in patients with chronic kidney disease: a prospective cohort study. *Clin Exp Nephrol* 2017;**21**(3):504–12.
76. Schiff GD, Fung S, Speroff T, McNutt RA. Decompensated heart failure: symptoms, patterns of onset, and contributing factors. *Am J Med* 2003;**114**:625–30.
77. Cedillo-Couvert EA, Ricardo AC, Chen J, Cohan J, Fischer MJ, Krousel-Wood M, Kusek JW, et al. Self-reported medication adherence and CKD progression. *KI Report* 2018;**3**:645–61.
78. Williams DR, González HM, Neighbors H, Nesse R, Abelson JM, Sweetman J. Prevalence and distribution of major depressive disorder in African Americans, Caribbean blacks, and non-Hispanic whites results from the National Survey of American Life. *Arch Gen Psychiatr* 2007;**64**(3):305–15.
79. Blazer DG, Kessler RC. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *Am J Psychiatry* 1994;**151**:979–86.
80. Norton JM, Moxey-Mims MM, Eggers PW, Narva AS, Star RA, Kimmel PL, Rodgers GP. Social determinants of racial disparities in CKD. *J Am Soc Nephrol* 2016;**27**(9):2576–95.

QUESTIONS AND ANSWERS

Question 1

When differentiating between depression and uremia in a patient with CKD, which of the following symptoms would be most indicative of a diagnosis of depression?

A. Weight loss
B. Suicidal ideation
C. Sleep difficulty
D. Loss of energy
E. Decreased libido

Answer: B

Answers A, C, D, and E are incorrect because weight loss, sleep difficulty, loss of energy, and decreased libido are all symptoms that can overlap between depression and uremia. The correct answer is **B**, suicidal ideation, as it is the only symptom listed that is unique to the presentation of depression.

Question 2

It is important to diagnose and treat depression in CKD because:

A. Depression has been found to be associated with decline in eGFR
B. Patients with depression are more likely to experience adverse outcomes such as increased number of hospitalizations
C. Depression may be associated with greater cognitive decline in patients with CKD
D. Depression has been found to be a predictor of mortality in patients with CKD
E. All of the above

Answer: E

Depression can have a significant impact on the course of CKD progression. Research suggests that depression is a significant predictor of eGFR and adverse outcomes such as increased number of hospitalizations and mortality. Furthermore, research indicates that depression may be associated with greater cognitive decline. Therefore, the correct answer is **E,** all of the above.

Question 3

The most prominent psychiatric presentation in patients with CKD is:

A. Anxiety Disorders
B. Substance abuse disorders
C. Depression
D. Psychosis
E. Body Dysmorphic Disorder

Answer: C

The correct answer is **C**, Depression, with studies reporting prevalence rates between 20% and 30%. Answer A is incorrect because although there is growing evidence that anxiety disorders may have an impact on patients with CKD, early research suggests that these disorders are not more prevalent in patients with CKD compared to the general population. Answer B is incorrect because although comorbid substance abuse disorders can be very detrimental for patients with CKD, they have not been found to be as highly prevalent among this population. Answers D and E are incorrect in that there is no evidence that these conditions are prominent in patients with CKD.

Question 4

Which of the following has NOT been identified as a significant predictor of HRQOL in patients with CKD?

A. CRP
B. Sleep difficulty
C. CVD
D. Being male and under the age of 65
E. Pain

Answer: D

The correct answer is **D**, being male and under the age of 65. In a large-scale, longitudinal study data revealed that early-stage CKD patients who were female and/or over the age of 65 had worse perception of QOL. Answers A and C are incorrect as CRP and CVD have been identified as medical factors that predict HRQOL, along with GFR and diabetes. Answers B and E are incorrect as sleep difficulty and pain have been found to be associated with poor QOL in patients with CKD.

Question 5

During a visit with her nephrologist a 63-year-old woman with CKD reveals that she has not been taking her antihypertensive medication on a regular basis. During the physician's inquiry, the patient is tearful and appears frustrated as she describes her difficulties with learning how and when to take her various medications. This is an example of what kind of barrier to adherence?

A. Depression
B. Cost of medication
C. Health beliefs
D. Access to care
E. Regimen complexity

Answer: E

The correct answer is **E**, regimen complexity, as the patient has clearly indicated that she has difficulty

following specific instructions regarding the dosage and administration of her medications. Answer A is incorrect because even though the patient is tearful while talking about her problems, she has clearly communicated to the physician that her primary difficulty is due to learning her prescription regimen. Answers B and D are incorrect in that the patient has not indicated that the cost of medication or access to the pharmacy present a problem for her in adhering to her prescription. Answer C is incorrect because the patient does not appear to make decisions about adhering to her prescription based on beliefs about her condition or the efficacy of her medication.

Question 6

Which of the following is true regarding mental health disparities within CKD?

A. Prevalence of depression is greater in Blacks with CKD compared to Hispanics with CKD

B. Prevalence of depression is greater in Hispanics with CKD compared to Blacks with CKD

C. Utilization of depression treatment is low among Blacks and Hispanics with CKD

D. Utilization of depression treatment is high among Blacks and Hispanics with CKD

E. Women with CKD are less likely to use antidepressants

Answer: C

The correct answer is **C**. Research indicates that Black and Hispanic patients with CKD who present with elevated depressive affect are less likely to use antidepressant medication, compared to non-Hispanic White patients with CKD. Answer D is incorrect because utilization of depression treatment is lower among Blacks and Hispanics with CKD. Answers A and B are incorrect as there is no evidence of greater or lesser prevalence of depression within the Black or Hispanic CKD population. Answer E is incorrect as women are actually more likely to use antidepressants when presenting with depressive affect.

CHAPTER

28

Ophthalmic Issues in Chronic Kidney Disease

Andrew Kummer[a], *Monica Dalal*[b], *Marc Weber*[c], *Emily Y. Chew*[d]

[a]HealthPartners Nephrology, St. Paul, MN, United States; [b]Medical Faculty Associates, George Washington University, Washington, DC, United States; [c]Kidney Specialists of Minnesota, Minneapolis, MN, United States; [d]Division of Epidemiology and Clinical Applications, National Eye Institute, National Institutes of Health, Bethesda, MD, United States

Abstract

There is a high prevalence of comorbid eye disease in patients with chronic kidney disease (CKD), end-stage renal disease (ESRD), and kidney transplant patients. The most common links are secondary from diabetes and hypertension. However, there are other disease states that link the kidneys and eyes, ranging from a host of systemic diseases such as sarcoidosis to ophthalmic complications of kidney transplantation. This chapter reviews the relationship between the kidneys and eyes in the setting of a variety of primary and secondary diseases. Early ophthalmic evaluation in the face of visual changes in these patients is of paramount importance. In addition, there may be a role for routine ophthalmology screening in any patient with stage 3 CKD or higher. Future studies focusing on the preventive benefit of such screening programs will benefit patients with kidney diseases.

INTRODUCTION

The association of kidney disease with eye pathology is well established. The most common links are secondary from diabetes and hypertension. However, there are other disease states that link the kidneys and eyes, ranging from a host of systemic diseases such as sarcoidosis to ophthalmic complications of kidney transplantation. This chapter reviews the relationship between the kidneys and eyes in the setting of a variety of primary and secondary diseases.

OPHTHALMIC FINDINGS IN HYPERTENSIVE NEPHROPATHY

Hypertension accounts for 30% of all kidney diseases, making it the second-leading cause after diabetes mellitus.[1] To date, there have been no population studies that have established an expected prevalence of hypertensive retinopathy in a cohort of patients with hypertensive nephropathy. Two cross-sectional studies have reported that in their group of hypertensive patients, 36% had microalbuminuria and 38% had hypertensive retinal changes. In addition, these two variables were strongly associated, suggesting a fairly high rate of nephropathy in those patients with hypertensive retinal pathology.[2,3]

Systemic hypertension causes diffuse and focal retinal arteriolar vasoconstrictions, which have been noted to be common in long-standing hypertension.[4] More significant pathology occurs when there is a breakdown of the inner blood–retinal barrier, leading to extravasation of red blood cells and plasma. This results in the classic findings of retinal hemorrhages, cotton-wool spots, intraretinal lipid accumulation, and macular stars.[4] However, these findings are not observed in most patients. Rather, the usual findings are arteriosclerotic changes in the retina, typically characterized by vascular thickening.[4] Despite several large population studies examining this link, it remains unclear if the retinal vascular changes are a cause of hypertension or a result of this disease.[5,6]

Severe or acute hypertension can cause additional pathology. With hypertensive emergency, occlusion of the retinal capillaries may occur. In addition, choroidal vessel hypertension can cause fibrinoid necrosis of choroidal arterioles and result in occlusion and ischemia of this blood supply, which can then lead to a breakdown of the outer blood–retinal barrier.[4] Finally, extreme accelerated hypertension can cause edema of the optic disk and swelling of the optic nerve.[4]

OPTHALMOLOGIC COMPLICATIONS IN CHRONIC KIDNEY DISEASE AND DIALYSIS PATIENTS

Retinopathy and Other Fundus Pathology

Retinopathy may be the best known ocular complication of chronic kidney disease (CKD). Recent population studies have examined the prevalence of retinopathy and other fundus pathology in patients with CKD.[7–9] A cross-sectional study found that 45% of all patients with CKD had retinal pathology that required follow-up with an ophthalmologist.[7] In addition, 25% of patients were diagnosed with retinopathy, typically secondary to hypertension and/or diabetes.[7] Furthermore, they found that those with an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2 had a three times higher risk for being diagnosed with retinopathy. Similarly, retinopathy conferred a twice as great risk of developing CKD compared to those without.[8] Not only is the prevalence of retinopathy more common in CKD, but the severity has been shown to be inversely related to GFR.[9] In a study of 90 individuals with CKD on the transplant list, only 17% were found to have a normal ophthalmologic examination. The results also showed that 62% had hypertensive retinopathy, while 80% (8/10) with diabetes had diabetic retinopathy.[10]

Other fundus pathology also appears to be increased in prevalence in CKD patients. Microaneurysms, retinal hemorrhages, soft exudates, and arteriovenous nicking were all found to be risk factors for the development of CKD.[7,8]

Red Eyes and Corneal Inflammation

One of the most common complications involving the eye in patients treated with hemodialysis is inflammation and hyperemia of the episcleral tissue and conjunctivae. This inflammation seems to arise from several different mechanisms. Patients treated with dialysis can develop limbal epithelial erosions as a result of calcium deposits, resulting in focal inflammation and hyperemia.[11] (Figure 28.1).

A more diffuse form of hyperemia involving the cornea has also been linked to calcium deposits. Calcium salt deposition appears to be the inciting factor, with the main risk of this process linked to the precipitation product of S[Ca] and S[P].[12] Tokuyama et al. found that conjunctival and corneal calcifications were associated with longer dialysis times, higher calcium−phosphate product, higher PTH levels, and decreased bone mineral density. Interestingly, S[Ca] itself was not significantly associated with pathology.[13] Another study suggested a correlation of the ocular surface calcification with elevated blood urea nitrogen level.[14] Symptoms tend to improve on lowering the S[Ca] phosphate product, typically below 55. Additional treatment can be offered in the form of topical antihistamines, vasoconstrictors, or lubricants.[12,13]

Conjunctival and corneal calcifications should be of particular interest to nephrologists, given the predictive values of these findings for important outcomes in dialysis patients. A study of conjunctival and corneal calcifications and cardiovascular disease with carotid artery examinations showed that the intimal media thickness measurements, reflecting atherosclerosis of the carotid artery, was the best predictor of the development of ocular calcification.[15] The results suggested that perhaps ischemia played an important role in the development of calcification on the ocular surface of people treated with hemodialysis. Hsiao et al. examined the impact of mild, moderate, and severe conjunctival and corneal calcification scores on all cause 1-year mortality in 109 chronic dialysis patients.[16] They found that calcification was significantly associated with all-cause mortality. Those with the most severe conjunctival and corneal calcification had significantly lower survival at 1 year.[16] Figure 28.2 demonstrates band keratopathy, which can be seen in such patients.

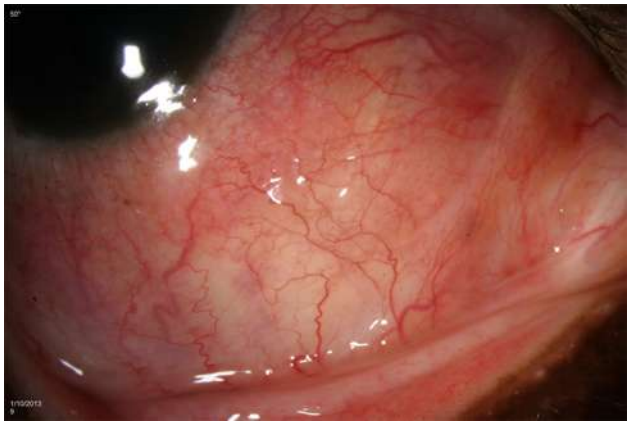


FIGURE 28.1 The conjunctiva of this eye demonstrates inflammation and hyperemia of the episcleral tissue.

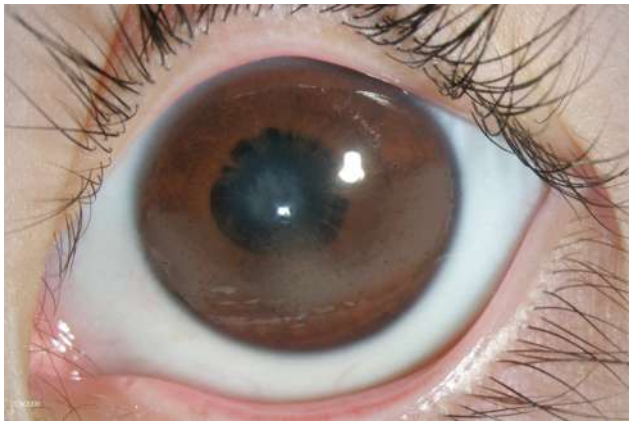


FIGURE 28.2 Band keratopathy is the horizontal band of calcific plaques across the interpalpebral zone of the cornea.

Intraocular Pressure

Many studies indicate intraocular pressure increases in those undergoing hemodialysis, although this has been somewhat of a controversial issue over the years.[17–20] The exact etiology remains unclear, but it has been hypothesized to be related to the underlying inherent hypervolemic and low oncotic pressure state of end-stage renal disease (ESRD) itself.[19,21] Others speculate that elevated intraocular pressure is related to a decrease in serum osmolality during hemodialysis, which results in an increase in fluid volume in the posterior chamber of the eye.[16,22] Dinc et al. set out to address whether or not dialysis treatments result in an increase in intraocular pressure.[20] This group found that changes in corneal thickness observed during hemodialysis may affect the accuracy of intraocular pressure measurements.[21] Increased oxidative stress related to kidney disease has been implicated as a potential cause of elevated intraocular pressure. Oxidative stress has been shown to impair the function of the trabecular meshwork that allows for normal drainage of aqueous humor through the anterior chamber.[18,20] Research in this area is ongoing.

Treatment of increased intraocular pressure in dialysis patients is similar to that in the general population, consisting of agents that decrease aqueous humor production (beta-blockers, alpha-2 adrenergic agonists, and acetazolamide), agents that increase humor filtration and drainage (prostaglandin agonists and miotic agents), or procedures such as surgical trabeculectomy in patients not sufficiently responsive to medical treatments.[21] Acetazolamide may not be the preferred agent in patients with kidney disease due to its propensity to worsen metabolic acidosis, hyperphosphatemia, and hypocalcemia. In dialysis patients, altering the dialysis prescription to decrease the rate of solute clearance and improve volume management may aid in preventing dialysis-associated elevation of intraocular pressure.[16,22]

Cataracts

There has been much speculation regarding whether kidney disease confers an increased risk for the development of cataracts. Much of the uncertainty stems from the fact that dialysis patients often have comorbidities that can contribute to cataract formation, including advanced age, diabetes, hypertension, corticosteroid use, ultraviolet light exposure, and hyperparathyroidism.[22–24] Although prior observational studies may suggest a connection between dialysis and cataracts, a more recent population-based study found that kidney function had no effect on the incidence of cataracts after adjusting for known risk factors.[23,24] One proposed mechanism for cataract formation in dialysis patients centers around urea trapping in the lens during the interdialytic interval, resulting in repeated osmotic shifts.[22–24] Surgical removal of cataracts is well tolerated by dialysis patients.

Retinal Detachment

Retinal detachment in dialysis patients is rare but has been the subject of case reports.[25,26,] As there were no hypertensive crises present at the time of retinal detachment, it was proposed that kidney failure and/or dialysis-related issues may have been responsible. The underlying mechanism is unclear but may be related to focal alterations of choriocapillary permeability and subsequent edema in the subretinal space.[25] A more recent case-control analysis of medical health records in Taiwan indicated an increased risk of serous retinal detachment in people with ESRD treated with dialysis (adjusted HR = 3.86, 95% CI = 1.15–12.96).[27] Prompt diagnosis is critical, as vision loss can be complete, resulting in blindness. Treatment is surgical and is often urgent or emergent.

Optic Neuropathy

Patients treated with hemodialysis are prone to developing anterior ischemic optic neuropathy owing to two risk factors in particular: intradialytic hypotension and anemia.[21] In addition, rapid ultrafiltration may increase blood viscosity and compromise retinal blood flow to the point where ischemia can occur.[28] Compromise of the retinal blood flow watershed area usually presents with loss of the inferior visual field.[22] One observational study noted that approximately 10% of patients suffered this malady over a 1-year follow-up period.[29] Prompt recognition of symptoms and diagnosis with subsequent restoration of adequate perfusion is key to allow maximal vision recovery.[22]

Patients with advanced CKD (but not on dialysis) have been reported to develop temporary blindness, classically known as uremic amaurosis.[30] Transient blindness can develop over minutes to hours and typically resolves over a period of days, sometimes after initiation of dialysis. The pathogenesis of this disorder is unknown, but it is speculated to involve dysfunction of the visual and/or paravisual cortices of the brain.[30] Others propose that the mechanism involves a defect in the optic nerve, with the pathogenesis secondary to uremia and chronic risk factors. The mainstay of treatment is initiation of dialysis, but there may also be a therapeutic role for corticosteroids.[22,31]

Optic neuropathy is also associated with medications used to treat kidney diseases. OKT3 (an immunomodulating drug) has been historically used in kidney transplantation and is associated with the development of optic neuropathy. Deferoxamine (an iron and aluminum

FIGURE 28.3 Age-related macular degeneration consists of drusen (round, yellow lesion located at the level of the retinal pigment epithelium). These can give way to the atrophic or neovascular form of late AMD.

chelator) is associated with both optic neuropathy and color blindness, although the underlying mechanisms are unclear.[22,32]

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) (Figure 28.3) may be related to the development of CKD.[33,34] A recent cohort study found that, after adjusting for multiple risk factors, those with a Cockcroft-Gault estimated GFR less than 60 mL/min/1.73 m^2 had three times greater odds of developing AMD compared to those with kidney function above this threshold.[33] Another study also found significant results for this comparison, as well as a greater than eleven times increased odds of having macular degeneration that was considered severe.[34] Evaluation of National Health and Examination (NHANES, 2005–2008) results found an association of early AMD, which currently has no effective therapy, with CKD.[35] Furthermore, a meta-analysis of 12 studies found a positive association of chronic renal disease with AMD, but there were many inconsistencies and limitations among the studies.[36] Early detection and treatment of CKD may be reasonable to help identify those at risk for AMD and prevent subsequent complications.

OPHTHALMIC FINDINGS IN DIABETES

Diabetes continues to be the leading cause of ESRD in the US.[37] In some studies, diabetic nephropathy, as ascertained by albuminuria, proteinuria, or kidney failure, is found to be a risk factor associated with progression of retinopathy.[38,39] Diabetic retinopathy is a leading cause of new cases of blindness in people aged 20–74 years in the US.[34,40] Diabetic retinopathy can be divided into two main categories: "nonproliferative" diabetic retinopathy (NPDR) and "proliferative" retinopathy (PDR). This retinopathy classification is based on an understanding of the influence of individual characteristics on the risk of progression from NPDR to proliferative stages. Macular edema is also an important etiology for vision loss and can occur at any stage. These changes can be detected with careful ophthalmologic examination and additional testing such as fluorescein angiography and optical coherence tomography.

Epidemiology of Diabetic Retinopathy

Data from population-based studies such as the Wisconsin Epidemiologic Study of Diabetic Retinopathy provide valuable information regarding the prevalence of diabetic retinopathy. In patients with onset of diabetes at 30 years of age or older (presumably type 2) with a duration of less than 5 years, 24%–40% have retinopathy.[41] These rates increase to 53%–84% with a duration of diabetes of 15–19 years. PDR develops in 25% of patients with a duration of 25 or more years of diabetes. In the younger onset group (presumably type 1 diabetes), either proliferative or nonproliferative changes were seen in 13% of patients with less than a 5-year duration of diabetes, and in 90% of patients with a duration of 10–15 years.[42] PDR was present in approximately 25% of patients with a 15-year duration of disease. The prevalence of diabetic macular edema does not vary as much by diabetes type and is approximately 18%–20%.

Risk Factors for Progression of Retinopathy

Medical management of risk factors for progression of retinopathy is essential. These include glucose, hypertension, and cholesterol control. Severity of diabetic retinopathy is associated with poorer glucose control. Although intensive therapy does not prevent retinopathy completely, it does reduce the risk of the development and progression of diabetic retinopathy.[43] A decreased risk of retinopathy was associated with intensive blood pressure control in comparison to less-intensive blood pressure control in a randomized study.[44] Finally, lowering elevated serum lipids may reduce visual loss as increased serum levels of cholesterol are associated with increased severity of hard exudates and development of PDR.[45,46]

Nonproliferative Diabetic Retinopathy

NPDR includes a wide variety of retinal abnormalities that occur well before neovascularization. These

changes include hemorrhages and microaneurysms, venous beading, intraretinal microvascular abnormalities (IRMA), cotton-wool spots, and hard exudates.

Microaneurysms are small saccular or fusiform capillary dilatations seen as small red dots with ophthalmoscopy. Microaneurysms alone (without hemorrhages) do not appear to contribute substantially to the risk of retinopathy progression. The presence of intraretinal hemorrhages, however, especially if present in all four midperipheral retinal quadrants, does predict risk of progression to proliferative retinopathy (Figure 28.4).[47]

Venous beading refers to irregular constriction and dilatation of venules in the retina. "Beading" is a nonspecific sign of retinal ischemia. Beading is a good predictor of risk for retinopathy progression if present in two of the four midperipheral retinal quadrants.[47]

IRMAs are shunt vessels that are enlarged hypercellular capillaries adjacent to or surrounding areas of occluded capillaries. They appear as dilated, telangiectatic capillaries within the retina. They strongly indicate the likelihood of retinopathy progression, even if present in only one midperipheral field.[47]

Cotton-wool spots (or soft exudates) are areas of nerve fiber ischemia or infarction with axonal swelling of the nerve fiber layer induced by areas of retinal capillary closure. They appear as opaque gray or white areas in the retina with "soft" or feathery edges. Although they are a sign of poor retinal perfusion and are easily seen, they have a poor predicative value for retinopathy progression.[47]

Hard exudates are lipid and lipoprotein deposits, usually found in the outer layers of the retina. They have a "waxy" appearance with sharply defined borders and result from leakage from abnormally permeable microaneurysms or capillaries in the retina. Therefore, these lesions are often accompanied by retinal edema and form circinate clusters surrounding areas of leaking microaneurysms. Elevated blood cholesterol is associated with increased severity and extent of hard exudates.[45,46]

Mild to moderate NPDR are related to decompensation of the retinal vasculature by years of diabetic damage. Early signs include small and less-extensive intraretinal hemorrhages, microaneurysms, and hard exudates. As NPDR progresses, increasing retinal ischemia develops and the risk of developing neovascularization increases. The triad of more extensive intraretinal hemorrhages, venous beading, and IRMAs comprises a more florid variety of NPDR, associated with a higher risk of progression to proliferative retinopathy. The Early Treatment Diabetic Retinopathy Study (ETDRS) "4-2-1" rule helps identify eyes in the severe or very severe NPDR groups.[47] The four midperipheral retinal quadrants are assessed for presence and severity of hemorrhages, venous beading, and IRMA.

Eyes with any one of these three features are considered to have severe NPDR: (1) hemorrhages in all four quadrants, (2) venous beading in two quadrants, or (3) IRMA in one quadrant (see Figure 28.5). Eyes with severe NPDR have a 26% chance of progressing to PDR in 1 year and a 48% chance in 3 years. Eyes with two or more of these features are considered to have very severe NPDR. They have a 50% chance of developing PDR in 1 year and a 71% chance in 3 years.

FIGURE 28.4 This montage of the right eye shows diffuse intraretinal hemorrhages in all four retinal quadrants, which indicates severe nonproliferative diabetic retinopathy.

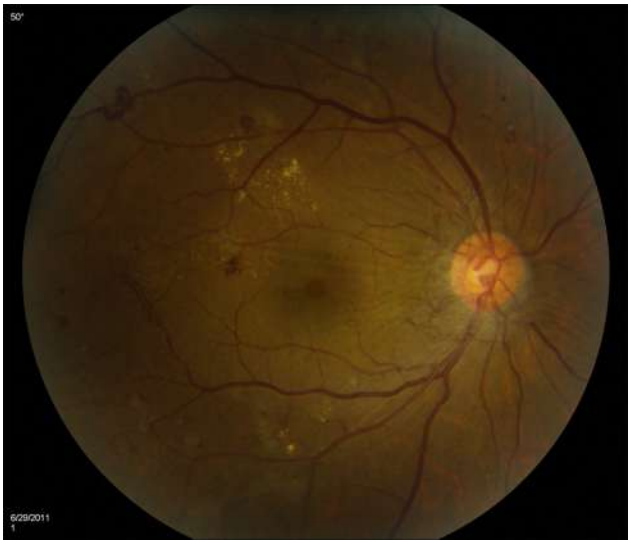


FIGURE 28.5 This right eye has evidence of neovascularization of the disc and neovascularization elsewhere, representing proliferative diabetic retinopathy.

Proliferative Diabetic Retinopathy

In contrast to the changes in NPDR, those of PDR are no longer contained within the retina. PDR consists of neovascularization of the disc (NVD) and neovascularization elsewhere in the retina (NVE), which can lead to preretinal and vitreous hemorrhage (Figure 28.5). NVD comprises newly formed blood vessels, often associated with fibrous tissue, which grow from the optic nerve along the posterior surface of the vitreous and into the vitreous. NVD is associated with a high risk of hemorrhage and severe visual loss without laser photocoagulation. NVE refers to new vessels growing from the retina to proliferate on the posterior surface of the vitreous in a location away from the optic nerve, frequently along the temporal vascular arcades. Although NVE does not carry the same high risk for severe visual loss as does NVD, it may still require treatment or careful monitoring if not treated. NVD and NVE can hemorrhage behind the vitreous or into the vitreous space, decreasing vision. The subsequent contraction of fibrous proliferation can lead to retinal detachment with serious threat to vision.

Patients with proliferative retinopathy are at higher risk for developing severe visual loss (visual acuity less than 5/200). The Diabetic Retinopathy Study (DRS) identified four retinopathy factors associated with an increased risk of developing severe visual loss.[48] The risk factors are separate but cumulative: (1) presence of any new vessels in the eye, (2) presence of new vessels on or near the optic disc, (3) moderate or severe new vessels (greater than 1/4 disc area), and (4) vitreous hemorrhage. The presence of three or four risk factors places the eye in the "high-risk proliferative retinopathy" group. Without treatment, 50% develop severe visual loss in 5 years. Eyes with one or two risk factors are considered to have "early PDR" and are in a lower risk group.

Macular Edema

Diabetic macular edema is the most common cause of visual impairment from diabetes. It can occur in any stage of retinopathy; however, it is not usually present in the first 5–7 years of disease. Macular edema is edematous thickening of the macula (the area responsible for central vision) that can lead to blurring of vision by disturbing the architecture of the retina (Figure 28.6). Macular edema can be detected by ophthalmoscopy or optical coherence tomography. When thickening involves or threatens the center of the macula, it is considered to be "clinically significant" and carries a higher risk of visual loss. Eyes with "clinically significant macular edema" have a 32% chance of developing moderate visual loss (a decrease of 3 lines or more) in 3 years without treatment.[49]

FIGURE 28.6 The macula of this eye has edema, which is best seen clinically with stereoscopic viewing and the hard exudate is indicative of presence of macular edema.

Management

The treatment of diabetic retinopathy is based on the results of two major randomized clinical trials, the DRS and the ETDRS. Treatment for PDR is laser photocoagulation, involving applying multiple laser burns in the peripheral retina and posterior portion of the retina sparing the macula. The DRS results demonstrated a 50% reduction in severe visual loss (visual acuity of 5/200 or worse) in eyes with severe nonproliferative and proliferative retinopathy that received photocoagulation.[50] The rate of progression to neovascularization or to high-risk retinopathy stages was very low, and laser photocoagulation is not recommended for eyes with mild to moderate NPDR.[50] As the retinopathy advances to the severe or very severe nonproliferative or early proliferative stage, the risk–benefit ratio becomes more favorable, and it is reasonable to consider initiating photocoagulation before the development of high-risk proliferative retinopathy.[51]

Current treatments for diabetic macular edema include laser and intravitreal antivascular endothelial growth factor (anti-VEGF) injections. The mainstay of treatment for macular edema has been laser therapy, which involves small, mild-intensity laser burns targeted at areas of leakage in the macula[45,49] known as "focal macular photocoagulation." However, intravitreal injections of anti-VEGF are now also considered a first-line treatment and have been shown by several studies to be superior to laser therapy alone.[48–55]

Vision loss from diabetes can be reduced by appropriate diagnosis and proper treatment. However, patients are often asymptomatic until retinopathy has advanced beyond the stages in which treatment is most effective. Periodic detailed eye examinations are crucial for detecting and monitoring retinal changes before irreversible damage has occurred.

KIDNEY TRANSPLANT–RELATED OCULAR COMPLICATIONS

Those patients who have received a kidney transplant are not immune to the onset of ocular disease. The prevalence of ocular complications in kidney transplant patients has been described to be as high as 52% and often related to immunosuppression medications.[56] A common complication is posterior subcapsular cataract formation, typically thought to be a result of corticosteroid therapy. Other noninfectious complications include steroid-induced elevated intraocular pressure, as well as vascular complications that are typically associated with underlying disease. The remaining described complications after transplant are infectious in nature, with characteristic pathogens being cytomegalovirus, mucormycosis, cryptococcus, herpes simplex, and herpes zoster.[56] Prompt diagnosis, adjustment of immunosuppression, and prolonged antibiotic treatment are needed for ocular infections that carry a high risk of blindness and disseminated disease.

OCULORENAL SYSTEMIC DISEASES

There are a host of either acquired or genetic diseases that can result in pathologic findings in both the kidneys and the eyes. Understanding this relationship opens an opportunity to solidify an often elusive diagnosis in a noninvasive fashion.

Autoimmune Diseases

Systemic Lupus Erythematosus

Kidney involvement occurs in approximately 50% of those with systemic lupus erythematosus (SLE). Ophthalmic disease, however, is also common in patients with SLE. The range of these conditions is vast, though most are relatively rare. The most common symptom or finding is keratoconjunctivitis sicca, or dry eyes. The remaining findings range in severity from subtle skin findings to vision-threatening complications, including ischemic retinal vasculitis (Figure 28.7).[57] Complaints of the onset of blurry vision or double vision may be the result of cranial nerve palsies or optic neuropathy. Permanent vision loss may result from vascular complications, which may either be inflammatory or thrombotic in nature. Table 28.1 provides a comprehensive list of ocular findings in patients with SLE.

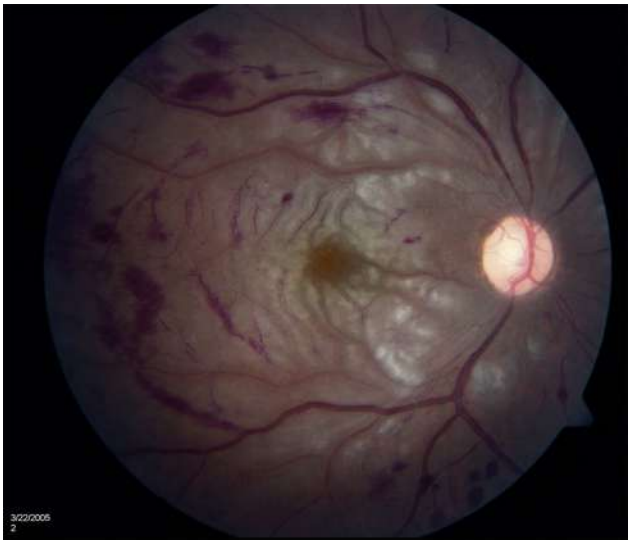


FIGURE 28.7 This right fundus shows marked retinal infarction from ischemic retinal vasculitis in systemic lupus erythematosus.

TABLE 28.1 A Comprehensive List of Ocular Findings in Systemic Lupus Erythematosus

Ocular Item	Finding
Sclera	Episcleritis Scleritis
Eyelid	Cutaneous manifestations
Retina	Retinal vasculitis Cotton-wool exudates Retinal hemorrhages Serous retinal detachment Retinal occlusive vasculitis Retinal venous thrombosis
Neurologic	Cranial nerve palsies Optic neuropathy Inflammatory pseudotumor of the orbit
Vascular	Transient ischemic attack (TIA) Amaurosis fugax Cerebrovascular accident (CVA)
Cornea	Keratoconjunctivitis sicca Secondary Sjögren's syndrome

See reference 48.

Hydroxychloroquine is often used as part of the treatment for SLE. Despite retinal toxicity being relatively rare, it is generally recommended that all patients started on hydroxychloroquine have a baseline ophthalmic examination.[58] In addition, all patients with kidney disease should be screened annually by an ophthalmologist.[58] The classic finding is known as a "bull's eye maculopathy." Bull's eye maculopathy is essentially a peripheral retinal lesion from which many

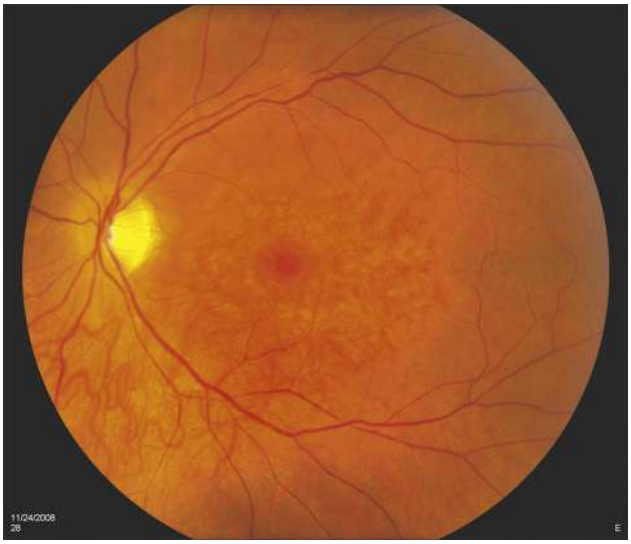


FIGURE 28.8 Plaquenil or hydroxychloroquine toxicity is manifested with atrophy of the retinal pigment epithelium with preservation of the center of the macula, consistent with "bull's eye maculopathy."

patients do not have symptoms until they develop advanced disease. This necessitates vigilant screening practices to detect early disease.[58] (Figure 28.8).

Granulomatosis with Polyangiitis and Microscopic Polyangiitis

Granulomatosis with polyangiitis (GPA) (formerly Wegener's Granulomatosis) and microscopic polyangiitis (MPA) are well known for their effects on both the lungs and kidneys. Less appreciated are the ocular complications of these diseases, which occur in 28–58% of patients.[57,59] Of these patients 15–20% have orbit disease. Proptosis is the usual symptom observed. Proptosis is the result of severe and long-term inflammation in the orbits. Not surprisingly, many of these patients have vision compromise either from compression of the optic nerve or vascular ischemia of this structure.[59] Up to 8% of patients suffer vision loss.[59]

Conjunctivitis in the setting of GPA has been associated with a higher incidence of subglottic stenosis, a life-threatening complication. Therefore, the finding of conjunctivitis in these patients must lead to an airway examination.[59,60]

Other important ocular findings in GPA and MPA include scleritis, episcleritis, peripheral ulcerative keratitis, and uveitis.[57]

Churg-Strauss Syndrome

Churg-Strauss syndrome is a condition that consists of eosinophilic and granulomatous inflammation capable of affecting multiple organs. Its most common manifestations are in the lungs and upper airways. Kidney involvement is also common, often presenting as focal interstitial eosinophilic nephritis or a focal segmental glomerulosclerosis-like pattern of injury. Ocular findings include conjunctival granulomas, scleritis, episcleritis, uveitis, cranial nerve palsies, and retinal arterial occlusion.[58]

Antiglomerular Basement Membrane Disease (Goodpasture's Syndrome)

Similar to the linear deposition of IgG on the basement membranes in lung and kidney tissue, this process can also occur on the basement membrane of the choroid (Bruch's membrane) and the basement membranes of the choroidal blood vessels. The resulting pathology includes retinal detachment, choroidal ischemia/infarction, and macular edema. Other possible pathologies include conjunctivitis, scleritis, retinal vasculitis, and occlusion of retinal vessels.[61]

Tubulointerstitial Nephritis and Uveitis Syndrome

Tubulointerstitial nephritis in conjunction with uveitis (TINU) is a clinical entity that classically affects young women. These patients commonly present with kidney dysfunction, but uveitis may be the presenting symptom in up to 36% of TINU cases.[57] Although the interstitial nephritis component of this syndrome often resolves completely, uveitis tends to be chronic or relapsing.[62] The uveitis is nongranulomatous, typically limited to the anterior segment, and responds well to topical or systemic antiinflammatory treatments.[63]

Sarcoidosis

Noncaseating granulomatous inflammation is the hallmark feature of this multisystem disease. Although classically involving the lung and mediastinal lymph nodes, both kidney and ocular involvement can occur. Kidney involvement is typically mild and is often the result of tubulointerstitial nephritis, hypercalcemia, granulomatous inflammation, and nephrocalcinosis, though glomerulonephritis has also been reported with sarcoidosis.[57] The classic ocular finding in sarcoidosis is granulomatous uveitis, though retinal periphlebitis, macular edema, retinal neovascularization, and granuloma formation can occur as well[57] (See Figure 28.9).

Treatment of uveitis typically involves corticosteroids. Milder cases are often amenable to topical corticosteroids, whereas more severe and chronic cases may necessitate intravitreal injections.[64] Other agents that have been used include methotrexate, azathioprine, mycophenolate, leflunomide, and anti-TNF agents.[64]

Others

There are other autoimmune diseases with oculorenal manifestations. These include giant cell arteritis, Takayasu's arteritis, polyarteritis nodosa, Behçet's disease, primary antiphospholipid antibody syndrome, Sjögren's

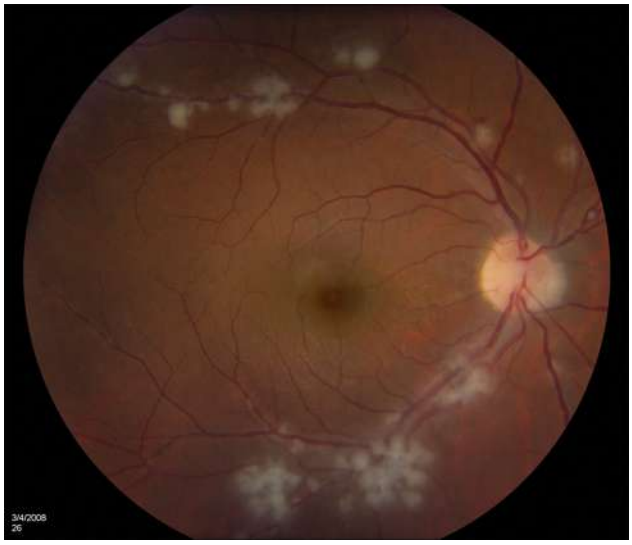


FIGURE 28.9 This patient has evidence of sarcoidosis-associated uveitis with evidence of periphlebitis and multiple granulomas along the retinal vessels.

syndrome, and cryoglobulinemia. The ocular and kidney findings associated with these diseases are summarized in Table 28.2.

Genetic Conditions

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common familial form of kidney disease. Ophthalmic disease is not a primary manifestation of ADPKD. A characteristic appearance of the eyelid, however, may be helpful in initial diagnosis. One study followed 75 families, with at least one member with ADPKD.[65] In 32% of these families at least one affected person had blepharochalasis, a condition that causes the upper eyelid to fold underneath the rest of the lid, obscuring the proximal portion of the eyelashes. This finding may be helpful in determining a cause of CKD in an undiagnosed person, particularly in cases that are sporadic in nature.

TABLE 28.2 The Ocular and Kidney Findings Associated with Autoimmune Diseases

Disease	Renal Findings	Ocular Findings
Behcet's disease	Rare—Nephrosclerosis, amyloidosis, glomerulonephritis	Common—Anterior uveitis, retinal vasculitis Rare—Neovascularization, strabismus, vitreous hemorrhage, cataracts, glaucoma
Cryoglobulinemia	Common—Membranoproliferative glomerulonephritis	Common—Inflammatory orbital pseudo tumor leading to acute orbital expansion Rare—Retrolental fibroplasias
Giant cell arteritis	Common—Minimal proteinuria, hematuria, red blood cell casts Rare—Intrarenal vasculitis, renal artery vasculitis, membranous glomerulopathy	Common—Anterior ischemic optic neuropathy Rare—Central retinal artery occlusion, chronic ocular ischemia, ophthalmoparesis
Polyarteritis nodosa	Common—Renal arteritis and ischemia	Common—Choroidal vasculitis
	Rare—Renal arterial aneurysm rupture with hematoma formation, renal vein thrombosis	Rare—Granulomatous scleritis, chronic nongranulomatous iridocyclitis, retinal detachment, retinal fusiform aneurysms, perivasculitis of several structures, stromal keratitis, cataract, posterior ischemic optic neuropathy, uveitis, hypertensive retinopathy
Primary antiphospholipid antibody syndrome	Common—Renal artery thrombosis, thrombotic microangiopathy	Common—Retinal vasculitis, vitritis, retinal detachment, central retinal artery occlusion
Sjögren's syndrome	Common—Tubulointerstitial nephritis	Common—Keratoconjunctivitis sicca
	Rare—Immune complex-mediated glomerulonephritis, mesangial nephropathy, renal pseudolymphoma, hemolytic uremic syndrome, amyloidosis, mixed cryoglobulinemia, obstructive nephropathy, renal artery vasculitis	Rare—Corneal melting
Takayasu's arteritis	Common—Renal artery stenosis, tubulointerstitial nephritis	Common—Retinal arteriovenous shunts, retinal artery occlusion, anterior ischemic optic neuropathy
	Rare—Glomerulonephritis, amyloidosis	

See Reference 48.

TABLE 28.3 Conditions in which Both Kidney Impairment and Ophthalmic Complications Occur

Disease	Renal Findings	Ocular Findings
Bardet–Biedl syndrome	Polycystic kidney disease, abnormal calyces, diffuse cortical loss	Retinal dystrophy, retinitis pigmentosa, blindness
Fabry disease	Polycystic disease	Cornea verticillata, tortuous conjunctival/retinal vessels, "Fabry cataract"
Inherited proximal renal tubular acidosis	Proximal renal tubular acidosis	Bilateral glaucoma, cataracts, band keratopathy
LCAT deficiency syndrome	Diffuse lipid accumulation, proteinuria, kidney failure	Arcus lipoides corneae, retinal hemorrhages, optic disc protrusion, Bruch's membrane rupture
Nail–patella syndrome	Glomerular basement membrane (GBM) abnormalities, fibrillar collagen deposition in GBM	Microcornea, sclerocornea, congenital cataract, abnormal iris pigmentation (Lester's sign), congenital glaucoma
Primary hyperoxaluria	Oxalate nephrocalcinosis, nephrolithiasis	Crystalline retinopathy, maculopathy
Sturge–Weber syndrome	Renal hemangiomas	Congenital glaucoma, choroidal hemangiomas, nevus of Ota, buphthalmos
Tuberous sclerosis	Renal angiomyolipomas, polycystic kidney disease, renal cell carcinoma	Retinal hamartomas, retinal depigmentation, angiofibromas of the eyelid
von-Hippel Lindau disease	Renal cell carcinoma, polycystic kidney disease	Retinal hemangioblastomas

See references 63–76.

Alport Syndrome

Although progressive hereditary nephritis and senorineural hearing loss are the hallmark manifestations of Alport Syndrome (AS), ocular signs have been reported. Most ocular abnormalities are associated with X-linked AS, which is by far the most common.[66] Dot-and-fleck retinopathy is found in up to 85% of AS patients, though the most common conditions causing decreased visual acuity are lenticular in nature. Anterior lenticonus occurs in approximately 25% of patients, whereas posterior lenticonus and posterior polymorphous corneal dystrophy occur much less frequently. The retinopathy usually becomes apparent around the time of kidney failure, whereas anterior lenticonus typically presents later in life. Dot-and-fleck retinopathy in combination with a family history of AS and kidney failure is diagnostic of an incident AS case, whereas the mere presence of anterior lenticonus or posterior polymorphous corneal dystrophy is highly suggestive of the disease without any other evidence.[67] Other reported ocular features of AS include microcornea, arcus, iris atrophy, cataracts, spontaneous lens rupture, spherophakia, recurrent corneal erosion, and retinal pigmentation.[67,68]

Cystinosis

This rare, autosomal recessive lysosomal storage disease affects primarily the kidneys but also the bone marrow, pancreas, skeletal muscles, brain, and eyes.[69] Eye disease manifests with crystal deposition in the cornea, conjunctiva, and iris, typically at very young ages. However, with the advent of kidney transplantation, patients are living much longer lives, and additional ophthalmic complications have been reported. In particular, superficial punctate keratopathy, severe peripheral neovascularization, various iris abnormalities, and band keratopathy range from 40% to 73% in prevalence in these patients.[70] Glaucoma has also been reported as a result of iris thickening and posterior synechiae.[69]

Others

Several other conditions exist in which both kidney impairment and ophthalmic complications occur (Table 28.3).[71–84]

CONCLUSION

It is clear that there is a high prevalence of comorbid eye disease in patients with CKD, ESRD, and kidney transplant patients. Early ophthalmic evaluation in the face of visual changes in these patients is of paramount importance. In addition, there may be a role for routine ophthalmology screening in any patient with stage 3 CKD or higher. Future studies focusing on the preventive benefit of such screening programs will certainly shed light on the potential benefits of this collaboration.

References

1. U.S. Renal Data System. *Annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States, National Institutes of Health.* Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 2011.
2. Shantha GPS, Kumar AA, Bhaskar E, et al. Hypertensive retinal changes, a screening tool to predict microalbuinuria in hypertensive patients: a cross-sectional study. *Nephrol Dial Transplant* 2010; **25**:1839–45.
3. Shantha GPS, Bhaskar E, Kumar AA, et al. Accuracy of retinal changes in predicting microalbuminuria among elderly hypertensive patients: a cross-sectional study from a teaching hospital in south India. *Int Urol Nephrol* 2009;**41**:137–43.
4. Murphy RP, Lam LA, Chew EY. Hypertension. In: Ryan SJ, editor. *Retina*. 4th ed. Philadelphia, PA: Elsevier, Inc; 2006. p. 1377–82.
5. Knudtson MD, Lee KE, Hubbard LD, et al. Revised formulas for summarizing retinal vessel diameters. *Curr Eye Res* 2003;**27**:143–9.
6. Wong TY, Shankar A, Klein R, et al. Prospective cohort study of retinal vessel diameters and risk of hypertension. *Br Med J* 2004; **329**:79.
7. Grunwald JE, Alexander J, Maguire M, et al. Prevalence of ocular fundus pathology in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2010;**5**:867–73.
8. Wong TY, Coresh J, Klein R, et al. Retinal microvascular abnormalities and renal dysfunction: the Atherosclerosis Risk in Communities Study. *J Am Soc Nephrol* 2004;**15**:2469–76.
9. Grunwald JE, Alexander J, Ying G-S, et al. Retinopathy and chronic kidney disease in the chronic renal insufficiency cohort (CRIC) study. *Arch Ophthalmol* 2012;**130**:1136–44.
10. Chen H, Zhang X, Shen X. Ocular changes during hemodialysis in patients with end stage renal disease. *BMC Ophthalmol* 2018;**18**:208.
11. Klaassen-Broekema N, van Bijsterveld P. Diffuse and focal hyperaemia of the outer eye in patients with chronic renal failure. *Int Ophthalmol* 1993;**17**:249–54.
12. Klaassen-Broekema N, van Bijsterveld P. Red eyes in renal failure. *Br J Ophthalmol* 1992;**76**:268–71.
13. Tokuyama T, Ikeda T, Sato K, et al. Conjunctival and corneal calcification and bone metabolism in hemodialysis patients. *Am J Kidney Dis* 2002;**39**:291–6.
14. Sati A, Jha A, Moulick PS, et al. Corneal endothelial alterations in chronic renal failure. *Cornea* 2016;**35**:1320–5.
15. Caliskan S, Hekimoğlu A, Çelikay O, et al. Association between conjunctival and corneal calcification and atherosclerotic changes in the carotid artery in maintenance hemodialysis patients. *Cornea* 2017;**36**:68–73.
16. Hsiao C-H, Chao A, Chu S-Y, et al. Association of severity of conjunctival and corneal calcification with all-cause 1-year mortality in maintenance haemodialysis patients. *Nephrol Dial Transplant* 2011;**26**:1016–23.
17. Tovbin D, Belfair N, Shapria S, et al. High postdialysis urea rebound can predict intradialytic increase in intraocular pressure in dialysis patients with lowered intradialytic hemoconcentration. *Nephron* 2002;**90**:181–7.
18. Nongpiur MD, Wong TY, Sabanayagam C, et al. Chronic kidney disease and intraocular pressure, the Singapore Malay Eye Study. *Ophthalmology* 2010;**117**:477–83.
19. Tokuyama T, Ikeda T, Sato K. Effect of plasma colloid osmotic pressure on intraocular pressure during hemodialysis. *Br J Ophthalmol* 1998;**82**:751–3.
20. Dinc UA, Ozdek S, Aktas Z, et al. Changes in intraocular pressure and corneal and retinal nerve fiber layer thickness during hemodialysis. *Int Ophthalmol* 2010;**30**:337–40.
21. Evans RD, Rosner M. Ocular abnormalities associated with advanced kidney disease and hemodialysis. *Semin Dial* 2005;**18**: 252–7.
22. Mullaem G, Rosner MH. Ocular problems in the patient with end-stage renal disease. *Semin Dial* 2012;**25**:403–7.
23. Angra SK, Goyal JL. Haemodialysis cataract. *Indian J Ophthalmol* 1987;**35**:82–3.
24. Huynh SC, Kifley A, Strippoli GFM, Mitchell P. Is renal impairment a predictor of the incidence of cataract or cataract surgery? Findings from a population-based study. *Ophthalmology* 2005;**112**: 293–300.
25. Troiano P, Buccianti G. Bilateral symmetric retinal detachment and multiple retinal pigment epithelial detachments during haemodialysis. *Nephrol Dial Transplant* 1998;**13**:2135–7.
26. Gass JD. Bullous retinal detachment and multiple retinal pigment epithelial detachments in patients receiving hemodialysis. *Graefes Arch Clin Exp Ophthalmol* 1992;**230**:454–8.
27. Chang YS, Weng SF, Chang C, et al. Risk of serous retinal detachment in patients with end-stage renal disease on dialysis. *PLoS One* 2017;**12**.
28. Nagaoka T, Takeyama Y, Kanagawa S, et al. Effect of hemodialysis on retinal circulation in patients with end stage renal disease. *Br J Ophthalmol* 2004;**88**:1026–9.
29. Jackson TL, Farmer CK, Kingswood C, et al. Hypotensive ischemic optic neuropathy and peritoneal dialysis. *Am J Ophthalmol* 1999; **128**:109–11.
30. Tyler HR. Neurologic disorders seen in the uremic patient. *Arch Intern Med* 1970;**126**:781–6.
31. Winkelmayer WC, Eigner M, Berger O, et al. Optic neuropathy in uremia: an interdisciplinary emergency. *Am J Kidney Dis* 2001;**37**: E23.
32. Porter JB, Huehns ER. The toxic effects of desferrioxamine. *Baillieres Clin Haematol* 1989;**2**:459–74.
33. Liew G, Mitchell P, Wong TY, et al. CKD increases the risk of age-related macular degeneration. *J Am Soc Nephrol* 2008;**19**:806–11.
34. Deva R, Alias MA, Colville D, et al. Vision-threatening retinal abnormalities in chronic kidney disease stages 3 to 5. *Clin J Am Soc Nephrol* 2011;**6**:1866–71.
35. Cheng Q, Saaddine JB, Klein R, Rothenberg R, Chou CF, Il'yasova D. Early age-related macular degeneration with cardiovascular and renal comorbidities: an analysis of the National Health and Nutrition Examination Survey, 2005-2008. *Ophthalmic Epidemiol* 2017;**24**(6):413–9.
36. Chen YJ, Yeung L, Sun CC, Huang CC, Chen KS, Lu YH. Age-related macular degeneration in chronic kidney disease: a meta-analysis of observational studies. *Am J Nephrol* 2018;**48**(4):278–91.
37. U.S Renal Data System. *USRDS 2002 annual data report: atlas of end-stage renal disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2002.
38. Davis MD, Fisher MR, Gangnon RE, Barton F, Aiello LM, Chew EY, Ferris III FL, Knatterud GL. Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss, ETDRS report no 18. *Investig Ophthalmol Vis Sci* 1998;**39**:233–52.
39. Rand LI, Prud'homme GJ, Ederer F, Canner PL, the Diabetic Retinopathy Study Research Group. Factors influencing the development of visual loss in advanced diabetic retinopathy, DRS report no 10. *Investig Ophthalmol Vis Sci* 1985;**26**:983–91.
40. Eye Disease Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol* 2004;**122**:477–85.
41. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 1984;**102**:527–32.
42. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* 1984;**102**:520–6.

43. The Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus. The Diabetes Control and Complictions Trial. *Arch Ophthalmol* 1995;**113**: 36–51.
44. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;**317**:703–13.
45. Klein BE, Moss SE, Klein R, Surawicz TS. The Wisconsin epidemiologic study of diabetic retinopathy. XIII. Relationship of serum cholesterol to retinopathy and hard exudate. *Ophthalmol Times* 1991;**98**:1261–5.
46. Chew EY, Klein ML, Ferris III FL, Remaley NA, Murphy RP, Chantry K, Hoogwerf BJ, Miller D, for the ETDRS Research Group. Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. ETDRS report number 22. *Arch Ophthalmol* 1996;**114**:1079–84.
47. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. *Ophthalmol Times* 1991;**98**: 823–33.
48. The Diabetic Retinopathy Study Research Group. Four risk factors for severe visual loss in diabetic retinopathy. The third report of the Diabetic Retinopathy Study. *Arch Ophthalmol* 1979;**97**:654–5.
49. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. ETDRS report number 1. *Arch Ophthalmol* 1985;**103**:1796–806.
50. The Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. *Am J Ophthalmol* 1976;**81**:383–96.
51. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmol Times* 1991;**98**(Suppl. p):767–85.
52. Diabetic Retinopathy Clinical Research Network, Elman MJ, Qin H, Aiello LP, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmol Times* 2012;**119**:2312–8.
53. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. RESTORE Study Group. "The RESTORE Study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. *Ophthalmol Times* 2011;**118**:615–25.
54. Nguyen QD, Shah SM, Khwaja AA, et al. READ-2 study group. "Two-year outcomes of the ranibizumab for edema of the mAcula in diabetes (READ-2) study. *Ophthalmol Times* 2010;**117**:2146–51.
55. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. *Arch Ophthalmol* 2012;**130**:972–9.
56. Das T, Gupta A, Sakhuja V, et al. Ocular complications in renal allograft recipients. *Nephrol Dial Transplant* 1991;**6**:649–55.
57. Izzedine H, Bodaghi B, Launay-Vacher V, Deray G. Oculorenal manifestations in systemic autoimmune diseases. *Am J Kidney Dis* 2004;**43**:209–22.
58. Marmor MF, Kellner U, Lai TY, et al. Revised recommendations on screening for chloroquine and hyroxychloroquine retinopathy. *Ophthalmology* 2011;**118**:415–22.
59. Tarabishy AB, Schulte M, Papaliodis GM, Hoffman GS. Wegener's granulomatosis: clinical manifestations, differential diagnosis, and management of ocular and systemic disease. *Surv Ophthalmol* 2010; **55**:429–44.
60. Robinson MR, Lee SS, Sneller MC, et al. Tarsal-conjunctival disease associated with Wegener's granulomatosis. *Ophthalmology* 2003; **110**:1770–80.
61. Jampol LM, Lahov M, Albert DM, Craft J. "Ocular clinical findings and basement membrane changes in Goodpasture's syndrome. *Am J Ophthalmol* 1975;**79**:452–63.
62. Mandeville JT, Levinson RD, Holland GN. The tubulointerstitial nephritis and uveitis syndrome. *Surv Ophthalmol* 2001;**46**:195–208.
63. Takemura T, Okada M, Hino S, et al. Course and outcome of tubulointerstitial nephritis and uveitis syndrome. *Am J Kidney Dis* 1999; **34**:1016–21.
64. Baughman RP, Lower EE, Kaufman AH. Ocular sarcoidosis. *Semin Respir Crit Care Med* 2010;**31**:452–62.
65. Meyrier A, Simon P. Drooping upper eyelids and polycystic kidney disease. *J Am Soc Nephrol* 1994;**5**:1266–70.
66. Seymenoğlu G, Baser E. Ocular manifestations and surgical results in patients with Alport Syndrome. *J Cataract Refract Surg* 2009;**35**: 1302–6.
67. Colville DJ, Savige J. Alport syndrome: a review of the ocular manifestations. *Ophthalmic Genet* 1997;**18**:161–73.
68. Rhys C, Snyers B, Pirson Y. Recurrent corneal erosion associated with Alport's syndrome: *rapid communication*. *Kidney Int* 1997;**52**: 208–11.
69. Tsilou E, Zhou M, Gahl W, et al. Ophthalmic manifestations and histopathology of infantile nephropathic cystinosis: report of a case and review of the literature. *Surv Ophthalmol* 2007;**52**: 97–105.
70. Tsilou ET, Rubin BI, Reed GF, et al. Age-related prevalence of anterior segment complications in patients with infantile nephropathic cystinosis. *Cornea* 2002;**21**:173–6.
71. O'Dea D, Parfrey PS, Harnett JD, et al. The importance of renal impairment in the natural history of Bardet-Biedl syndrome. *Am J Kidney Dis* 1996;**27**:776–83.
72. Sodi A, Ioannidis AS, Mehta A, et al. Ocular manifestations of Fabry's disease: data from the Fabry outcome survey. *Br J Ophthalmol* 2007;**91**:210–4.
73. Igarahsi T, Inatomi J, Sekine T, et al. Novel nonsense mutation in the Na^+/HCO_3^- cotransporter gene (SLC4A4) in a patient with permanent isolated proximal renal tubular acidosis and bilateral glaucoma. *J Am Soc Nephrol* 2001;**12**:713–8.
74. Igarashi T, Inatomi J, Sekine T, et al. Mutations in SLC4A4 cause permanent isolated proximal renal tubular acidosis with ocular abnormalities. *Nat Genet* 1999;**23**:264–6.
75. Borysiewicz LK, Soutar AK, Evans DJ, et al. Renal failure in familial lecithin: cholesterol acyltransferase deficiency. *Q J Med* 1982;**51**: 411–26.
76. Hørven I, Egge K, Gjone E. Corneal and fundus changes in familial LCAT-deficiency. *Acta Ophthalmol* 1974;**52**:201–10.
77. Bongers EMHF, Gubler M-C, Knoers NVAM. Nail-patella syndrome. Overview on clinical and molecular findings. *Pediatr Nephrol* 2002;**17**:703–12.
78. Punjabi OS, Riaz K, Mets MB. Crystalline retinopathy in primary hyperoxaluria. *J AAPOS* 2011;**15**:214–6.
79. Small KW, Letson R, Scheinman J. Ocular findings in primary hyperoxaluria. *Arch Ophthalmol* 1990;**108**:89–93.
80. Thomas-Sohl KA, Vaslow DF, Maria BL. Sturge-Weber syndrome: a review. *Pediatr Neurol* 2004;**30**:303–10.
81. Celebi S, Alagöz G, Aykan U. Ocular findings in Sturge-Weber syndrome. *Eur J Ophthalmol* 2000;**10**:239–43.
82. Rowley SA, O'Callaghan FJ, Osborne JP. Ophthalmic manifestations of tuberous sclerosis: a population based study. *Br J Ophthalmol* 2001;**85**:420–3.
83. Rizk D, Chapman AB. Cystic and inherited kidney diseases. *Am J Kidney Dis* 2003;**42**:1305.
84. Lonser RR, Glenn GM, McClellan W, et al. von Hippel-Lindau disease. *Lancet* 2003;**361**:2059–67.

QUESTIONS AND ANSWERS

Question 1

A 46-year-old man presents for initial evaluation of CKD. S[Cr] is currently 1.5 mg/dL, corresponding to an eGFR of 50 mL/min/1.73 m^2. S[Cr] was normal 3 years ago. He has no history of diabetes mellitus. He has had hypertension for approximately 15 years. He does not have a family history of kidney disease. His urinalysis shows no RBCs or WBCs and has trace albumin on dipstick. His only complaint is increasing blurry vision, which he notes in both eyes. He states this has been slowly progressive for at least five years. You make the referral to ophthalmology, but as you are doing so you attempt to formulate a differential diagnosis of this visual problem. All of the following fundus pathologies are associated with increased risk of CKD **except**?

A. Microaneurysms
B. Retinal hemorrhages
C. Macular degeneration
D. Soft exudates
E. Arteriovenous nicking

Answer: C

Several fundus pathologies convey a risk for developing CKD according to some recent studies. The Chronic Renal Insufficiency Cohort study published a cross-sectional study in 2010 demonstrating an association between fundus pathology and the presence of CKD. Interestingly, this association also appeared to be stronger in males, non-whites, those with diabetes, and those under the age of 50.[7] This is consistent with an earlier prospective cohort study published in 2004 from the Atherosclerosis Risk in Communities database. Here, it was found that the presence of microaneurysms, retinal hemorrhages, soft exudates, and arteriovenous nicking was associated with a greater risk of later-developing CKD. They found no such risk with focal arteriolar narrowing or changes in arteriole-to-venule ratio.[8] Macular degeneration putting people at risk for CKD was not looked at in these studies, though there is some early evidence that the presence of CKD may increase the risk of later developing macular degeneration.[33,34]

Question 2

You see patients at the local dialysis unit as part of your monthly rounds. Your next patient is a 53-year-old man with ESRD secondary to focal segmental glomerulosclerosis who has been on dialysis for four years. Adequacy on dialysis has been acceptable and hemoglobin is at goal. There are no access issues and his electrolytes are acceptable. He complains of itchy, red eyes, which seems to be getting worse over the past couple of weeks. He wonders if he has developed allergies, though he denies rhinitis or cough. Examination demonstrates diffuse corneal erythema. Based on this appearance, you suspect corneal inflammation from calcium deposition. All of the following have been identified as risk factors in this process with the **exception** of:

A. Hypercalcemia
B. Longer dialysis times
C. Decreased bone mineral density
D. Hyperparathyroidism
E. Calcium x phosphorus product

Answer: A

Calcium deposition resulting in corneal inflammation is a problem stemming from calcium and phosphate mishandling and disturbances in the endocrine processes governing these ions. The most comprehensive study looking at this issue was a cross-sectional study from Japan published in 2002.[13] 44 men had corneal calcification scores detected by slit lamp examination. Several risk factors were evaluated. Longer dialysis times and decreased bone mineral density were associated with higher calcification scores but were more likely to represent background compliance factors. Higher PTH levels and calcium x phosphate product were strongly associated with higher corneal calcification scores, as were S[P] levels. However, interestingly, there was no significant association of hypercalcemia with this process.

Question 3

A 21-year-old woman comes to your office for initial evaluation of hematuria and proteinuria. A college sports examination included a urinalysis that demonstrated 2+ proteinuria, which then was followed by a protein:creatinine ratio of 1.8 g protein/g creatinine. She also had 20 RBC per high power field. S[Cr] is 1.2 mg/dL. She denies any current health problems. She has no history of hypertension or diabetes. She wears hearing aids for sensorineural hearing loss, which was diagnosed in childhood. Her father died when she was 5 years old, and she thinks he was treated with dialysis. She is unaware of anyone else in her family with kidney disease. She does not take nonsteroidal inflammatory drugs or any other medications. She has no history of kidney stones and history of frequent urinary tract infections. Review of systems was only notable for decreasing visual acuity over the past 6 months.

BP is 132/78 mm Hg with a pulse of 65 bpm. Physical examination is unremarkable other than the presence of hearing aids. In addition to collecting various serologies and planning a biopsy in the coming months (she would

like to wait until after the soccer season), you refer her to ophthalmology for decreasing visual acuity. Their findings included anterior lenticonus and dot-and-fleck retinopathy. The following criteria allow you to diagnose Alport's syndrome with the **exception** of:

A. Family history of Alport's syndrome
B. Sensorineural hearing loss
C. Evidence of kidney disease
D. Dot-and-fleck retinopathy

Answer: B

This young woman with the recent discovery of an elevated S[Cr], microscopic hematuria, and subnephrotic range proteinuria in the absence of known systemic disease raises concern regarding a primary glomerular disorder. The fact that she has sensorineural hearing loss and a probable family history of kidney disease raises the suspicion of Alport syndrome, but certainly other glomerular pathologies still need to be considered. Recent studies, however, have suggested that the presence of a family history of Alport's, evidence of kidney disease, and dot-and-fleck retinopathy is virtually diagnostic of Alport's syndrome.[67] Anterior lenticonus is seen in approximately 25% of cases. Posterior polymorphous corneal dystrophy is rare, but when present, is also nearly exclusive to Alport Syndrome.[66] Although characteristic of many types of Alport Syndrome, the presence or absence of hearing loss is not part of the clinical triad suggested by Colville et al.[67] It should be noted that many X-linked cases are not associated with hearing loss, causing many cases of Alport Syndrome to be missed by physicians expecting the presence of hearing problems.

Question 4

A 57-year-old man with CKD is referred for initial evaluation. He has a history of diabetes mellitus for 7 years and was recently diagnosed with hypertension and hypercholesterolemia, for which he was started on medication. He denies any systemic complaints and reports his last hemoglobin A1c was at goal. The patient recently underwent his first diabetic eye screening examination with ophthalmology and brought a copy of the report to you. It states he has moderate nonproliferative diabetic retinopathy without macular edema in both eyes. The patient is concerned about his ocular findings and the effect it will have on his vision if it progresses. All of the following have been identified as risk factors for progression of diabetic retinopathy **except**

A. Venous beading
B. Cotton-wool spots
C. Intraretinal hemorrhages
D. Poorly controlled cholesterol
E. Poorly controlled hypertension

Answer: B

Medical management of risk factors for progression of retinopathy is essential and includes glucose, hypertension, and cholesterol control. Severity of diabetic retinopathy is associated with poorer glucose control. Although intensive therapy does not prevent retinopathy completely, it does reduce the risk of the development and progression of diabetic retinopathy.[43] Intensive blood pressure control in comparison to less intensive blood pressure control is also associated with decreased retinopathy.[44] Additionally, increased serum cholesterol levels are associated with increased severity of hard exudates and development of proliferative diabetic retinopathy.[45,46] The Early Treatment Diabetic Retinopathy Study (ETDRS) "4-2-1" rule helps identify eyes in the severe or very severe NPDR groups.[47] Eyes with any one of these three features are considered to have severe NPDR: (1) hemorrhages in all four quadrants, (2) venous beading in two quadrants, or (3) IRMA in one quadrant, and have a 26% chance of progressing to proliferative diabetic retinopathy in 1 year and a 48% chance in 3 years. Although cotton-wool spots are a sign of poor retinal perfusion, they have poor predictive value for retinopathy progression.[47]

Question 5

A 62-year-old woman with CKD presents for routine follow-up. She has poorly controlled diabetes for the past 20 years. The patient was seen by ophthalmology yesterday for "floaters" in her right eye that appeared suddenly 3 days ago while she was watching television. The floaters obscure portions of her vision, but she denies any discomfort. The medical record from the ophthalmologist states the patient has proliferative diabetic retinopathy in both eyes with a vitreous hemorrhage in the right eye. The patient tells you she is scheduled to return to the ophthalmologist for treatment in a few days, but states the office is too far away and she would like to know if her vision will improve on its own. You tell her diabetic retinopathy is the leading cause of new cases of blindness in people aged 20–74 years in the US, and it is important to follow up for treatment. All of the following have been identified as risk factors for moderate or severe vision loss for which ocular treatment is recommended **except**

A. Vitreous hemorrhage
B. Intraretinal hemorrhages
C. Presence of new vessels on or near the optic disc
D. Moderate or severe new vessels (greater than 1/4 disc area)
E. Clinically significant macular edema

Answer: B

NPDR includes a wide variety of retinal abnormalities that occur well before neovascularization. These changes include intraretinal hemorrhages and microaneurysms, venous beading, IRMA, cotton-wool spots, and hard exudates. Although the presence of intraretinal hemorrhages, especially if present in all four retinal quadrants, predicts progression to PDR, intraretinal hemorrhages alone are not a risk factor for moderate or severe vision loss and do not require ocular treatment. In contrast, PDR consists of NVD and neovascularization elsewhere in the retina, which can lead to preretinal and vitreous hemorrhage. The Diabetic Retinopathy Study identified four retinopathy factors associated with an increased risk of developing severe visual loss without treatment.[48] The risk factors are separate but cumulative: (1) presence of any new vessels in the eye, (2) presence of new vessels on or near the optic disc, (3) moderate or severe new vessels (greater than 1/4 disc area), and (4) vitreous hemorrhage. Presence of three or four risk factors places the eye in the "high-risk proliferative retinopathy" group. Without treatment, 50% of such patients develop severe visual loss in 5 years. Another important cause of visual loss is macular edema. Eyes with clinically significant macular edema have a 32% chance of developing moderate visual loss in 3 years without treatment.[49]

CHAPTER

29

Neurologic Complications of Chronic Kidney Disease

Stephen Seliger[a], *Salina P. Waddy*[b]

[a]Department of Medicine, Division of Nephrology, University of Maryland School of Medicine, Baltimore, MD, United States; [b]Atlanta Veterans Administration, Department of Neurology, Decatur, GA, United States

Abstract

Neurologic outcomes in chronic kidney disease (CKD) patients are pervasive. The most common are cognitive impairment, stroke, seizures, and peripheral neuropathies. Despite a strong graded association between measures of renal function and cognitive function, cognitive impairment in CKD patients is largely undiagnosed. Annual and predialysis cognitive screening is critical to avoid adverse outcomes of missed diagnoses of cognitive impairment: medication noncompliance and inability to make informed decisions regarding initiating dialysis. Cerebrovascular disease, neurodegenerative disease, and inflammation contribute to a CKD model of accelerated vascular cognitive impairment. Risk of stroke increases significantly in CKD and ESRD patients, up to sevenfold during the month of dialysis initiation. Aggressive treatment with erythropoiesis-stimulating agents increases stroke risk appreciably. For stroke prevention in atrial fibrillation, warfarin and dose-adjusted newer anticoagulants appear effective in stage 3 CKD patients but are unproven or contraindicated in CKD stage 4 or higher. Management of uremic polyneuropathy, mononeuropathies, and uremic pruritus is described in this chapter.

INTRODUCTION

Central and peripheral neurologic disorders in chronic kidney disease (CKD) patients are pervasive but are frequently underdiagnosed and their impact often underappreciated. The common neurologic complications in the CKD population are cognitive impairment, seizure, stroke, and peripheral neuropathies.[1]

COGNITIVE IMPAIRMENT IN CKD

Cognitive impairment is highly prevalent in CKD patients. Multiple studies have confirmed a graded association between renal function or albuminuria and cognitive impairment. Despite cognitive impairment being highly prevalent in the ESRD population, it is substantially underdiagnosed. In studies of HD patients,[2,3] only 4% of patients with cognitive impairment had received a medical record diagnosis. As early stage CKD patients on average have much less frequent healthcare contact than HD patients, the likelihood of underdetection in earlier stage CKD patients is probably greater.

Definitions of Cognitive Impairment (in the Non-CKD and CKD Populations)

Most studies describe the frequency of global cognitive impairment, measured on a test of overall cognitive function such as the Mini-Mental State Exam,[4] or of impairment in individual cognitive domains, including memory, attention, language, visual–spatial, calculations, and executive function. Executive function encompasses judgment and planning, including the ability to make informed healthcare decisions. Some studies measure diagnosed dementia, usually according to Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria.

Mild cognitive impairment (MCI) is impairment that is no longer consistent with normal aging but has not progressed to dementia. MCI most often involves early short-term memory loss (amnestic MCI) or impairment in one or more other cognitive domains such as language or executive function (nonamnestic MCI). MCI is often defined as performing 1.5–1.99 standard deviations below standardized norms on a given cognitive test,[5,6] but the definition varies. The conversion rate from MCI to dementia is approximately 15% per year in elderly patients without CKD[6] and is higher in those

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00029-2

who carry the apolipoprotein E4 (APOE4) allele.[7] APOE4 is a genetic factor that confers increased risk of Alzheimer disease (AD).

Dementia is defined by DSM IV criteria as chronic persistent and usually progressive cognitive impairment in two or more cognitive domains (usually including memory) that substantially affects daily function, represents a decline in premorbid function, and is not due to concomitant acute delirium.[8] Dementia is often defined in research studies as performing two or more standard deviations below population-defined norms in at least two cognitive domains.

Dementia is the umbrella term for moderate to severe chronic cognitive impairment. AD is the most common type of dementia in the general US population and the most common neurodegenerative dementia. Hippocampal and cerebral atrophy are eventual prominent features of AD. Vascular dementia, due to both large- and small-vessel pathology and often accompanying white matter disease, is the second most common type, alone or in combination with AD. Dementia associated with Parkinson's disease (sometimes called Lewy body disease), frontal–temporal dementia, and other dementia syndromes account for the remaining approximately 20% of dementias in patients without CKD.[9]

Delirium is a syndrome of acute cognitive impairment characterized by acute onset, inattention, disorganized thinking, and an altered state of consciousness, including sleep–wake cycle disturbance. Other common symptoms include psychomotor agitation or retardation, memory loss, and disorientation. Delirium is defined by abrupt onset and fluctuating course, in contrast to the chronic insidious progressive nature of dementia. Delirium was previously believed to be transient. It is now established, however, that delirium often leads to sustained cognitive decline, especially in patients with preexisting dementia, and to a loss of on average one activity of daily living over 6 months of follow-up in non-CKD patients.[10–12] Delirium is often due to an acute intercurrent medical condition such as a urinary tract infection, a medication side effect, or electrolyte imbalance. Interventions that result in bed-restriction or decreased mobility such as physical restraints, urinary catheters, or intravenous lines also increase the risk of delirium. Delirium is often multifactorial, so the actual cause may be difficult to ascertain. The presence of dementia increases the risk of delirium, and they often coexist. As delirium occurs three times as often in patients with dementia[13] as in those without, the development of delirium should trigger suspicion of an underlying dementia. However, because the symptoms of delirium are difficult to distinguish from those of dementia, for patients with no previous diagnosis of cognitive impairment who develop delirium, it is recommended to wait for a period of approximately a month after the delirium episode to conduct a full dementia assessment.

The Confusion Assessment Method is the most commonly used instrument to assess the presence of delirium. The Confusion Assessment Method is a brief standardized validated instrument with questions regarding four features: (1) acute onset or fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness (such as hypervigilance, lethargy, or stupor). The diagnosis of delirium requires the presence of features 1 and 2, and either 3 or 4. Other symptoms may be present such as disorientation, psychomotor agitation or retardation, hallucinations, sleep–wake cycle disturbance, and memory loss.[14]

Epidemiology of Cognitive Impairment in CKD

The true population prevalence and incidence of cognitive impairment in CKD are difficult to estimate because most studies were not population based but conducted in clinic or referral populations. Among 80 stage 3–4 CKD clinic patients, 23% had severely impaired executive function and 28% scored poorly on delayed memory test.[15] In the 2006 US Renal Data System Annual Data Report using Medicare claims data, the prevalence of dementia was 7.6% in the CKD cohort, increasing to 16.8% among patients aged 85 years or older.[16] However, these rates are substantially underestimated because Medicare claims are an insensitive measure of dementia in populations in whom cognitive function is infrequently assessed.

Multiple reports describe a graded cross-sectional relationship between estimated glomerular filtration rate (eGFR) and cognitive impairment. As renal function declines, so does cognitive function.[17–20] In the Reasons for Geographic and Racial Differences in Stroke study, the prevalence of cognitive impairment increased with declining eGFR starting at eGFR<60 mL/min/1.73 m^2 and paralleled the prevalence of cerebrovascular disease (Figure 29.1).[18–20] In the Heart, Estrogen/Progesterone Study among menopausal women, each 10 mL/min/1.73 m^2 decrement in eGFR corresponded to an approximately 15–25% increase in risk of impairment in executive function, language, and memory.[19] Using a cognitive battery, the Chronic Renal Insufficiency Cohort study found that eGFR<30 compared with 45–59 mL/min/1.73 m^2 was associated with greater impairment in most cognitive domains.[20]

The Systolic Blood Pressure Intervention Trial (SPRINT) was a study of intensive compared with standard blood pressure goals. Patients with diabetes and those with a history of stroke were excluded. Of the more than 9000 SPRINT participants, 2707 had complete

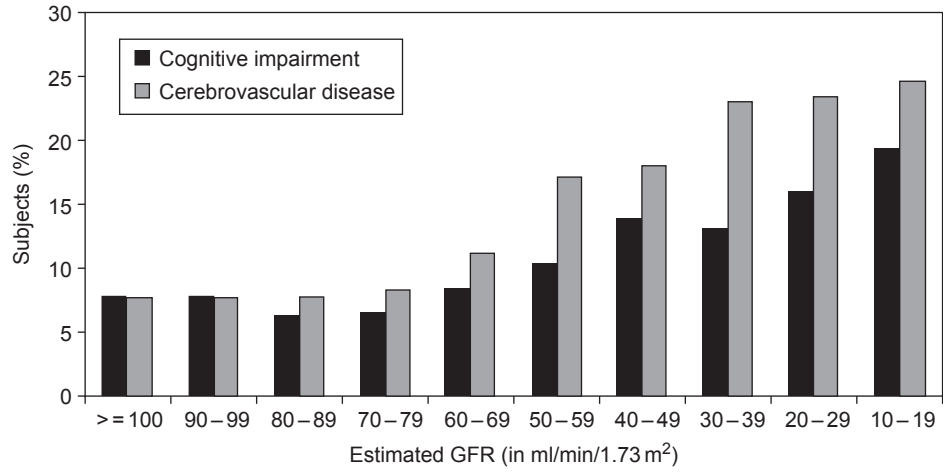


FIGURE 29.1 Unadjusted prevalence of cognitive impairment and cerebrovascular disease by estimated glomerular filtration rate (eGFR). *Reference 18, Copyright 2008 Elsevier Inc, reproduced with permission.*

assessments of cognitive function. A subset of 637 participants underwent brain imaging. Mean age was 68 years, more than a third were women, and almost a third were Black. Mean eGFR was 70.8 ± 20.9 mL/min/1.73 m^2. Median urine albumin:creatinine ratio (UACR) was 9.7 mg/g. In this cross-sectional assessment, higher UACR was associated with worse global cognitive function, executive function, memory, and attention, in adjusted analyses. Increased urinary albumin excretion was associated with cognitive performance typical of older people. Lower eGFR was independently associated with worse global cognitive function and memory. In adjusted models, higher urinary albumin excretion was associated with larger abnormal white matter volume. There was no relationship detected between this parameter and eGFR. The findings suggested vascular disease may be associated with abnormal cognitive function in this population.[21]

A longitudinal relation between baseline eGFR and declines in global cognitive function and cognitive domains has also been reported.[18,22–28] In the Cardiovascular Health Study, serum creatinine concentration (S[Cr]) >1.5 mg/dL in men and >1.3 mg/dL in women was associated with a 37% increased risk of incident dementia over 6 years.[27] In the Health, Aging, and Body Composition (Health ABC) Study, adjusted odds ratios for cognitive decline were 1.32 for baseline eGFR 45–59 mL/min/1.73 m^2 and 2.43 for <45 mL/min/1.73 m^2 (stage 3b CKD). In the Rush Memory and Aging Project, the effect on global cognitive function of 15 mL/min/1.73 m^2 lower eGFR at baseline was similar to 3 years of aging and equivalent to about 75% of the effect of the APOE-4 allele, which confers up to twofold increased risk of AD.[29] Baseline eGFR also predicted cognitive decline in the specific cognitive domains of memory and verbal fluency. Decline in eGFR over 5 years was associated with decline in global cognition, verbal episodic memory, and abstract reasoning in the Maine-Syracuse Longitudinal Study of 590 community-dwelling individuals with mean age of 62 years, and mean baseline eGFR of 78.4 mL/min/1.73 m^2. In that study, a decline in eGFR of 30 mL/min/1.73 m^2 over 5 years was equivalent to a decline in global cognitive function of approximately 7 years of aging.[28]

Serum cystatin C concentration is another parameter used to measure renal function that has been studied in relation to cognitive impairment. Cystatin C colocalizes with amyloid in the brains of AD patients, and elevated serum cystatin C concentrations in the Health ABC study were shown to be associated with increased risk of baseline cognitive impairment and cognitive decline.[30] Studies in animal models suggest that higher concentrations of cystatin C may have a protective effect against AD.[31]

Albuminuria may be a more sensitive biomarker for cognitive impairment than eGFR both cross-sectionally and longitudinally, because it is a measure of microvascular endothelial function and more likely to reflect similar vascular integrity in the cerebrovascular system.[32–34] In the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial,[32] urinary albumin excretion, measured as albumin:creatinine ratio (ACR) >30 μg/mg, was associated with performance in the lowest tertile on a verbal memory test and was equivalent to 3.6 years of aging on the Digit Symbol Substitution Test of processing speed/executive function. In contrast, eGFR was not associated with any cognitive measure in that study. In the Nurses' Health Study, ACR levels as low as 5 μg/mg were associated with cognitive decline equivalent to 2–7 years of aging in global cognitive function, verbal memory, and verbal fluency.[33]

Pathophysiology of Cognitive Impairment in CKD: the Brain–Kidney Connection

The pathophysiology of cognitive impairment in CKD may be an accelerated model of vascular cognitive impairment, superimposed on and parallel with mechanisms leading to neurodegenerative disease such as AD. Cognitive impairment in CKD is nonlinear and multifaceted. Ischemic cerebrovascular disease, including small-vessel arteriolar disease, is central to the model as both a common intermediary outcome and a major contributor to chronic cognitive impairment. Chronic inflammation and underlying vascular endothelial pathology also appear to play substantial roles.

The brain and kidneys can be considered end organs on parallel trajectories subject to shared cardiovascular risk factors and microvascular pathologic processes mediated by inflammatory[35] and oxidative processes, occurring in similar low-resistance vascular beds and endothelial structures.[36] Impaired endothelial function in the brain manifests as blood–brain barrier defects,[37,38] and increased susceptibility to microinfarcts, lacunar infarcts, and white matter changes.[39] Similarly, impaired endothelial function in the kidney manifests as impaired glomerular filtration with secondary increased glomerular permeability, or proteinuria. Independently, the effects of uremic toxins, disrupted calcium–phosphate metabolism, other metabolic disturbances, and a potential genetic predisposition to exaggerated inflammatory response may accelerate the rate of cognitive decline in CKD patients.[40] At the cellular and molecular level in the kidney, microvascular endothelial dysfunction in the glomerulus leads to abnormal glomerular permeability, which may trigger tubulointerstitial inflammation, secondary renal fibrosis, and progression of CKD.[41] Mitochondrial dysfunction that triggers inflammation may be prevalent in CKD.[42]

Uremic Encephalopathy

Uremic encephalopathy is a complication of both acute and chronic renal diseases. Uremic encephalopathy is characterized by a general sensorial clouding and may include other features such as headaches, dysarthria, gate instability, asterixis, action tremors, convulsions, and multifocal myoclonus.[43,44] If untreated, uremic encephalopathy can progress to coma. Uremic encephalopathy is generally attributed to the accumulation of uremic toxins, although there may be additional CKD-related contributions related to hormonal dysregulation, hypertension, fluid and electrolyte disturbances, and drug toxicity. Symptoms of uremic encephalopathy generally improve with dialysis or renal transplantation.

Model of Pathways Leading to Cognitive Impairment in CKD

Several models of the mechanisms of cognitive impairment in CKD patients have been proposed.[45–47] Figure 29.2 describes a modified version of a model previously proposed by Kurella and Yaffe.[47]

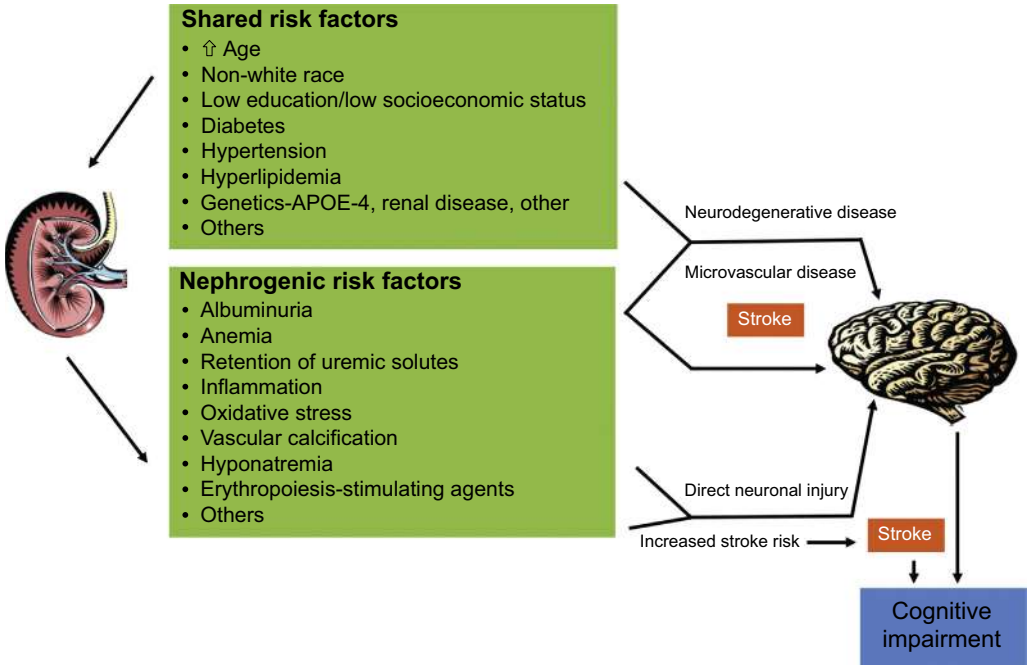


FIGURE 29.2 Mechanisms of cognitive impairment in chronic kidney disease patients. *Adapted from reference 47. Copyright 2011 Macmillan Publishers Ltd, reproduced with permission.*

Risk Factors for Cognitive Impairment in CKD

Shared risk factors that contribute to renal disease and low brain reserve appear in the top box (Figure 29.2). Risk factors for cognitive impairment in CKD patients are similar to those for dementia due to AD, vascular cognitive impairment, and combined types of dementia in the non-CKD population.[48–50] Lifestyle factors including the Mediterranean diet[51–53] and physical activity[54] appear to protect against cognitive impairment and incident cognitive decline in the general population. APOE-4, presenilin-1, other genetic variants, and Sortilin-related receptor 1 protein predispose to neurodegeneration. The gene ABCA7 (ATP-binding cassette transporter) is associated with almost double the risk of AD in African Americans, an effect similar to that of the APOE-4 gene in white patients.[55]

Nephrogenic factors appear in the middle box (Figure 29.2). Both shared and nephrogenic risk factors increase the risk of neurodegenerative disease, microvascular disease including white matter disease, and macrovascular disease or stroke. Each of these outcomes can contribute to cognitive impairment *via* direct neuronal injury. The role of erythropoiesis-stimulating agents (ESAs) in mediating cognitive impairment in CKD patients is controversial. Higher doses of ESAs increase risk of stroke in CKD patients as delineated in the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study,[56] but these agents may also decrease risk of neuronal apoptosis and secondary cognitive impairment.[57]

In CKD populations, aging and nonvascular factors are overshadowed by a 10–15% annual stroke incidence,[58] a high prevalence of cardiovascular risk factors including hypertension (80%) and diabetes (50–60%),[16] markedly elevated levels of inflammatory markers and homocysteine,[59] vascular endothelial dysfunction, cardiovascular events, and carotid atherosclerosis, all of which contribute to vascular dementia and neurodegenerative diseases such as AD[60] (Figure 29.2). The additional contributions of factors secondary to CKD, such as uremia, anemia, higher circulating levels of guanidine compounds,[61] endothelial dysfunction, and metabolic disturbances, are not well defined.[45] In the Health ABC study, CKD accounted for approximately 10% of the cognitive impairment risk that was unexplained by demographic factors and comorbid conditions.[26]

Importance of Making the Diagnosis of Cognitive Impairment: Avoiding Adverse Outcomes of a Missed Diagnosis

It is important for the clinician to become comfortable using brief cognitive screening instruments to make the diagnosis of cognitive impairment in CKD patients, to avoid multiple potential adverse outcomes of a missed diagnosis. Potential adverse outcomes related to missed diagnoses potentially include undetected medication and dietary noncompliance, secondary increased iatrogenic hospitalizations, and inability to make informed decisions regarding dialysis initiation. Dementia in CKD patients more than doubles the risk of death and is associated with a greater risk of death than in HD patients (hazard ratios [HRs] 2.26 and 1.86, respectively).[16] Advantages of early diagnosis of dementia in non-CKD patients also apply to CKD patients. These include substantial savings for the family and society due to decreased crisis-driven hospitalizations and delayed nursing home entry by up to 1.5 years.[62]

Other advantages of early diagnosis are that it potentially (a) identifies the most likely causes of cognitive impairment, including potentially treatable causes such as depression, delirium, or recent subdural hematoma; (b) enables early treatment to potentially delay progression; (c) allows enrollment in clinical trials; (d) helps families understand the symptoms of cognitive impairment and associated behaviors and obtain help from dementia specialists in managing them; (e) provides families with appropriate referrals to the Alzheimer's Association and dementia support groups; (f) enables improved management of comorbid conditions, decreases anxiety for patients and caregivers, and avoids crisis-driven acute and long-term care[62]; and (g) allows patients and families to plan together for future care and financial arrangements before dementia becomes advanced.

Cognitive Impairment Screening Instruments

Cognitive impairment screening instruments vary in sensitivity and length. Several instruments allow brief screening in the clinic setting. Most of these instruments can be administered by nonhealthcare professionals (Table 29.1).[47] The briefest test is the 3-minute Mini-Cog,[63] which is insensitive to MCI but identifies most dementia cases. The Mini-Cog consists of immediate recall of three words, followed by clock-drawing and then uncued recall of the same three words. The 8-minute Folstein's Mini-Mental State Exam is the most commonly used brief instrument, but it is copyrighted and does not measure executive functions.[4]

Two longer assessment tools (8–10 minutes) provide more information and are more sensitive for diagnosing MCI and measuring executive function.[64] The St. Louis Mental Status test (SLUMS) and the Montreal Cognitive Assessment (MOCA) are freely available. Both test the major cognitive domains of verbal memory, executive function, and visuospatial function.[65] The MOCA is

TABLE 29.1 Performance Characteristics of Selected Dementia Screening Instruments

Instrument	Administration Time (minutes)	Domains Evaluated	Sensitivity	Specificity	Positive Screen Cutpoint	Validation Reference Standard	Validated in CKD or ESRD	Comments
Clock-drawing task	1–3	Visuospatial executive function	85	85	Various	Clinical assessment for dementia	No	Less cultural bias. Evaluates executive function
Mini-Cog	3–4	Visuospatial executive function recall	76	89	2	Neuropsychological battery	No	Clock-drawing task plus uncued recall of three words
Mini-Mental State Exam (MMSE)	7–10	Orientation, recall attention visuospatial	71–92	56–96	23–25	Clinical assessment for dementia	No	Norms available. Copyrighted. Does not assess executive function well
St. Louis University Mental Status Exam (SLUMS)	7–10	Orientation, recall attention visuospatial executive function	98–100	91–100	21.5	Clinical assessment for dementia	No	Evaluates executive function
Montreal Cognitive Assessment (MoCA)	10	Orientation, recall attention visuospatial, verbal fluency executive function	100	87	25	Neuropsychological battery	No	Evaluates executive function

CKD, chronic kidney disease; *ESRD*, end-stage renal disease. Note: the sensitivity, specificity, and positive screen cutpoints listed above are for the general population, as most of the above tests have not been validated in patients with CKD.
Adapted from reference 47. Copyright 2011 Macmillan Publishers Ltd, reproduced with permission.

now used as a global cognitive screening examination in ongoing and recently completed clinical trials, such as SPRINT, which has enrolled CKD participants.[66]

Because cognitive impairment is so common in CKD patients, annual cognitive screening is strongly recommended, especially before dialysis initiation to assess ability to make informed decisions.[47]

Diagnosis of Cognitive Impairment

The most important component in the diagnosis of cognitive impairment is an accurate history. The onset, duration, fluctuation, and nature and severity of cognitive impairment must be clarified, including behavioral symptoms, functional impairment, and coexistent symptoms of depression or sleep disorders. Elucidating a comprehensive history often requires interviewing caregivers and multiple family members. A physical examination and neurologic examination also need to be performed. For patients with previously undiagnosed cognitive impairment, brain imaging with computed tomography or magnetic resonance imaging is recommended to rule out potentially remediable causes such as subdural hematomas, brain tumors, and infection, and to detect stroke and severity and localization of brain atrophy and white matter disease. Brain imaging is critical if focal neurologic signs are present. Standard laboratory screening tests include complete blood count, chemistry panel, vitamin B_{12} level, and thyroid-stimulating hormone level to exclude common reversible hematologic or metabolic causes of cognitive dysfunction. For patients with high premorbid intelligence or for whom assessment of ability to make informed decisions is needed, a referral for detailed neuropsychologic testing is recommended. Depression commonly coexists with early dementia, and treatment with selective serotonin reuptake inhibitors is usually well tolerated. Delirium must be ruled out as a cause of acute cognitive impairment using the Confusion Assessment Method.[14]

Treatment of Cognitive Impairment in CKD Patients

There have been no clinical trials in CKD patients of dementia medications that are currently used in the general population. Several treatment options are available,

but their efficacy is controversial. These medications may be effective for 6–24 months in delaying the progression of cognitive impairment.[7] Any reversal of symptoms is minimal.

The two primary classes of dementia medications are cholinesterase inhibitors and *N*-methyl D-aspartate receptor antagonists. The cholinesterase inhibitors include donepezil, rivastigmine[67] (available in oral form and as a patch), and galantamine.[68] Their primary side effects are gastrointestinal disturbances. These include nausea and loose stools for approximately the first week, which usually resolve, mild anorexia and weight loss, dizziness, and, less frequently, insomnia. The medication should be withdrawn if severe nightmares occur, as they usually do not resolve. For CKD patients, a lower maximum dose of galanatime is recommended. Galantamine is contraindicated in end-stage renal disease (ESRD) patients. Memantine,[69] the *N*-methyl D-aspartate receptor antagonist, causes fewer gastrointestinal side effects except constipation but can occasionally cause acute delirium after initial doses. The drug should be discontinued if this occurs. Dose reduction is recommended for patients with eGFR<30 mL/min/1.73 m^2.

Behavioral disturbances such as increased agitation or paranoia, associated with moderate to severe dementia, are common and very stressful for patients and their caregivers. To evaluate new behavioral symptoms, a full clinical assessment should be conducted to rule out pain or delirium secondary to an acute medical illness, especially urinary tract infections or medication changes. Behavioral disturbances can also be due to environmental triggers such as changes in location or caregivers, or to nursing shift changes in the chronic care setting. Only after behavioral management trials and treatment of acute medical conditions have been employed should pharmacologic treatment be considered under guidance from a dementia expert because medication effectiveness is not well established and side effects can be substantial.[70] Atypical antipsychotics specifically are associated with modestly increased risk of cardiovascular disease and death.[71]

In the SPRINT MIND study, completed after the main study was stopped by the Data Safety Monitoring Board, the primary cognitive outcome was occurrence of probable dementia. Secondary cognitive outcomes included development of MCI and a composite outcome of MCI or probable dementia.[72] Among the 9361 randomized participants, 91.5% completed at least one follow-up cognitive assessment after a median intervention period of approximately 3.3 years. After a median follow-up of a little more than 5 years, probable dementia developed in a lower proportion of participants in the intensive treatment group compared to the standard treatment group (HR, 0.83; 95% CI, 0.67–1.04). Intensive BP control was associated with reduced risk of MCI (HR, 0.81; 95% CI, 0.69–0.95) and the combined rate of MCI or probable dementia (HR, 0.85; 95% CI, 0.74–0.97). The intervention did not result in a detectable significant reduction in the risk of developing probable dementia, perhaps because of reduced power due to early termination of the study, and fewer than expected cases of dementia. In subsequent analyses, the effects were determined to be similar in subgroups. The study therefore holds great promise for prevention of dementia in the CKD population, but further work will be necessary to establish definitive conclusions and treatment recommendations.[73]

Health Policy Implications

Currently, neither a cognitive history nor an assessment is required for CKD patients before, at, or any time after dialysis initiation. Given the rate of cognitive impairment in advanced CKD, many patients may lack adequate judgment to weigh the benefits and risks of initiating dialysis, or to withdraw from dialysis once initiated. Therefore there is a need to screen for cognitive impairment before dialysis initiation. The prognosis for HD patients with dementia is poor. In one study of nursing home ESRD patients, most experienced a rapid decline in physical function and more than half died 6 months after initiation.[74] The 2010 Renal Physicians' Association guidelines suggest that foregoing dialysis or withdrawing it from patients with advanced dementia is appropriate. Each case requires individual consideration and careful shared decision-making with patients and families.

Conclusion

Several studies have confirmed a graded association between renal function and cognitive function. Symptomatic and subclinical ischemic cerebrovascular disease, neurodegenerative disease, and inflammation appear to play large roles in a proposed model of accelerated vascular cognitive impairment in CKD patients. Annual and predialysis cognitive screening in CKD patients is critical to confirm a diagnosis of cognitive impairment, avoid adverse outcomes of missed diagnoses, and improve clinician awareness of the potential effects of cognitive impairment on medication, fluid, and dietary compliance, and on the ability to make informed decisions regarding dialysis initiation. While much remains to be learned regarding the pathophysiology of cognitive impairment in patients with CKD, the public health implications of its substantial burden are immediate. The role and timing of intensive blood pressure control in CKD patients at risk of developing dementia requires further study.

STROKE IN CHRONIC KIDNEY DISEASE

Cerebrovascular disease including stroke is a common, serious, and disabling disease within the CKD population. An update to the definition of stroke by the American Heart Association and affirmed by the American Academy of Neurology states that stroke includes the following: central nervous system (CNS) infarction including silent CNS infarction, ischemic stroke, intracerebral hemorrhage (ICH) including silent cerebral hemorrhage, stroke caused by ICH, subarachnoid hemorrhage (SAH), stroke caused by SAH, stroke caused by cerebral venous thrombosis, and stroke not otherwise specified.[75] Even though the definition of stroke is complex, studies in patients with CKD often focus on broadly defined stroke criteria, such as ischemic stroke, or ICH. Studies also include emerging data regarding CNS infarction (including silent CNS infarction). Both conditions can lead to cognitive impairment and cognitive deficits.

Stroke is common in all stages of CKD but increases significantly as kidney function worsens. The incident stroke rate is 1.9–3.6 times higher (depending on age, eGFR, and race) for those with incident CKD compared to those without CKD, and the risk of stroke in stage 5 CKD is double that of stage 3. A critical period, studied in patients who were at least 67 years old and had Medicare as the primary payor, is the time before and after the initiation of dialysis. A year before initiation, the baseline stroke rate in CKD patients was 0.15%–0.20% of patients per month. Stroke rates began rising approximately 3 months before initiation of dialysis and increased two- to threefold during the month before initiation, peaking during the month after the start of dialysis. The findings suggest the transition from CKD care to ESRD therapy may be fraught and that care must be taken to decrease the incidence of stroke during this period.[76]

The rate of incident stroke in incident CKD Medicare patients ages 67–85 years as reported in the 2009 USRDS Annual Data Report is estimated at 9.0/100 patient-years (pt-yrs) (Figure 29.3). The incident stroke rate in prevalent CKD patients is about two-thirds of the rate in incident CKD patients, or about 5–6.0/100 pt-yrs overall. The effect of CKD on stroke risk is even greater in younger individuals. Using the Ingenix i3 database of community-dwelling individuals aged 50–64 years, stroke is 4.6–7.6 times more frequent in incident CKD patients than in non-CKD patients. The absolute incidence is lower in this younger cohort, ranging from approximately 1.6–2.2/100 pt-yrs, or about one quarter the rate of the older Medicare cohort. In both the incident and prevalent CKD cohorts, the risk of stroke increases substantially with age and CKD stage. In CKD, the risk of incident stroke is also 50% higher for African Americans compared to white Medicare beneficiaries, similar to reports in non-CKD populations.[58]

Silent stroke describes lesions found incidentally on brain imaging in asymptomatic patients. Silent stroke increases the risk of subsequent stroke by over 10-fold (2.79/year compared to 0.21%/year) compared to those without previous silent stroke in the general population.[77]

Stroke Risk in CKD

Results from several observational studies suggest that CKD patients are at significantly increased risk of acute stroke compared with those without CKD.[74–79] This excess risk is not explained by common comorbid conditions or traditional vascular risk factors.

In a meta-analysis of 21 published reports, CKD, defined as eGFR less than 60 mL/min/1.73 m^2, was associated with a 43% greater risk of stroke (95% confidence interval [CI], 1.31–1.57).[79] As GFR decreases the rate of stroke increases. A dose–response relationship was observed. Risk was increased 22% for patients with eGFR 40–59 and 77% for those with eGFR less than 40 mL/min/1.73 m^2. Associations did not differ for hemorrhagic vs. ischemic stroke but were significantly greater for fatal stroke (relative risk [RR] 1.97) than for a combined outcome of fatal and nonfatal stroke (RR 1.37). However, overall heterogeneity was substantial across individual studies in a magnitude of reported associations and in types of patients studied (e.g., atrial fibrillation, postmenopausal women with coronary disease), methods of estimating renal function, and adjustment covariates included in statistical models.

Albuminuria is an independent risk factor for stroke even after accounting for reduced GFR. For example, among community-dwelling older adults, microalbuminuria was associated with nearly doubled risk of incident stroke among those with and without decreased eGFR.[80] These results were confirmed by a meta-analysis of 12 observational studies including 48,596 participants. Albuminuria was associated with a 92% greater RR of stroke compared to those without albuminuria. This association was significant in studies conducted in the general population, in diabetic and hypertensive patients, and in patients with prior stroke.[81]

Risk Factors and Mediators of Stroke

Few studies have specifically examined the factors that predict stroke in CKD patients, or that may potentially mediate the relationship between CKD and stroke

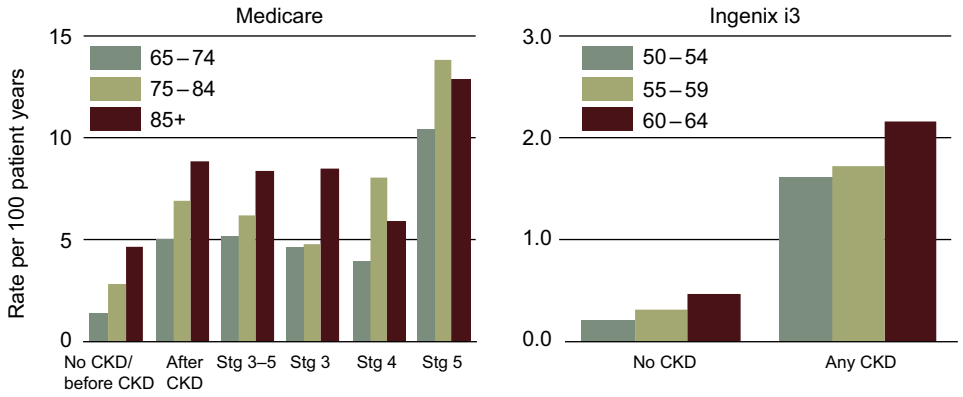


FIGURE 29.3 Rate of incident of stroke in incident chronic kidney disease (CKD) and non-CKD patients, by age and CKD status. *Reference 58. The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government.*

(Figure 29.4). In general, estimated associations between CKD and stroke are attenuated after adjustment for multiple vascular risk factors and prevalent cardiac disease, raising the possibility that these associations represent the effect of unmeasured or residual confounding by other vascular risk factors or comorbidity severity. Alternatively, shared susceptibility to adverse end-organ effects in the brain and kidneys from vascular disease could identify individuals vulnerable to both stroke and renal disease.[36] This seems a plausible explanation for the increased stroke risk in patients with microalbuminuria and intact GFR, for whom low-level elevations in albuminuria may identify systemic vasculopathy with increased risk of major vascular events.

For patients with more impaired renal function, a direct causal effect of CKD on stroke risk is plausible, with potential mediators including retained uremic toxins, and metabolic consequences of decreased renal function including hyperhomocysteinemia and altered mineral metabolism, increased oxidative stress and inflammation, and anemia. The role of these factors in the pathogenesis of stroke in CKD patients has not been examined in detail in epidemiologic studies, although evidence indicates that hyperphosphatemia is associated with greater cardiovascular mortality in CKD, and greater serum phosphate concentration is associated with increased stroke risk in the general population.[82,83]

Evidence indicates that CKD may interact synergistically with anemia to contribute to stroke risk. Among 3015 adult diabetic participants in a combined sample of four general population cohorts, anemia in CKD was associated with an 81% greater risk of stroke compared to those without anemia. In contrast, anemia

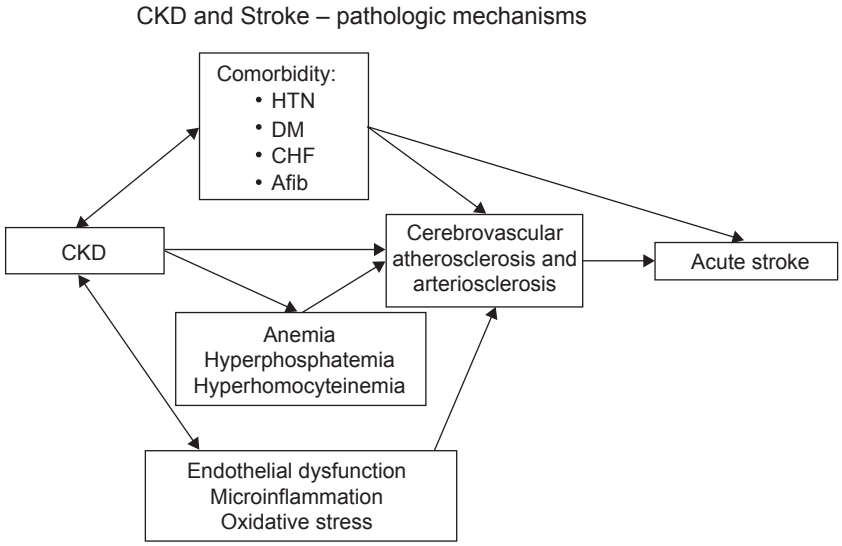


FIGURE 29.4 Pathologic mechanisms of chronic kidney disease (CKD) and stroke. *Afib*, atrial fibrillation; *CHF*, congestive heart failure; *DM*, diabetes mellitus; *HTN*, hypertension.

did not predict incident stroke among participants without CKD.[84] Physiological studies suggest that chronic anemia can cause adverse remodeling of the left ventricle and the peripheral arteries, leading to maladaptive cardiac hypertrophy and arteriosclerosis.[85] The resulting vascular stiffening may contribute to end-organ damage including cerebral ischemic injury such as acute stroke.

Erythropoiesis-Stimulating Agents and Stroke Risk

Given the epidemiological and physiologic data linking anemia to excess stroke risk in CKD, pharmacological correction of anemia with ESAs might be expected to be an effective preventive therapy. In addition to stimulating erythropoiesis, ESAs show direct neuroprotective effects in experimental models of cerebral ischemia.[86] Conversely, ESAs may have direct and indirect effects that could plausibly increase the risk of stroke, including increased blood pressure, acute endothelial dysfunction, platelet activation, and decreased cerebral blood flow due to rapid changes in red cell mass.

Results of large randomized clinical trials and observational studies conducted among CKD patients suggest that ESAs, especially when dosed to target high hemoglobin levels, increase the risk of stroke to a clinically significant degree. In the TREAT study, diabetic non–dialysis-dependent CKD patients with anemia were randomized to weekly darbepoetin with a goal hemoglobin of 13 g/dL or to placebo. During follow-up, the RR of fatal or nonfatal stroke (a secondary trial endpoint) was 92% greater in the active than in the control group.[56] In a *post hoc* multivariate analysis, this effect of treatment on stroke risk was similar to the effect of prior stroke. This analysis failed to find an effect of on-treatment changes in blood pressure, hemoglobin, or platelet count with risk of stroke.[87] In contrast, no excess stroke risk was identified among 1432 anemic CKD patients in the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial randomized to epoetin alfa with high (13.5 g/dL) vs. normal (11 g/dL) hemoglobin targets.[88] However, this trial was terminated early for futility, and the number of observed stroke events was too small to allow conclusions regarding the cerebrovascular safety of the intervention.

In an observational case-control study among Veterans Administration outpatients with non-dialysis-dependent CKD and anemia, those with prior ESA treatment were 30% more likely to be stroke cases, after adjustment for potential confounders.[89] The association between ESA use and stroke was particularly strong (odds ratio 1.85) among CKD patients with evidence of cancer under active oncology care, whereas no significant association was observed among CKD patients without cancer (odds ratio 1.07). ESA-treated CKD patients with active cancer received initial ESA doses 2.5–4 times higher than those without cancer, despite similar pretreatment hemoglobin concentrations. Whether their greater stroke risk compared to ESA-treated patients without cancer is explained by the higher ESA dosing they received, or by other stroke risk factors concurrent in cancer patients—such as greater inflammation or increased thrombotic potential—is unclear. Patients with active cancer were specifically excluded from both the TREAT and the CHOIR studies.

Primary and Secondary Stroke Prevention

No RCTs have been designed specifically to test the efficacy of stroke prevention strategies in patients with non–dialysis-dependent CKD. However, limited data regarding treatment effects are derived from *post hoc* subgroup analyses of RCTs conducted in the general population, from RCTs in CKD populations of therapies designed to prevent all cardiovascular events (for which stroke was a secondary or tertiary outcome), and from observational cohort studies.

For patients with symptomatic severe (≥70% diameter reduction) carotid stenosis, carotid endarterectomy (CEA) has long been established as an effective intervention for secondary stroke prevention.[90] However, observational studies have suggested that non–dialysis-dependent CKD patients have a much higher risk of perioperative mortality and other complications after CEA,[91,92] raising questions about the risk–benefit tradeoff in these patients. In a *post hoc* subgroup analysis of data from the North American Symptomatic Carotid Endarterectomy Trial (NASCET), patients with stage 3 CKD (mean eGFR 49 mL/min/1.73 m^2) had a fourfold higher risk of cardiac complications than those with normal renal function, but no excess risk of mortality.[93] However, they also experienced a markedly greater benefit from CEA than from standard medical therapy, with an 82% RR reduction of recurrent stroke. In contrast, CKD patients with moderate carotid stenosis (50–69% diameter reduction) experienced no significant benefit in stroke reduction.

Atrial fibrillation is an important risk factor for stroke in the general population, and risk of stroke is 40% greater among atrial fibrillation patients who also have CKD stage 3B or higher.[94] Warfarin therapy has been the mainstay of stroke prevention among atrial fibrillation patients estimated to be at high stroke risk. However, reports have suggested that warfarin use in

maintenance dialysis patients may be associated with a paradoxically increased risk of stroke,[95] especially hemorrhagic stroke,[96] raising concerns about its safety in non−dialysis-dependent CKD patients. Hart et al. performed a *post hoc* subgroup analysis of the Stroke Prevention in Atrial Fibrillation (SPAF) 3 trial, which compared adjusted-dose warfarin with combination aspirin plus fixed low-dose warfarin among high-risk atrial fibrillation patients.[97] Among the 805 participants with stage 3 CKD (42%) (mean eGFR 49 mL/min/1.73 m^2), adjusted-dose warfarin reduced the risk of ischemic stroke or systemic thromboembolism by 76%, an effect size similar to that among participants with normal eGFR. No excess risk of major hemorrhage was observed with adjusted-dose warfarin in the CKD participants. As the renal impairment was relatively modest, whether the same risk−benefit ratio favoring warfarin also applies to more advanced CKD is unclear. Somewhat discrepant results were reported from an observational cohort study among patients with nonvalvular atrial fibrillation, using Danish national patient registry data.[98] CKD not requiring renal replacement therapy was identified by diagnosis codes, not by renal function measurement, likely resulting in significant underascertainment. Warfarin use was associated with a 16% lower risk of stroke or systemic thromboembolism (RR 0.84), but this association did not meet the conventional threshold of significance ($p = 0.07$). However, warfarin-treated participants were at a 36% greater risk for major bleeding after other risk factors were accounted for.

Warfarin has been a mainstay of oral anticoagulation, but the new oral anticoagulants (NOACs) such as dabigatran,[99] rivaroxaban,[100] and apixaban[101] are increasingly being used, as they have been shown to be efficacious for non-CKD patients. In addition, the NOACs provide increased simplicity for healthcare management because they do not require laboratory monitoring, have fewer drug−drug interactions, and necessitate fewer dietary restrictions (compared to vitamin K in warfarin use). However, NOAC use can be complex in CKD patients because NOACs rely at least partly on renal excretion for elimination. Use of NOACs has not been studied in clinical trials specifically designed with CKD patients. Importantly, the major trials that demonstrated efficacy for SPAF excluded patients with advanced (typically stage 4 or higher CKD) renal impairment.[102] Eikelboom et al. conducted a *post hoc* subgroup analysis of the Apixaban *Versus* Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or are Unsuitable for Vitamin K Antagonist Treatment trial, which compared apixaban with aspirin among chronic atrial fibrillation patients who were not candidates for warfarin.[103] Apixaban was dose-reduced among patients with S[Cr] greater than 1.5 mg/dL. Results suggested a similar treatment advantage of apixaban over aspirin among patients with stage 3 CKD (mean eGFR 49 mL/min/1.73 m^2) compared with non-CKD patients, with a RR reduction of 68%. There was no excess risk of major bleeding with apixaban among CKD patients. In the Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation trial comparing apixaban to warfarin, the effect of apixaban also did not differ significantly by renal function.[104] (Patients with creatinine clearance less than 30 mL/min were excluded.) Apixaban, compared with warfarin, reduced the risk of hemorrhage among participants with eGFR less than 50 mL/min/1.73 m^2 (HR 0.48; 95% CI 0.37−0.64) to a greater extent than among those with intact renal function. Additional studies regarding the safety and efficacy of apixaban in various levels of renal disease have demonstrated the net benefit of apixaban over warfarin.[105]

Similar evidence for a favorable risk−benefit ratio in CKD patients was reported for rivaroxaban vs. warfarin in a *post hoc* subgroup analysis of the Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial.[106,107]

Dabigatran—a direct thrombin inhibitor—is contraindicated in those with eGFR less than 30 mL/min/1.73 m^2. A subgroup analysis did not find any difference in the effect of dabigatran compared to warfarin for the prevention of stroke or thromboembolism among those with eGFR 30−50 mL/min/1.73 m^2 compared to $\geq$80 mL/min/1.73 m^2.[108] However, the relative benefit and risk of dabigatran in stroke prevention in CKD stage 3 patients is a topic of ongoing uncertainty and debate.[109] There is no readily available method for monitoring drug concentrations or anticoagulant effects of dabigatran.

Unlike warfarin, for which there is extensive experience in reversing, monitoring, and fine-tuning the degree of anticoagulation, the NOACs have emerging methods for reversing anticoagulant effects, which include the development of new medications and development of NOAC-specific strategies. Idarucizumab is a Food and Drug Administration−approved monoclonal antibody fragment to reverse dabigatran. Other types of pro-coagulant clotting agents, known as bypass agents, are being studied and used by some to reverse numerous types of NOACs.[110] Use of these newer reversal agents need additional study in patients with CKD as concerns about the safety of NOACs in those with renal impairment exist. In addition to the safety concerns in CKD, there are challenges to reversal agent availability, due to lack of widespread stocking of the newer agents and the high price of the reversal agents.

HMG CoA-reductase inhibitors have been demonstrated to reduce the risk of both initial and recurrent stroke in the general population. However, two large multicenter trials in maintenance HD patients showed no reduction in total stroke with rosuvastatin or atorvastatin vs. placebo, and a doubling of fatal stroke with atorvastatin in the Deutsche Diabetes Dialyze Study (4D) trial.[111,112] The Study of Heart and Renal Protection (SHARP) trial examined the effects of simvastatin 20 mg plus ezetimibe 10 mg daily vs. placebo on atherosclerotic events among CKD patients, including those requiring RRT (roughly one-third of the total sample).[113] The risk of nonhemorrhagic stroke was reduced by 25% in the active treatment group (RR 0.75; 95% CI, 0.60–0.94). The effects of stroke risk were not reported separately for study participants with non–dialysis-dependent CKD, although there was a significant effect on all atherosclerotic events in this subgroup (RR 0.78). Additional evidence for the effect of statins is provided by subgroup analyses of general population clinical trials. A meta-analysis estimated a summary RR reduction of 39% for fatal and nonfatal strokes (RR 0.61; 95% CI, 0.38–0.98) with statin therapy compared to placebo. However, most included clinical trials constituting this meta-analysis intentionally excluded patients with advanced CKD. Statin therapy did not result in excess risk of major adverse effects, including myalgias, cancer, or abnormal liver or muscle enzyme concentrations.

Antiplatelet agents such as glycoprotein IIb/IIIa inhibitors or clopidogrel are recommended for primary and secondary prevention of stroke among patients at high vascular risk.[114] However, no clinical trials have specifically examined their effectiveness or safety in CKD patients. There are only limited data from secondary subgroup analyses of clinical trials. A meta-analysis found an "uncertain effect" of these agents on risk of stroke in CKD patients (RR 0.66; CI, 0.16–2.78).[115] The risk of minor bleeding was increased by 70% in CKD patients randomized to antiplatelet drugs.

Thrombolytic Therapy

Since the late 1990s, tissue plasminogen activator (tPA, or specifically alteplase) has been an important and increasingly utilized treatment for acute stroke, in the general population.[116] Guidelines by the American Heart Association and American Stroke Association regarding the treatment of acute ischemic stroke have informed the field regarding the use of alteplase.[117] There are several recent outcomes that are important to patients with kidney dysfunction in terms of both efficacy and safety. Participants with a lower eGFR (less than 60 mL/min/1.73 m^2) received less benefit from the administration of alteplase, compared to participants with normal eGFR at 24 hours (coefficient −2.3, 95% CI −3.7 to −0.9; $p = 0.002$) and at 7 days (coefficient −3.5, 95% CI −5.3 to −1.7; $p < 0.001$). With modeling, each 10 mL/min/1.73 m^2 decline in eGFR was associated with a 0.4 decrease in NIHSS improvement in the setting of alteplase use.[118]

There are concerns regarding the potential for bleeding and hemorrhage risk that occurs in CKD patients with use of tPA. The safety of tPA in CKD was recently studied by Ovbiagele et al. through the retrospective Get With the Guidelines-Stroke Program (GWTG-Stroke).[119] The CKD patients had a higher unadjusted odd of symptomatic intracranial hemorrhage or serious systemic hemorrhage, while also being more likely to die in the hospital (adjusted odds ratio, 1.22; 95% CI: 1.14–1.32) or have an unfavorable functional status at discharge (adjusted odds ratio, 1.13; 95% CI: 1.07–1.19), compared to patients with normal kidney function. This was further studied and confirmed through a meta-analysis of seven studies, which included 7168 CKD patients with IS and treated with tPA to show that there was a higher risk of symptomatic ICH and mortality, while also having an increased risk of poor outcome at 3 months.[120]

SPRINT

The SPRINT trial results showed that the intensive target resulted in a significantly lower rate of major cardiovascular events and death from any cause.[66] CKD patients comprised 28% of study participants.[121] A SPRINT-CKD subgroup analysis showed that the intensive treatment target had a lower rate of cardiovascular events (HR, 0.81; 95% CI, 0.63–1.05) and all-cause death (HR, 0.72; 95% CI, 0.53–0.99) than the standard treatment group.

Conclusion

Patients with non–dialysis-dependent CKD (whether defined by reduced eGFR or albuminuria cutoffs) are at a significantly increased risk of acute stroke compared with individuals without evidence of renal disease. This may represent a direct causal relationship of renal disease on stroke risk, or shared susceptibilities to end-organ damage in both the brain and the kidneys among patients with vascular risk factors or established vascular diseases. Although anemia is associated with a marked increase in stroke risk in CKD patients, and is a plausible mediator for the CKD/stroke association, aggressive correction of anemia with ESAs increases the risk of stroke appreciably. However, the precise mechanisms that mediate this risk, and the relative contributions of ESA dose vs. achieved or targeted

hemoglobin levels in increasing risk, remain unclear. A *post hoc* subgroup analysis suggests a large benefit in secondary prevention of stroke with CEA in selected patients with stage 3 CKD, although at the cost of greater perioperative complications. Statins, warfarin, and dose-adjusted oral anticoagulants in patients with atrial fibrillation appear at least as effective among stage 3 CKD patients as among non-CKD patients for stroke prevention. However, no clinical trial data support the use of warfarin or newer anticoagulants among patients with CKD stage 4 or higher. Use of newer anticoagulants is contraindicated for patients with stage 5 CKD. There is emerging evidence regarding the use of these newer NOAC and DOAC agents in addition to strategies to optimize efficacy, while providing the drug safely in addition to the recent introduction of reversal agents. Data are insufficient to indicate a benefit in stroke prevention of glycoprotein IIb/IIIa inhibitors or clopidogrel as antiplatelet therapy.

NEUROLOGICAL AND MUSCULAR DISEASE

Peripheral neuropathies and myopathies are common complications of renal dysfunction and contribute significantly to disability and reduced quality of life. While these conditions are typically more prevalent and more severe in ESRD, it is important to recognize that they often become clinically relevant during the latter stages of CKD. Data on the prevalence of these conditions in CKD are very limited, and it is likely that many of these conditions are either underdiagnosed or misdiagnosed.

Uremic Somatic Polyneuropathy

Somatic polyneuropathy is a highly prevalent and potentially disabling complication of advanced CKD.[43,44,122] Somatic polyneuropathy is characterized by mixed sensory and motor dysfunction in a symmetrical, length-dependent distribution and typically presents with lower extremity pain, hypoesthesia, and/or paresthesias. Sensory dysfunction expands proximally as the disease progresses and is eventually complicated by weakness and muscle wasting. Estimates of the prevalence of uremic somatic polyneuropathy vary greatly.[16,123] This likely relates, in part, to the relatively high prevalence of nonuremic polyneuropathies in CKD populations, which confound diagnosis. Diabetes mellitus is the most common nonuremic etiology of polyneuropathy in CKD populations, although contributions from other nonuremic sources such as alcohol use, amyloidosis, and systemic vasculitides should always be considered in the evaluation of such patients.[44]

The pathogenesis of somatic polyneuropathy in CKD patients remains incompletely understood and may be multifactorial. Advanced stage disease nerve biopsies typically demonstrate axonal degeneration and secondary segmental demyelination.[124] Accordingly, nerve conduction studies characteristically show significant reductions in sensory and motor amplitudes, with more moderate reductions in conduction velocities.[125] Early theories attributed uremic axonal damage to CKD-related accumulation of "middle molecules," i.e., renally cleared mid-range molecular weight substances such as β_2-microglobulin and parathyroid hormone.[126] However, this hypothesis remains unproven, and parathyroid hormone is the only middle molecule for which some evidence of neurotoxicity exists.[127,128] More recent work indicates that hyperkalemia may play an important role in pathogenesis.[129,130]

Management of uremic somatic polyneuropathy includes dialysis and supportive medical therapy. Adequate dialysis generally prevents neuropathic progression, but complete clinical reversibility is uncommon.[131] Accordingly, rapid symptom progression remains an important indicator of dialysis insufficiency. Medical management includes nutritional supplementation (with drugs such as biotin, pyridoxine, cobalamin, thiamine), routine foot care, and pain management with tricyclic antidepressants (such as amitriptyline) and anticonvulsants (such as pregabalin).[43,44,122] The potential role of hyperkalemia in neurotoxicity has also led to efforts to reduce interdialytic potassium concentrations by dietary therapy.[130] Proper management of uremic somatic polyneuropathy also includes diagnosis and treatment of other conditions, which may contribute to polyneuropathy, such as diabetes mellitus and alcohol use.

Renal transplantation remains the only treatment that consistently reverses uremic somatic polyneuropathy. Neurological recovery after renal transplantation is often dramatic and rapid, with measurable improvements in nerve conduction velocities days after surgery.[132] Clinical recovery is often achieved within several months of transplantation in mild cases but may take longer in more severe cases.[133]

Uremic Autonomic Neuropathy

Dysfunction of autonomic nerves can also occur in patients with advanced CKD.[43,44,122] Common autonomic manifestations include postural and interdialytic hypotension, cardiac arrhythmias, impaired sweating, gastrointestinal dysmotility, and sexual dysfunction. Because CKD-related autonomic neuropathies do not

always coexist with somatic polyneuropathies, it is not clear if they are manifestations of the same or separate processes.[134] Parasympathatic dysfunction tends to predominate in CKD-related autonomic neuropathy, whereas sympathetic dysfunction tends to be more common in diabetes-related disease.[43] While the true burden and clinical significance of CKD-related autonomic neuropathy is unknown, it is important to note that studies in dialysis patients associate autonomic dysfunction with sudden cardiac death.[135,136]

Diagnosis of autonomic neuropathy in CKD patients can be challenging, due to the nonspecific nature of clinical symptoms and an incomplete correlation between symptoms and common clinical diagnostics, such as resting R−R interval variation and blood pressure responses to sustained handgrip.[134] For example, diagnosis of gastrointestinal dysfunction due to autonomic neuropathy in CKD patients can be particularly challenging because CKD-related uremic toxins, ischemia, and decreased clearance of gastrointestinal hormones may produce similar symptoms. Similarly, diagnosis of sexual dysfunction related to autonomic neuropathy in male and female CKD patients requires exclusion of other factors commonly associated with CKD, including vascular disease, hormonal dysregulation, nutritional deficiencies, depression, and medications.[137−139] As with uremic somatic polyneuropathy, renal transplantation provides the most effective treatment for uremic autonomic neuropathy.[122] Specific medical therapies include sildenafil for erectile dysfunction, midodrine for hypotension, and renally dosed metoclopramide for impaired gastrointestinal mobility.[140]

Uremic Mononeuropathies

Carpal tunnel syndrome (CTS) is the most common mononeuropathy related to CKD.[43,44,122] CTS results from median nerve compression in the carpal tunnel of the wrist and typically presents as weakness or paresthesias in the hand, and dull, aching discomfort in the hand, forearm, or upper arm.[141] These symptoms are often exacerbated by repetitive actions, sustained hand positions, and sleep and are mitigated by position changes and hand shaking. Initial sensory symptoms may progress to weakness and atrophy as axonal loss occurs. Diagnosis of CTS is typically clinical, with confirmation provided by electrophysiologic testing when needed.[141] Nerve conduction studies characteristically show reductions in distal median conduction velocities due to axonal compression. Conduction amplitudes are typically preserved in the early stages of CTS but may be reduced in later stages if axonal loss occurs.

CTS is a long-term complication of renal insufficiency and typically presents after dialysis initiation. The prevalence of CTS increases with dialysis duration, affecting up to 30% of patients treated with dialysis for more than 10 years.[142] The increased prevalence of CTS in CKD and ESRD populations is primarily attributed to amyloidosis from β_2-microglobulin accumulation,[143,144] although uremic tumoral calcinosis and complications of arteriovenous fistula creation are also implicated.[145,146]

Treatment of mild CTS involves conservative strategies, such as activity modification and nocturnal splinting.[141] Corticosteroid injections may improve symptoms, although relapse is common and procedure-related median nerve injury is a risk. Surgical decompression of the carpal tunnel is indicated for patients with severe symptoms. Renal transplantation remains the only definitive preventive therapy.[144]

Uremic Pruritus

Pruritus is a common complication of advanced CKD.[147,148] While uremic pruritus (UP) is often associated with dialysis, most patients develop symptoms before dialysis initiation. UP is usually episodic and more intense at night. Pruritic sensation can be generalized or localized, and patients typically present with skin excoriations. Aside from being an obvious threat to quality of life, UP may have greater implications. The recent large DOPPS II study associated UP with sleep disorders and increased mortality.[149]

The pathogenesis of UP is incompletely understood and likely multifactorial. Potential contributing factors include calcium and phosphorus metabolic abnormalities, uremic toxin accumulation, cytokine dysregulation and systemic inflammation, cutaneous xerosis, damage and dysregulation of peripheral and somatic nerves, intrinsic opioid system dysregulation, and common comorbid conditions such as advanced age, diabetes mellitus, iron deficiency anemia, and viral hepatitis.[147,148] The management of UP remains challenging. To date, there are no definitive therapies for UP short of renal transplant. General treatment strategies include skin emollients, mineral metabolism regulation, and dialysis optimization.[147,148] Gabapentin, ultraviolet phototherapy, and nalfurafine, a κ-opioid receptor agonist, have also been shown to be effective and well tolerated.[150−152] Erythropoietin and previously common therapies such as antihistamines and serotonin receptor antagonists have not been proven effective.[147]

Uremic Myopathy

Uremic myopathy is a general term used to describe the constellation of functional and structural muscle abnormalities commonly associated with chronic

uremia.[153] Uremic myopathy is characterized by proximal weakness, muscle atrophy, limited exercise tolerance, and rapid fatigability.[154] Symptoms typically appear when GFR is below 25 mL/min/1.73 m^2, and disease progression tends to parallel the decline in renal function.[153] Patients affected by uremic myopathy generally have normal creatine kinase levels, and electromyography studies and tissue biopsies only occasionally show muscle fiber atrophy.[153,155] The pathogenesis of uremic myopathy is not completely understood but has been linked to factors such as uremic toxins, insulin resistance, carnitine deficiency, and hyperparathyroidism.[153] Care must be taken to rule out contributions from simple water and electrolyte disturbances, which can underlie similar presentations. Management of uremic myopathy includes provision of adequate HD, correction of anemia, exercise therapy, nutritional supplementation, and treatment of secondary hyperparathyroidism.[153] While both CKD and dialysis therapy lead to disorders in carnitine metabolism that may contribute to muscular dysfunction, the benefits of carnitine supplementation in these conditions remain incompletely established.[156,157] However, given the favorable safety profile of carnitine and the potentially debilitating nature of muscular dysfunction, carnitine supplementation on a trial basis may be recommended for patients who do not respond to standard therapy.[156,157]

Conclusion

CKD is associated with several forms of neuromuscular disease that can significantly diminish quality of life. Many of these conditions first become clinically significant in patients with advanced or long-standing CKD. Proper diagnosis and treatment of these conditions is challenging but is an important component in the comprehensive care of CKD patients. Additional work is needed to further characterize the prevalence and clinical course of these conditions in CKD populations.

SUMMARY

Neurologic outcomes in CKD patients are prevalent. The most common neurologic complications in CKD patients are cognitive impairment, stroke, and peripheral neuropathies. Despite a strong graded association between measures of renal function and cognitive function, cognitive impairment in CKD patients is largely undiagnosed. Annual and predialysis cognitive screening is critical to avoid adverse outcomes of missed diagnoses of cognitive impairment, such as medication noncompliance and inability to make informed decisions regarding initiating dialysis. Early dementia diagnosis decreases anxiety for patients and caregivers, avoids crisis-driven acute and long-term care, and allows patients and families to plan for future care and financial arrangements. Cerebrovascular disease, uremic encephalopathy, neurodegenerative disease, and inflammation contribute to a model of accelerated vascular cognitive impairment in patients with CKD. Aggressive treatment with ESAs increases stroke risk appreciably. Warfarin and dose-adjusted newer anticoagulants appear effective for stroke prevention in stage 3 CKD patients with atrial fibrillation, but such therapy is unproven or contraindicated in higher CKD stages. Neuromuscular disease in advanced CKD patients, such as uremic peripheral neuropathies, uremic myopathy, and pruritucan significantly diminish patient perception of quality of life. Proper diagnosis and treatment of these conditions is a challenging but important component in the comprehensive care of CKD patients.

References

1. Murray AM, Seliger S, Stendhal JC. Neurologic complications of chronic kidney disease. In: *Chronic Renal Disease*. San Diego: Academic Press; 2015. p. 249–65 [chapter 21].
2. Kurella M, Mapes DL, Port FK, Chertow GM. Correlates and outcomes of dementia among dialysis patients: the dialysis outcomes and practice patterns study. *Nephrol Dial Transplant* 2006;**21**(9):2543–8.
3. Murray AM, Tupper DE, Knopman DS, Gilbertson DT, Pederson SL, Li S. Cognitive impairment in hemodialysis patients is common. *Neurology* 2006;**67**(2):216–23.
4. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**(3):189–98.
5. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004;**256**(3):183–94.
6. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV. Current concepts in mild cognitive impairment. *Arch Neurol* 2001;**58**(12):1985–92.
7. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005;**352**(23):2379–88.
8. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-IV)*. 4th ed. Washington, DC: American Psychiatric Association; 1994. p. 124–33.
9. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB. Prevalence of cognitive impairment without dementia in the United States. *Ann Intern Med* 2008;**148**(6):427–34.
10. Murray AM, Levkoff SE, Wetle TT, Beckett L, Cleary PD, Schor JD. Acute delirium and functional decline in the hospitalized elderly patient. *J Gerontol* 1993;**48**(5):M181–6.
11. Gross AL, Jones RN, Habtemariam DA, Fong TG, Tommet D, Quach L. Delirium and long-term cognitive trajectory among persons with dementia. *Arch Intern Med* 2012;**172**(17):1324–31.
12. Pandharpande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT. BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;**369**(14):1306–16.

13. Inouye SK. Delirium in older persons. *N Engl J Med* 2006;**354**(11): 1157–65.
14. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;**113**(12):941–8.
15. Kurella TM, Chertow GM, Luan J, Yaffe K. Cognitive impairment in chronic kidney disease. *J Am Geriatr Soc* 2004;**52**(11):1863–9.
16. Renal U.S. *Data system USRDS 2006 annual data report: atlas of chronic kidney disease & end-stage renal disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2006.
17. Elias MF, Elias PK, Seliger SL, Narsipur SS, Dore GA, Robbins MA. Chronic kidney disease, creatinine and cognitive functioning. *Nephrol Dial Transplant* 2009;**24**(8):2446–52.
18. Kurella TM, Wadley V, Yaffe K, McClure LA, Howard G, Go R. Kidney function and cognitive impairment in US adults: the reasons for geographic and racial differences in stroke (REGARDS) study. *Am J Kidney Dis* 2008;**52**(2):227–34.
19. Kurella TM, Yaffe K, Shlipak MG, Wenger NK, Chertow GM. Chronic kidney disease and cognitive impairment in menopausal women. *Am J Kidney Dis* 2005;**45**(1):66–76.
20. Yaffe K, Ackerson L, Kurella TM, Le Blanc P, Kusek JW, Sehgal AR. Chronic kidney disease and cognitive function in older adults: findings from the chronic renal insufficiency cohort cognitive study. *J Am Geriatr Soc* 2010;**58**(2):338–45.
21. Weiner DE, Gaussoin SA, Nord J, Auchus AP, et al. Cognitive function and kidney disease: baseline data from the Systolic Blood Pressure Intervention Trial (SPRINT). *Am J Kidney Dis* 2017;**70**: 357–67.
22. Feng L, Yap KB, Yeoh LY, Ng TP. Kidney function and cognitive and functional decline in elderly adults: findings from the Singapore longitudinal aging study. *J Am Geriatr Soc* 2012;**60**(7): 1208–14.
23. Slinin Y, Paudel ML, Ishani A, Taylor BC, Yaffe K, Murray AM. Kidney function and cognitive performance and decline in older men. *J Am Geriatr Soc* 2008;**56**(11):2082–8.
24. Etgen T, Sander D, Chonchol M, Briesenick C, Poppert H, Förstl H. Chronic kidney disease is associated with incident cognitive impairment in the elderly: the INVADE study. *Nephrol Dial Transplant* 2009;**24**(10):3144–50.
25. Buchman AS, Tanne D, Boyle PA, Shah RC, Leurgans SE, Bennett DA. Kidney function is associated with the rate of cognitive decline in the elderly. *Neurology* 2009;**73**(12):920–7.
26. Kurella TM, Chertow GM, Fried LF, Cummings SR, Harris T, Simonsick E. Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. *J Am Soc Nephrol* 2005;**16**(7):2127–33.
27. Seliger SL, Siscovick DS, Stehman-Breen CO, Gillen DL, Fitzpatrick A, Bleyer A. Moderate renal impairment and risk of dementia among older adults: the cardiovascular health cognition study. *J Am Soc Nephrol* 2004;**15**(7):1904–11.
28. Davey A, Elias MF, Robbins MA, Seliger SL, Dore GA. Decline in renal functioning is associated with longitudinal decline in global cognitive functioning, abstract reasoning and verbal memory. *Nephrol Dial Transplant* 2013;**28**:1810–9.
29. Qiu C, Kivipelto M, Aguero-Torres H, Winblad B, Fratiglioni L. Risk and protective effects of the APOE gene towards Alzheimer's disease in the Kungsholmen project: variation by age and sex. *J Neurol Neurosurg Psychiatry* 2004;**75**(6):828–33.
30. Yaffe K, Lindquist K, Shlipak MG, Simonsick E, Fried L, Rosano C. Cystatin C as a marker of cognitive function in elders: findings from the Health ABC study. *Ann Neurol* 2008;**63**(6):798–802.
31. Tizon B, Ribe EM, Mi W, Troy CM, Levy E. Cystatin C protects neuronal cells from amyloid-beta-induced toxicity. *J Alzheimer's Dis* 2010;**19**(3):885–94.
32. Murray AM, Barzilay JI, Lovato JF, Williamson JD, Miller ME, Marcovina S. Biomarkers of renal function and cognitive impairment in patients with diabetes. *Diabetes Care* 2011;**34**(8):1827–32.
33. Sajjad I, Grodstein F, Kang JH, Curhan GC, Lin J. Kidney dysfunction and cognitive decline in women. *Clin J Am Soc Nephrol* 2012; **7**(3):437–43.
34. Fried L. Albuminuria and cognitive impairment. *Clin J Am Soc Nephrol* 2012;**7**(3):376–8.
35. Himmelfarb J. Uremic toxicity, oxidative stress, and hemodialysis as renal replacement therapy. *Semin Dial* 2009;**22**(6):636–43.
36. Seliger SL, Longstreth WT. Lessons about brain vascular disease from another pulsating organ, the kidney. *Stroke* 2008;**39**(1):5–6.
37. Wardlaw JM, Sandercock PA, Dennis MS, Starr J. Is breakdown of the blood-brain barrier responsible for lacunar stroke, leukoaraiosis, and dementia? *Stroke* 2003;**34**(3):806–12.
38. Kalimo H. Does chronic brain edema explain the consequences of cerebral small-vessel disease? *Stroke* 2003;**34**(3):806–12.
39. Weiner DE, Bartolomei K, Scott T, Price LL, Griffith JL, Rosenberg I. Albuminuria, cognitive functioning, and white matter hyperintensities in homebound elders. *Am J Kidney Dis* 2009;**53**(3):438–47.
40. Buraczynska M, Ksiazek P, Zukowski P, Benedyk-Lorens E, Orlowska-Kowalik G. Complement factor H gene polymorphism and risk of cardiovascular disease in end-stage renal disease patients. *Clin Immunol* 2009;**132**(2):285–90.
41. Rodriguez-Iturbe B, Garcia GG. The role of tubulointerstitial inflammation in the progression of chronic renal failure. *Nephron Clin Pract* 2010;**116**(2):c81–8.
42. Manfredi AA, Rovere-Querini P. The mitochondrion – a Trojan horse that kicks off inflammation? *N Engl J Med* 2010;**362**(22): 2132–4.
43. Rizzo MA, Frediani F, Granata A, Ravasi B, Cusi D, Gallieni M. Neurological complications of hemodialysis: state of the art. *J Nephrol* 2012;**25**(2):170–82.
44. Brouns R, De Deyn PP. Neurological complications in renal failure: a review. *Clin Neurol Neurosurg* 2004;**107**(1):1–16.
45. Bugnicourt JM, Godefroy O, Chillon JM, Choukroun G, Massy ZA. Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. *J Am Soc Nephrol* 2013;**24**(3):353–63.
46. Murray AM. Cognitive impairment in the aging dialysis and chronic kidney disease populations: an occult burden. *Adv Chron Kidney Dis* 2008;**15**(2):123–32.
47. Kurella TM, Yaffe K. Dementia and cognitive impairment in ESRD: diagnostic and therapeutic strategies. *Kidney Int* 2011; **79**(1):14–22.
48. Casserly I, Topol E. Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. *Lancet* 2004;**363**(9415):1139–46.
49. Mielke MM, Rosenberg PB, Tschanz J, Cook L, Corcoran C, Hayden KM. Vascular factors predict rate of progression in Alzheimer disease. *Neurology* 2007;**69**(19):1850–8.
50. Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology* 2005;**65**(4):545–51.
51. Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. *Arch Neurol* 2009;**66**(2):216–25.
52. Feart C, Samieri C, Rondeau V, Amieva H, Portet F, Dartigues JF. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. *J Am Med Assoc* 2009;**302**(6):638–48.
53. Tsivgoulis G, Judd S, Letter AJ, Alexandrov AV, Howard G, Nahab F. Adherence to a Mediterranean diet and risk of incident cognitive impairment. *Neurology* 2013;**80**(18):1684–92.
54. Schmidt W, Endres M, Dimeo F, Jungehulsing GJ. Train the vessel, gain the brain: physical activity and vessel function and the impact on stroke prevention and outcome in cerebrovascular disease. *Cerebrovasc Dis* 2013;**35**(4):303–12.

55. Reitz C, Jun G, Naj A, Rajbhandary R, Vardarajan BN, Wang LS. Variants in the ATP-binding cassette transporter (ABCA7), apolipoprotein E 4, and the risk of late-onset Alzheimer disease in African Americans. *J Am Med Assoc* 2013;**309**(14):1483–92.
56. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;**361**(21):2019–32.
57. Maiese K, Li F, Chong ZZ. New avenues of exploration for erythropoietin. *J Am Med Assoc* 2005;**293**(1):90–5.
58. Renal U.S. *Data System. USRDS 2009 Annual Data Report: Atlas of chronic kidney disease & end-stage renal disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2009.
59. Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med* 2002;**346**(7):476–83.
60. Gorelick PB. Risk factors for vascular dementia and Alzheimer disease. *Stroke* 2004;**35**(11 Suppl. 1):2620–2.
61. De Deyn PP, Vanholder R, Eloot S, Glorieux G. Guanidino compounds as uremic (neuro)toxins. *Semin Dial* 2009;**22**(4):340–5.
62. Weimer DL, Sager MA. Early identification and treatment of Alzheimer's disease: social and fiscal outcomes. *Alzheimer's Dementia* 2009;**5**(3):215–26.
63. Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A. The mini-cog: a cognitive "vital signs" measure for dementia screening in multi-lingual elderly. *Int J Geriatr Psychiatry* 2000;**15**(11):1021–7.
64. Tariq SH, Tumosa N, Chibnall JT, Perry MH, Morley JE. Comparison of the Saint Louis University mental status examination and the mini-mental state examination for detecting dementia and mild neurocognitive disorder–a pilot study. *Am J Geriatr Psychiatry* 2006;**14**(11):900–10.
65. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;**53**(4):695–9.
66. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**: 2103–16.
67. *Rivastigmine [package insert]*. East Hanover, NJ: Novartis Pharmaceuticals Corp.; 2013.
68. *Galantamine [package insert]*. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2014.
69. *Memantine [package insert]*. St. Louis, MO: Forest Pharmaceuticals, Inc.; 2012.
70. Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 2006;**355**(15): 1525–38.
71. Ballard C, Waite J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database Syst Rev* 2006;(1):CD003476.
72. SPRINT MIND Investigators for the SPRINT Research Group, Williamson JD, Pajewski NM, Auchus AP, Bryan RN, et al. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *J Am Med Assoc* 2019;**321**(6): 553–61.
73. Yaffe K. Prevention of cognitive impairment with intensive systolic blood pressure control. *J Am Med Assoc* 2019;**321**(6):548–9.
74. Kurella TM, Covinsky KE, Chertow GM, Yaffe K, Landefeld CS, McCulloch CE. Functional status of elderly adults before and after initiation of dialysis. *N Engl J Med* 2009;**361**(16):1539–47.
75. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;**44**:2064–89.
76. Murray AM, Seliger S, Lakshminarayan K, et al. Incidence of stroke before and after dialysis initiation in older patients. *J Am Soc Nephrol* 2013;**24**(7):1166–73.
77. Moss AH. Revised dialysis clinical practice guideline promotes more informed decision-making. *Clin J Am Soc Nephrol* 2010; **5**(12):2380–3.
78. Kobayshi S, Okada K, Koide H, Bokura H, Yamaguchi S. Subcortical silent brain infarction as a risk factor for clinical stroke. *Stroke* 1997;**28**(10):1932–9.
79. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Low glomerular filtration rate and risk of stroke: meta-analysis. *BMJ* 2010;**341**:c4249.
80. Aguilar MI, O'Meara ES, Seliger S, Longstreth WT, Hart RG, Pergola PE. Albuminuria and the risk of incident stroke and stroke types in older adults. *Neurology* 2010;**75**(15):1343–50.
81. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Impact of microalbuminuria on incident stroke: a meta-analysis. *Stroke* 2010;**41**(11):2625–31.
82. Covic A, Kothawala P, Bernal M, Robbins S, Chalian A, Goldsmith D. Systematic review of the evidence underlying the association between mineral metabolism disturbances and risk of all-cause mortality, cardiovascular mortality and cardiovascular events in chronic kidney disease. *Nephrol Dial Transplant* 2009;**24**(5):1506–23.
83. Foley RN, Collins AJ, Ishani A, Kalra PA. Calcium-phosphate levels and cardiovascular disease in community-dwelling adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J* 2008;**156**(3):556–63.
84. Vlagopoulos PT, Tighiouart H, Weiner DE, Griffith J, Pettitt D, Salem DN. Anemia as a risk factor for cardiovascular disease and all-cause mortality in diabetes: the impact of chronic kidney disease. *J Am Soc Nephrol* 2005;**16**(11):3403–10.
85. London G. Pathophysiology of cardiovascular damage in the early renal population. *Nephrol Dial Transplant* 2001;**16**(Suppl. 2): 3–6.
86. Brines M, Cerami A. Emerging biological roles for erythropoietin in the nervous system. *Nat Rev Neurosci* 2005;**6**(6):484–94.
87. Skali H, Parving HH, Parfrey PS, Burdmann EA, Lewis EF, Ivanovich P. Stroke in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia treated with Darbepoetin Alfa: the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) experience. *Circulation* 2011;**124**(25):2903–8.
88. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D, Investigators CHOIR. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;**355**(20): 2085–98.
89. Seliger SL, Zhang AD, Weir MR, Walker L, Hsu VD, Parsa A. Erythropoiesis-stimulating agents increase the risk of acute stroke in patients with chronic kidney disease. *Kidney Int* 2011;**80**(3): 288–94.
90. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;**42**(1):227–76.
91. Debing E, Van den Brande P. Chronic renal insufficiency and risk of early mortality in patients undergoing carotid endarterectomy. *Ann Vasc Surg* 2006;**20**(5):609–13.
92. Sidawy AN, Aidinian G, Johnson ON, White PW, DeZee KJ, Henderson WG. Effect of chronic renal insufficiency on outcomes of carotid endarterectomy. *J Vasc Surg* 2008;**48**(6):1423–30.
93. Mathew A, Eliasziw M, Devereaux PJ, Merino JG, Barnett HJ, Garg AX. Carotid endarterectomy benefits patients with CKD and symptomatic high-grade stenosis. *J Am Soc Nephrol* 2010; **21**(1):145–52.

94. Go AS, Fang MC, Udaltsova N, Chang Y, Pomernacki NK, Borowsky L. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *Circulation* 2009;**119**(10):1363–9.
95. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. *J Am Soc Nephrol* 2009;**20**(10):2223–33.
96. Winkelmayer WC, Liu J, Setoguchi S, Choudhry NK. Effectiveness and safety of warfarin initiation in older hemodialysis patients with incident atrial fibrillation. *Clin J Am Soc Nephrol* 2011; **6**(11):2662–8.
97. Hart RG, Pearce LA, Asinger RW, Herzog CA. Warfarin in atrial fibrillation patients with moderate chronic kidney disease. *Clin J Am Soc Nephrol* 2011;**6**(11):2599–604.
98. Olesen JB, Lip GY, Kamper AL, Hommel K, Køber L, Lane DA. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med* 2012;**367**(7):625–35.
99. Connolly SJ, Wallentin L, Ezekowitz MD, et al. The long-term multicenter observational study of dabigatran treatment in patients with atrial fibrillation (RELY-ABLE) study. *Circulation* 2013;**128**(3):237–43.
100. Bansilal S, Bloomgarden Z, Halperin JL, et al. Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF trial). *Am Heart J* 2015;**170**(4):675–82.
101. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365**(11):981–92.
102. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;**364**(9):806–17.
103. Eikelboom JW, Connolly SJ, Gao P, Paolasso E, De Caterina R, Husted S. Stroke risk and efficacy of apixaban in atrial fibrillation patients with moderate chronic kidney disease. *J Stroke Cerebrovasc Dis* 2012;**21**(6):429–35.
104. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J* 2012;**33**(22):2821–30.
105. Pelliccia F, Rosanio S, Marazzi G, et al. Efficacy and safety of novel anticoagulants versus vitamin K antagonists in patients with mild and moderate to severe renal insufficiency: focus on apixaban. *Int J Cardiol* 2016;**225**:77–81.
106. Halperin JL, Hankey GJ, Wojdyla DM, et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Circulation* 2014;**130**:138–46.
107. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J* 2011; **32**(19):2387–94.
108. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–51.
109. Knauf F, Chanknos M, Berns JS, Perazella MA. Dabitragan and kidney disease: a bad combination. *Clin J Am Soc Nephrol* 2013;**8**: 1591–7.
110. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: guidance from the anticoagulation forum. *Am J Hematol* 2019;**94**(6):697–709.
111. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;**360**(14):1395–407.
112. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;**353**(3):238–48.
113. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**(9784):2181–92.
114. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2012;**157**(4):263–75.
115. Palmer SC, Di ML, Razavian M, Craig JC, Perkovic V, Pellegrini F. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2012; **156**(6):445–59.
116. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;**333**:1581–8.
117. Jauch EC, Saver JL, Adams Jr HP, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan Jr PW, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H, American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;**44**(3):870–947.
118. Power A, Epstein D, Cohen D, et al. Renal impairment reduces the efficacy of thrombolytic therapy in acute ischemic stroke. *Cerebrovasc Dis* 2013;**35**(1):45–52.
119. Ovbiagele B, Schwamm LH, Smith EE, Grau-Sepulveda MV, Saver JL, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Patterns of care quality and prognosis among hospitalized ischemic stroke patients with chronic kidney disease. *J Am Heart Assoc* 2014;**3**(3):e000905.
120. Jung JM, Kim HJ, Ahn H, Ahn IM, Do Y, Choi JY, Seo WK, Oh K, Cho KH, Yu S. Chronic kidney disease and intravenous thrombolysis in acute stroke: a systematic review and meta-analysis. *J Neurol Sci* 2015;**358**(1–2):345–50.
121. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol* 2017;**28**(9):2812–23.
122. Krishnan AV, Pussell BA, Kiernan MC. Neuromuscular disease in the dialysis patient: an update for the nephrologist. *Semin Dial* 2009;**22**(3):267–78.
123. Krishnan AV, Kieman MC. Neurological complications of chronic kidney disease. *Nat Rev Neurol* 2009;**5**:542–51.
124. Dyck PJ, Johnson WJ, Lambert EH, O'Brien PC. Segmental demyelination secondary to axonal degeneration in uremic neuropathy. *Mayo Clin Proc* 1971;**46**(6):400–31.
125. Laaksonen S, Metsarinne K, Voipio-Pulkki LM, Falck B. Neurophysiologic parameters and symptoms in chronic renal failure. *Muscle Nerve* 2002;**25**(6):884–90.
126. Babb AL, Ahmad S, Bergstrom J, Scribner BH. The middle molecule hypothesis in perspective. *Am J Kidney Dis* 1981;**1**(1):46–50.
127. Massry SG. Parathyroid hormone: a uremic toxin. *Adv Exp Med Biol* 1987;**223**:1–17.
128. Vanholder R, De SR, Hsu C, Vogeleere P, Ringoir S. Uremic toxicity: the middle molecule hypothesis revisited. *Semin Nephrol* 1994;**14**(3):205–18.

129. Bostock H, Walters RJ, Andersen KV, Murray NM, Taube D, Kiernan MC. Has potassium been prematurely discarded as a contributing factor to the development of uraemic neuropathy? *Nephrol Dial Transplant* 2004;**19**(5):1054–7.
130. Krishnan AV, Phoon RK, Pussell BA, Charlesworth JA, Bostock H, Kiernan MC. Altered motor nerve excitability in end-stage kidney disease. *Brain* 2005;**128**(Pt 9):2164–74.
131. Ogura T, Makinodan A, Kubo T, Hayashida T, Hirasawa Y. Electrophysiological course of uraemic neuropathy in haemodialysis patients. *Postgrad Med J* 2001;**77**(909):451–4.
132. Oh SJ, Clements RS, Lee YW, Diethelm AG. Rapid improvement in nerve conduction velocity following renal transplantation. *Ann Neurol* 1978;**4**(4):369–73.
133. Bolton CF. Electrophysiologic changes in uremic neuropathy after successful renal transplantation. *Neurology* 1976;**26**(2):152–61.
134. Vita G, Messina C, Savica V, Bellinghieri G. Uraemic autonomic neuropathy. *J Auton Nerv Syst* 1990;**30**(Suppl.):S179–84.
135. Jassal SV, Coulshed SJ, Douglas JF, Stout RW. Autonomic neuropathy predisposing to arrhythmias in hemodialysis patients. *Am J Kidney Dis* 1997;**30**:219–23.
136. Tozawa M, Iseki K, Yoshi S, Fukiyama K. Blood pressure variability as an adverse prognostic risk factor in end-stage renal disease. *Nephrol Dial Transplant* 1999;**14**:1976–81.
137. Palmer BF. Sexual dysfunction in uremia. *J Am Soc Nephrol* 1999; **10**:1381–8.
138. Foy CG, Newman JC, Berlowitz DR, Russell LP, Kimmel PL, SPRINT Study Research Group, et al. Blood pressure, sexual activity, and dysfunction in women with hypertension: baseline findings from the systolic blood pressure intervention trial (SPRINT). *J Sex Med* 2016;**13**(9):1333–46.
139. Foy CG, Newman JC, Berlowitz DR, Russell LP, Kimmel PL, SPRINT Study Research Group, et al. Blood pressure, sexual activity, and erectile function in hypertensive men: baseline findings from the systolic blood pressure intervention trial (SPRINT). *J Sex Med* 2019;**16**(2):235–47.
140. Barri YM, Golper TA. *Gastrointestinal disease in dialysis patients*. Waltham, MA: UpToDate; 2012.
141. Bland JD. Carpal tunnel syndrome. *BMJ* 2007;**335**(7615):343–6.
142. Hirasawa Y, Ogura T. Carpal tunnel syndrome in patients on long-term haemodialysis. *Scand J Plast Reconstr Surg Hand Surg* 2000;**34**(4):373–81.
143. Drueke TB. Beta2-microglobulin and amyloidosis. *Nephrol Dial Transplant* 2000;**15**(Suppl. 1):17–24.
144. Floege J, Ketteler M. Beta2-microglobulin-derived amyloidosis: an update. *Kidney Int Suppl* 2001;**78**:S164–71.
145. Cofan F, Garcia S, Combalia A, Segur JM, Oppenheimer F. Carpal tunnel syndrome secondary to uraemic tumoral calcinosis. *Rheumatology* 2002;**41**(6):701–3.
146. Thermann F, Kornhuber M. Ischemic monomelic neuropathy: a rare but important complication after hemodialysis access placement–a review. *J Vasc Access* 2011;**12**(2):113–9.
147. Manenti L, Tansinda P, Vaglio A. Uraemic pruritus: clinical characteristics, pathophysiology and treatment. *Drugs* 2009;**69**(3):251–63.
148. Narita I, Iguchi S, Omori K, Gejyo F. Uremic pruritus in chronic hemodialysis patients. *J Nephrol* 2008;**21**(2):161–5.
149. Pisoni RL, Wikstrom B, Elder SJ, Akizawa T, Asano Y, Keen ML. Pruritus in haemodialysis patients: international results from the dialysis outcomes and practice patterns study (DOPPS). *Nephrol Dial Transplant* 2006;**21**(12):3495–505.
150. Gunal AI, Ozalp G, Yoldas TK, Gunal SY, Kirciman E, Celiker H. Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. *Nephrol Dial Transplant* 2004;**19**(12):3137–9.
151. Gilchrest BA, Rowe JW, Brown RS, Steinman TI, Arndt KA. Relief of uremic pruritus with ultraviolet phototherapy. *N Engl J Med* 1977;**297**(3):136–8.
152. Wikstrom B, Gellert R, Ladefoged SD, Danda Y, Akai M, Ide K. Kappa-opioid system in uremic pruritus: multicenter, randomized, double-blind, placebo-controlled clinical studies. *J Am Soc Nephrol* 2005;**16**(12):3742–7.
153. Campistol JM. Uremic myopathy. *Kidney Int* 2002;**62**(5):1901–13.
154. Moore GE, Parsons DB, Stray-Gundersen J, Painter PL, Brinker KR, Mitchell JH. Uremic myopathy limits aerobic capacity in hemodialysis patients. *Am J Kidney Dis* 1993;**22**(2): 277–87.
155. Diesel W, Emms M, Knight BK, Noakes TD, Swanepoel CR, van Zyl Smit R. Morphologic features of the myopathy associated with chronic renal failure. *Am J Kidney Dis* 1993;**22**(5):677–84.
156. Calo LA, Vertolli U, Davis PA, Savica V. L carnitine in hemodialysis patients. *Hemodial Int* 2012;**16**:428–34.
157. Guarnieri G, Situlin R, Biolo G. Carnitine metabolism in uremia. *Am J Kidney Dis* 2001;**4**(Suppl. 1):S63–7.

QUESTIONS AND ANSWERS

Question 1

You are seeing a 75-year-old woman with stage 4 CKD in clinic for the first time for a scheduled follow-up. She is living with her husband in assisted living. He reports that she became more agitated yesterday and was up most of the night. Today she seems more confused and initially refused to get dressed, which is unusual for her. She has no fever but her appetite is poor. There has been no recent change in her medications. On examination, she is uncooperative, has difficulty tracking, and is easily distracted. The remainder of her exam is normal. What would be your next step?

A. Use the Mini-Cog to assess cognitive function
B. Obtain a urine culture and serum electrolytes
C. Use the Confusion Assessment Method to assess cognitive function
D. B and C
E. Refer to a neurologist, psychiatrist, or geriatrician

Answer: D

This patient is presenting with classic symptoms of delirium: acute onset confusion, decreased attention, disrupted sleep–wake cycle, and agitation. As she is living in assisted living, she may also have underlying dementia but has never been diagnosed with cognitive impairment. It is not possible to differentiate delirium from dementia on an initial evaluation. The best steps are to use the Confusion Assessment Method to confirm the diagnosis of delirium and obtain a urine culture and electrolytes. Urinary tract infection and serum electrolyte disturbance are two very common causes of delirium in the elderly, the latter being especially common in CKD. Medication change is another common cause, but her medications have not changed.

Question 2

Which of these statements is true?

A. Dementia in CKD patients more than doubles the risk of death
B. Brain imaging is recommended for most new cases of cognitive impairment
C. High cystatin C, albuminuria, and eGFR <45 mL/min/1.73.m^2 are associated with an increased risk of cognitive impairment
D. Delirium in the hospitalized elderly usually results in long-term cognitive and functional decline
E. All are true

Answer: E

All of these statements are true. Of note delirium in the hospitalized elderly rarely complete reverses, especially in those with underlying dementia.

Question 3

A 65-year-old man with stage 3 CKD (eGFR 45 mL/min/1.73 m^2) has an ischemic stroke affecting the right middle cerebral artery territory. A duplex ultrasound study demonstrates high-grade (>70%) stenosis in the right internal carotid artery. Which of the following statements is correct regarding the role of CEA in this patient?

A. This patient is at no greater risk for postoperative complications than a patient with similar comorbidity but without CKD
B. The benefit in ipsilateral stroke recurrence from CEA is similar to the benefit in patients with CKD and moderate-grade (50%–69%) carotid stenosis
C. CEA compared with standard medical therapy reduces the risk of ipsilateral stroke by approximately 80%
D. The benefit in prevention of recurrent stroke from CEA is similar to the benefit in patients with stage 5 CKD

Answer: C

A subgroup analysis from the NASCET clinical trial suggests that patients with stage 3 CKD and symptomatic high-grade internal carotid artery stenosis have an 82% lower risk of recurrent ipsilateral stroke with CEA compared with standard medical therapy. In contrast, no significant difference in stroke risk was observed with CEA among patients with moderate stenosis. This same analysis, and additional observational cohort studies, suggests an increased risk of postoperative cardiac complications (myocardial infarction, congestive heart failure, arrhythmia, and potentially death) in CKD patients undergoing CEA compared with patients with eGFR > 60 mL/min/1.73m^2. There are no data from clinical trials regarding effects of CEA vs. medical therapy in patients with stage 5 CKD.

Question 4

Which of the following statements about stroke risk in patients with non–dialysis-dependent CKD is true:

A. Lower eGFR but not greater albuminuria is associated with an increased risk of acute stroke
B. Patients with non–dialysis-dependent CKD and anemia are at greater risk for acute stroke than those with CKD but no anemia
C. ESAs reduce the risk of acute stroke in non–dialysis-dependent CKD patients with anemia

D. HMG CoA-reductase inhibitors (statins) are not effective in stroke prevention among patients with non−dialysis-dependent CKD
E. In patients with stage 3 CKD and atrial fibrillation, oral factor Xa inhibitors (e.g., apixaban) are less effective for stroke prevention than in patients without CKD

Answer: B

Meta-analyses of observational studies suggest that both albuminuria and lower eGFR are risk factors for acute stroke, independent of traditional vascular risk factors. Data from observational studies suggest that anemia is associated with greater risk of stroke among patients with non−dialysis-dependent CKD. However, the results of interventional and observational studies suggest that ESAs, especially when administered at high doses and/or targeting high hemoglobin concentrations, increase rather than reduce stroke risk. A summary of *post hoc* subgroup analyses of clinical trials involving statins suggest that statins reduce the risk of fatal and nonfatal strokes among patients with non−dialysis-dependent (primarily stage 3) CKD; these results are supported by the SHARP study, which found a 25% lower risk of nonhemorrhagic stroke among non−dialysis-dependent and dialysis-dependent CKD patients treated with simvastatin combined with ezetimibe. *Post hoc* subgroup analyses of clinical trials of oral factor Xa inhibitors suggest patients with stage 3 CKD have the same reduction in risk of stroke as those with preserved renal function, at least when reduced doses for lower renal function are used. These medications are contraindicated in patients with more advanced CKD.

Question 5

A 70-year-old man with long-standing CKD due to hypertension presents with 3 weeks of tingling and dull pain in the distal portions of both feet. His GFR is approximately 10−15 mL/min/1.73 m^2 and has declined only minimally over the past year. His exam is significant for decreased sensation to monofilament and vibration. He has repeatedly said that he is not interested in initiating dialysis. He does not have diabetes mellitus and does not drink alcohol. Which one of the following is the best initial treatment for his symptoms?

A. Ibuprofen
B. Amitriptyline
C. Oxycodone
D. Sertraline
E. Tramadol

Answer: B

The patient's presentation is consistent with uremic polyneuropathy. Amitriptyline, a tricyclic antidepressant, is regarded as a first-line agent for treatment of painful uremic polyneuropathy. Anticonvulsants such as pregabalin and valproate are also regarded as effective. While opioids such as tramadol and oxycodone may provide effective pain relief, potential problems with addiction, abuse, and overdose generally preclude their use as initial therapy. NSAIDs such as ibuprofen are contraindicated in CKD due to adverse effects on renal function. There are also theoretical concerns that NSAID-induced prostacyclin inhibition may impair nerve circulation and worsen nerve injury.

Question 6

A 52-year-old woman with advanced CKD due to diabetes mellitus has been experiencing daily episodes of itching for the past 2 weeks. The itching has been most intense at night and is interrupting sleep. Her GFR has declined significantly over the past 12 months and is now approximately 15 mL/min/1.73 m^2. Her exam is significant for dry, flaking skin with patches of erythema and excoriation on her arms and abdomen. She is scheduled for vascular access placement in the coming week in anticipation of hemodialysis initiation in the coming months. Which one of the following is the best initial treatment for her symptoms?

A. Odansetron
B. Oxycodone
C. Diphenhydramine
D. Topical emollient
E. Cetirizine

Answer: D

The patient's presentation is consistent with UP. Topical emollients are safe and inexpensive and have been shown to be very effective in reducing pruritic symptoms. Other potentially effective treatments include gabapentin, UVB phototherapy, and nalfurafine, a κ-opioid receptor agonist. Antihistamines such as diphenhydramine and cetirizine are widely used in the treatment of uremic pruritus, but their effectiveness is controversial. 5-HT_3 receptor agonists such as odansetron have not been proven effective. Opiates such as oxycodone are frequently associated with pruritic side effects and are not effective treatments for uremic pruritus.

CHAPTER

30

Hematologic Complications of Chronic Kidney Disease—Anemia and Platelet Disorders

Sarah J. Schrauben, Jeffrey S. Berns

Renal-Electrolyte and Hypertension Division, Department of Medicine, Perelman School of Medicine of the University of Pennsylvania School of Medicine, Philadelphia, PA, United States

Abstract

Anemia is a common complication of chronic kidney disease (CKD), particularly among patients whose glomerular filtration rate (GFR) is less than 30–40 mL/min. The pathogenesis of anemia in CKD is complex, but the central etiological factor is the relative deficiency of erythropoietin. Erythropoietin is produced in the kidneys by cortical peritubular interstitial fibroblast-like cells. The production of erythropoietin decreases as the functioning renal mass declines. Iron deficiency also commonly contributes to anemia in CKD. Iron metabolism is normally tightly regulated by hepcidin. Inflammation induces changes in hepcidin that reduces the availability of iron for erythropoiesis, which contributes to anemia in CKD patients. Erythrocytosis is a much less common occurrence in patients with CKD and is mostly seen in patients with polycystic kidney disease or following kidney transplantation. Defective platelet function with a bleeding tendency is well known to occur in patients with advanced CKD and uremia. The CKD stage at which platelet dysfunction becomes clinically relevant is not known. Therapies aimed at improving this acquired platelet dysfunction include initiation of dialysis, desmopressin (1-deamino-8-d-arginine vasopressin), cryoprecipitate, improvement in anemia, and estrogens.

ANEMIA OF CHRONIC KIDNEY DISEASE

Anemia is common among patients with chronic kidney disease (CKD), increasing in prevalence with progressively reduced kidney function (i.e. lower levels of glomerular filtration rate [GFR] or creatinine clearance).[1–3] The dominant factor controlling red blood cell (RBC) production in the bone marrow is the regulatory hormone, erythropoietin, which stimulates maturation and release of RBCs into the circulation. The primary basis for anemia in those with CKD is a relative deficiency of erythropoietin, although other factors may also contribute (Table 30.1). The anemia of CKD is hypoproliferative in nature, with a low circulating reticulocyte count and without increased bone marrow RBC progenitor cells. The RBCs in circulation in patients with CKD and anemia are typically normochromic and normocytic unless there is also superimposed iron, folate, or vitamin B12 deficiency.

The anemia of CKD is a major contributor to impaired quality of life and decreased functional capacity and is also associated with hospitalization risk, adverse cardiovascular disease outcomes, cognitive dysfunction, and death.[4,5] Clinical practice guidelines developed for the care of patients with CKD recommend the evaluation of anemia in those with CKD should begin when the hemoglobin [Hb] concentration is less than 13.0 g/dL in men (<130 g/L) and 12.0 g/dL (<120 g/L) in women (approximately equivalent to hematocrit levels of 39% and 36%, respectively).[6,7] Patients may have anemia related to CKD, but they are also at risk for all the other causes of anemia that can occur in the general population. Common factors associated with causing anemia in CKD are listed in Table 30.1. Recommended testing to evaluate anemia in patients with CKD includes a complete blood count, measuring the Hb concentration, red cell indices, white blood cell count and differential, and platelet count, absolute reticulocyte count, and serum ferritin level, transferrin saturation (TSAT), serum vitamin B12, and folate levels.[2,6] Other testing should be performed as clinically indicated. Abnormalities of white blood cell numbers and distribution and platelet count are not typically seen in CKD patients, so their presence should suggest other causes of anemia not related to CKD.

A Hb concentration less than 13.0 g/dL is seen in approximately 20% of CKD patients with GFR

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00030-9

TABLE 30.1 Factors Involved in the Anemia of Chronic Kidney Disease

Most Important, Common
Decreased erythropoietin synthesis
Relative erythropoietin deficiency
Important, Common
Iron deficiency (absolute)
Chronic blood loss, including from phlebotomy
Infection/inflammation—"anemia of chronic disease"
Less Important, Less Common, or of Uncertain Significance
Vitamin B12 and/or folate deficiency
"Uremic toxins"
Reduced red blood cell life span
Increased red blood cell fragility
Carnitine deficiency
Aluminum toxicity
Severe hyperparathyroidism
ACEIs/ARBs

45–60 mL/min and approximately 90% of patients with GFR below 15 mL/min.[1,3,8,9] Anemia associated with CKD is unusual when the GFR is over 60 mL/min (Figure 30.1), and therefore other causes of anemia should be considered in these patients. Severe anemia (Hb less than 10.0 g/dL) due to CKD alone is uncommon unless the GFR is less than 20–30 mL/min. At any given GFR level, anemia tends to be more common and severe among women compared to men, particularly below the age of 65 years, African Americans compared to whites, and those with diabetes compared to those without.[10–14] Anemia also tends to develop earlier in the course of CKD in those with diabetes compared to those without diabetes.[13]

Erythropoiesis and Erythropoietin

The erythopoietic system maintains homeostasis of the blood supply to achieve adequate tissue oxygen delivery. The dominant factor controlling RBC production in the bone marrow is the regulatory glycoprotein hormone, erythropoietin, which is produced mainly in the liver prenatally, but then predominantly by the kidneys shortly after birth. Synthesis of erythropoietin is stimulated by hypoxia in cortical peritubular interstitial fibroblast-like cells of the kidney. Erythropoietin interacts with receptors on RBC progenitor cells in the bone marrow to release mature RBCs into the bloodstream.[15–19]

Erythropoietin is a 165 amino acid, 30.5 kDa glycoprotein containing carbohydrate chains with variable sialic acid content. Various circulating erythropoietin isoforms contain different numbers of sialic acid residues, which stabilize the molecule in the circulation and are necessary for its biological activity.[20–22] Regulation of erythropoietin synthesis by peritubular fibroblasts is mediated primarily through binding of the hypoxia-inducible factor (HIF), a transcription factor comprised of HIFα and HIFβ subunits, to a hypoxia response element in the erythropoietin gene and other related hypoxia-responsive genes to increase their transcription.[23,24] In the presence of oxygen, HIFα subunits are hydroxylated and undergo ubiquination by the von Hippel-Lindau complex, leading to proteosomal degradation and reduced erythropoietin levels. In the presence of hypoxia, HIF degradation is impaired and the HIF transcription complex enhances transcription of the erythropoietin gene with subsequent translation and secretion of the hormone directly into the bloodstream.[25–27] Under normal, basal conditions, the

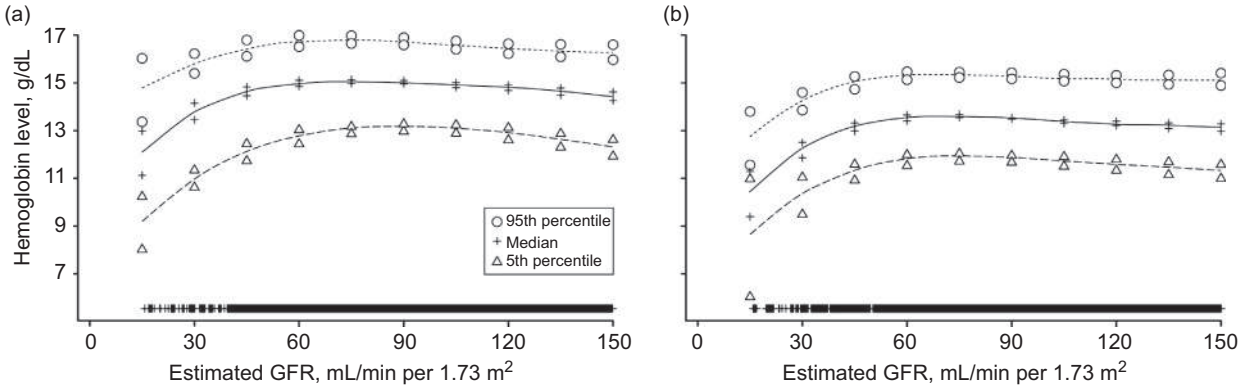


FIGURE 30.1 Median, 5th, and 95th percentiles of Hb levels among adult men (a) and women (b) 20 who participated in the Third National Health and Nutrition Examination Survey (1988–1994). All values are adjusted to the age of 60 years. *From reference 3.*

serum erythropoietin concentration is in the range of 0.01−0.03 U/mL. In response to anemia and hypoxia, circulating erythropoietin levels typically increase 100- to 1000-fold in individuals without kidney disease.[28]

The action of erythropoietin occurs after its interaction with the erythropoietin receptor, present in the highest quantities on the cell membranes of bone marrow erythroid precursor cells. Binding of erythropoietin to the erythropoietin receptor of erythroid progenitor cells induces a conformational change, leading to activation of a Janus tyrosine kinase-2 intracellular signaling cascade that increases the number of erythroid precursors.[29−31] In the absence of erythropoietin, erythroid precursors are rapidly lost due to apoptosis. In the presence of erythropoietin, there is reduced apoptosis and these cells develop into mature erythrocytes.[32−34]

In patients with relatively mild CKD and anemia, serum erythropoietin concentrations, although possibly within or even above the "normal range," are inappropriately low for the degree of anemia but remain correlated with the severity of anemia. As functioning nephron mass and GFR decline, generally below about 40 mL/min, serum erythropoietin levels fall, become clearly low, and no longer correlate with the degree of anemia. To what extent the impaired synthesis of erythropoietin is due to reduced numbers of erythropoietin-secreting peritubular fibroblasts or impairment in the hypoxia-sensing regulatory process controlling erythropoiesis has not been definitively established, but there is some evidence to suggest both may play a role.[35−37] Even in the presence of advanced CKD, erythropoietin synthesis increases with stimuli from acute hemorrhage and hypoxia, albeit to a lesser degree than in the absence of CKD. Measurement of serum or plasma erythropoietin levels is not recommended in the evaluation of patients with CKD and anemia.

Iron and Anemia of CKD

Effective erythropoiesis is dependent on adequate availability of both iron and erythropoietin. Iron balance, which includes the absorption of iron from the gastrointestinal (GI) tract, storage in the liver and other reticuloendothelial storage sites, and circulation throughout the body, is normally tightly regulated to maintain an adequate iron supply for effective erythropoiesis while avoiding iron overload and potential organ toxicity.[38] Iron deficiency is common in patients with CKD.

Iron deficiency can be "true," with insufficient body stores and characterized by markedly reduced or absent iron in the bone marrow, or "functional," in which total body iron stores are adequate, but the stored iron is prevented from being made available in the circulation to adequately support erythropoiesis. Functional iron deficiency can be due to administration of erythropoiesis stimulating agents (ESAs) or to what is often referred to as "anemia of chronic disease." Anemia of chronic disease appears to be mediated largely by inflammation *via* upregulation of the iron regulatory protein hepcidin that causes sequestration of iron.[38,39] Hepcidin is produced by the liver and cleared from the circulation by the kidneys and plays a key role in systemic iron homeostasis.[40] Hepcidin reduces intestinal iron absorption and inhibits release of iron from the reticuloendothelial macrophages and hepatocytes into plasma by inducing internalization and degradation of a cell membrane iron channel, ferroportin.[41−44] In animal models and humans with absent or reduced hepcidin synthesis, iron overload ensues, and in settings of increased hepcidin synthesis, severe iron deficiency is found. Hepcidin expression is increased in response to iron administration and systemic inflammation,[45,46] whereas it is decreased in response to anemia and hypoxemia.[47] Each of the mediators of changes in hepcidin synthesis acts through complex signaling pathways. For instance, the hemochromatosis protein, transferrin receptors 1 and 2, hemojuvelin, bone morphogenic protein 6, and several SMAD proteins, among others, are involved in iron-signal pathways, while inflammation also involves IL-6, Janus kinase, and STAT3 as well as other mediators. ESAs also directly inhibit hepcidin expression.[38,39,48,49] Hypoxic regulation of hepcidin synthesis appears to be mediated at least in part by the HIF pathway, whereas iron deficiency appears to modulate hepcidin expression *via* HIF and other pathways.

True, or absolute, iron deficiency is less common among CKD patients who are not treated with dialysis than those treated with dialysis. The exact prevalence, however, has not been well studied and likely varies among different populations as it does in the general population (for example, menstruating women compared to men and postmenopausal women). Patients with CKD not on dialysis are thought to have normal intestinal absorption of iron in the absence of elevated ferritin levels (which would suggest the presence of iron overload or systemic inflammation).[50,51] Oral iron supplements should be taken separately from calcium-containing phosphate binders, which can bind iron and reduce its availability. CKD patients on dialysis (CKD-HD) may have impaired iron absorption, as it has been shown that oral iron supplementation is no better than placebo for correction of iron deficiency. The gold standard for the diagnosis of iron deficiency is measurement of iron stores in bone marrow obtained on biopsy, but this is not used routinely, given the invasiveness of the procedure and evidence that determination of bone marrow iron does not accurately

predict responsiveness to intravenous iron supplementation.[52] Instead, iron stores are more commonly estimated by measuring serum iron, total iron-binding capacity, ferritin, and calculation of the percent TSAT. Other markers of iron status such as serum transferrin receptor, percent hypochromic RBCs, and reticulocyte Hb content have been studied but are not in widespread clinical use in the US. Although measurement of blood hepcidin levels is available, studies have not found that hepcidin testing is consistently predictive of response to iron supplementation or ESA therapy or of greater diagnostic value than ferritin level testing in CKD patients, and hepcidin is not used in routine clinical practice.[53,54]

True iron deficiency is diagnosed in patients with CKD when the TSAT is less than 20% and the serum ferritin concentration is less than 100 ng/dL.[2,52] These tests, however, have limited sensitivity, specificity, and predictive value. Patients with TSAT and ferritin levels above these limits will often respond to iron supplementation with an increase in Hb level, even when bone marrow iron staining does not indicate absolute iron deficiency.[55–57] The likelihood of responding to intravenous iron supplementation with a significant increase in Hb concentration is low among patients with serum ferritin concentrations above 500 ng/mL. Clinical practice guidelines for anemia management in patients with CKD suggest iron supplementation with intravenous iron or a short trial of oral iron when the TSAT is 30% or less and the serum ferritin concentration is 500 ng/mL or less.[7] Prior guidelines recommended that supplemental iron be provided to CKD patients with anemia when the serum ferritin was 100 ng/mL or less and the TSAT was 20% or lower.[6]

Other factors besides impaired erythropoietin synthesis and iron deficiency can contribute variably to anemia in CKD patients (Table 30.1).[58,59] Shortened RBC survival in uremic patients has been attributed to increased erythrophagocytosis, increased RBC osmotic fragility, decreased RBC deformability in the circulation, carnitine deficiency, RBC complement deposition and activation, and reduced RBC tolerance to oxidative stress.[60–64] These factors have for the most part been studied primarily in CKD-HD patients. It is very unlikely that any are clinically important contributors to the anemia of CKD in patients who are not treated with dialysis or have very advanced uremia. Angiotensin converting enzyme inhibitors (ACEIs), and to a lesser extent angiotensin receptor blockers (ARBs), have been suggested to exacerbate anemia in CKD patients due to increased synthesis of erythropoiesis inhibitors and alterations in renal blood flow and oxygen supply,[65–67] although this finding is controversial.[68] In addition to the supply of iron and erythropoietin, normal basal erythropoiesis and the ability to increase RBC production in response to hypoxia and anemia require adequate supplies of vitamin B12 and folate. Erythropoiesis can also be inhibited directly, as well as indirectly through effects on iron metabolism, by negative influences of inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interferon-γ, interleukin-6 (IL-6), and transforming growth factor-β (TGF-β).[69–75]

ERYTHROCYTOSIS IN PATIENTS WITH CKD

Patients with autosomal dominant polycystic kidney disease (ADPKD) often have anemia that is less severe than expected for their level of GFR, and some ADPKD patients have normal or even elevated Hb levels. Serum erythropoietin levels tend to be higher in patients with ADPKD compared to patients with other causes of CKD.[76,77] The kidneys are the source of this relatively increased erythropoietin synthesis, at least in part from interstitial cells in the vicinity of proximal tubule cysts. It is thought that local hypoxia, due to physical effects of enlarged cysts, leads to HIF activation and erythropoietin synthesis. A similar phenomenon has been described in patients with acquired renal cystic disease associated with long-standing HD treatment.[78]

Erythrocytosis is also seen in up to 20% of patients following kidney transplantation, usually within the first 1–2 years after transplantation.[79,80] The increase in plasma erythropoietin levels in this setting is due, at least in part, to increased erythropoietin production by the native kidneys, which do not respond to the usual feedback regulation, although the exact etiology of this phenomenon is not known.[81] This type of erythrocytosis may remit spontaneously or persist for years. Angiotensin II may also play a role in increasing erythropoietin, as the treatment with an ACEI or ARB is effective in reducing posttransplant erythrocytosis in most patients.[82–85] In extreme cases, phlebotomy may be necessary to reduce the risk of microvascular and thrombotic complications.

DISORDERS OF PLATELETS AND COAGULATION

An increased propensity to bleeding is present in patients with advanced CKD. Easy bruising and excessive bleeding from the skin, oral or nasal mucosa, respiratory, GI and urinary tracts, or following invasive procedures are well-known complications of advanced CKD, most notably in patients with advanced uremia and ESRD who have not been dialyzed or who are severely underdialyzed.[86,87] The bleeding tendency

seen with advanced CKD occurs despite usual normal platelet counts and normal or elevated levels of circulating clotting factors, von Willebrand factor (vWF), and fibrinogen, with normal partial thromboplastin time, prothrombin time, and International Normalized Ratio.[88] *In vivo* and *in vitro* measures of platelet function, such as the bleeding time[89] and tests of platelet aggregation or agglutination in response to epinephrine, adenosine diphosphate (ADP), or ristocetin consistently point to platelet dysfunction as a primary underlying defect for this bleeding tendency.[90–92] The specific factors in patients with advanced CKD that lead to impaired platelet function remains to be definitively identified but likely include factors intrinsic to and extrinsic to platelets. Contributing factors intrinsic to platelet dysfunction include abnormal expression of platelet glycoproteins, reduced release of ADP and serotonin from platelet granules, depressed prostaglandin metabolism, decreased platelet thromboxane A2 generation, impaired adhesion of platelet glycoprotein receptors (GPIIb/IIIa and GPIb/IX) to endothelial vWF, and abnormal platelet cytoskeletal assembly and intracellular singling pathways.[93–97] Contributing factors extrinsic to platelets include the action of "uremic toxins," anemia, increased NO, and cyclic guanosine monophosphate production, functional vWF abnormalities, decreased platelet production, and abnormal interactions between the platelet and the endothelium of the vessel wall.

The observation that uremic platelets mixed with normal plasma function normally has suggested a plasma factor as the culprit. It is also observed that mixing uremic plasma with normal platelets impairs platelet function.[98,99] Urea itself does not appear to impair platelet function or contribute to the uremic bleeding tendency seen in patients with uremia. Uremic toxins, such as guanidinosuccinic acid and phenolic compounds have been implicated in the impaired interaction between platelets and endothelial vWF multimers, thereby inhibiting ADP-mediate platelet aggregation.[100–102]

In addition to plasma abnormalities, there are also likely to be concomitant abnormalities of the vascular endothelium, at least with advanced uremia.[103] Abnormalities of the vascular endothelium appear to contribute to the impairment of platelet function in advanced CKD by impairing platelet adhesion and aggregation. Nitric oxide (NO) is an inhibitor of platelet function that is produced by endothelial cells. NO synthesis is increased in uremic patients, perhaps related to elevated levels of guanidinosuccinic acid.[104,105] Increased endothelial synthesis of platelet-inhibitory prostaglandins may also contribute.[106] Anemia contributes to platelet dysfunction by altering the flow pattern of circulating platelets to be directed more centrally within the blood vessel, instead of the normal peripheral flow, and thus, platelets are less likely to be in close contact with the endothelial surface.[107,108] Anemia may also impair platelet aggregation and plug formation by reducing availability of ADP and thromboxane, which are released by RBCs, and inhibit platelet function by reducing the availability of NO, which is bound by Hb.[109] Increased platelet surface expression of various receptors that might lead to enhanced platelet activation has also been described in patients with mild to moderate CKD. The clinical consequences of this are uncertain.

There is also some evidence to suggest that CKD is associated with an increased risk of venous thromboembolism. The etiology of this is unclear, but severity of proteinuria, underlying kidney disease, and elevated levels of fibrinogen and factor VIII may be involved.[110–114]

Treatment of Uremic Bleeding

It is unfortunately not known at what level of GFR platelet dysfunction becomes a significant clinical problem. Blood urea nitrogen and creatinine levels do not correlate well with bleeding in patients with advanced CKD.[90] Traditionally, the bleeding time has been the most common test used to assess bleeding tendency in uremia.[89] However, assessing the bleeding time in CKD patients has fallen out of favor due to its lack of sensitivity and specificity. As a result, in the absence of readily available and reliable tests of platelet function, clinical judgment must dictate decision-making regarding which patients are likely to respond to initiation of dialysis or other therapies to reverse platelet dysfunction (Table 30.2, Figure 30.2).

In undialyzed (or severely underdialyzed) patients with advanced uremia and uncontrolled bleeding, initiation of dialysis should be undertaken (if hemodialysis, not with anticoagulation), even though its effectiveness is variable and unreliable. The extent to which dialysis actually improves clinically significant bleeding remains uncertain, because most studies have examined effects on bleeding time or *in vitro* tests of platelet function that may or may not correlate with clinical bleeding, rather than evaluating active, clinical bleeding directly.[115–119] Bleeding time and some *in vitro* measures of platelet function improve in some but not all patients with initiation of dialysis. One study suggested that *in vitro* tests of platelet function improved with peritoneal dialysis but not hemodialysis.[119]

Besides initiation of dialysis, options for reversal of the platelet defect associated with kidney dysfunction include treatment with desmopressin (1-deamino-8-d-arginine vasopressin; DDAVP), cryoprecipitate, estrogens, recombinant human erythropoietin (or similar agents), tranexamic acid, and RBC transfusion. DDAVP,

TABLE 30.2 Treatments for Hemostasis Abnormalities of Chronic Kidney Disease

For acute/active bleeding

Initiation or intensification of dialysis (without anticoagulation if hemodialysis) Desmopressin (DDAVP)
Dose: 0.3–0.4 μg/kg IV or 3 ug/kg intranasally

Transfusion of packed red blood cells
Goal: Hemoglobin ~10 g/dL

Cryoprecipitate
Dose: 10 units IV (American Red Cross prepared) every 12 to 24 hr

For chronic bleeding or in preparation for invasive procedure

ESA to improve anemia
Goal: Hemoglobin ~10 g/dL

Conjugated estrogens
Dose: 0.6 mg/kg IV for 5 days; oral 50 mg daily; transdermal 17β-estradiol 50–100 μg/24 hr

To consider if above options are ineffective

Tranexamic acid
Dose: 10 mg/kg IV with infusion of 0.5–1.5 mg/kg/hr

Factor VII

a synthetic form of vasopressin, improves platelet function at least in part by stimulating release of large vWF multimers from endothelial cells.[120,121] DDAVP may also have direct effects on platelet aggregation and increase platelet surface GP Ib/IX and some circulating clotting factor concentrations such as factor VIII. DDAVP may be given intravenously or subcutaneously with reduction in the bleeding time within 1–2 hours, an effect lasting up to 8 hours. Tachyphylaxis, presumably due to depletion of endothelial stores of vWF multimers, limits the effectiveness of DDAVP after the first or second dose.[122] The short duration of action of DDAVP and the development of tachyphylaxis limit its use to attempt to prevent bleeding with invasive procedures (e.g. kidney biopsy, surgery) or use in the initial efforts to control active bleeding while also administering other therapies that have more prolonged effects. Many, but not all, patients treated with DDAVP have improvement in bleeding time.[123–126] Reduction in actual bleeding or reduction in bleeding risk with invasive procedures has never been documented with the use of DDAVP. The currently available studies on DDAVP have been

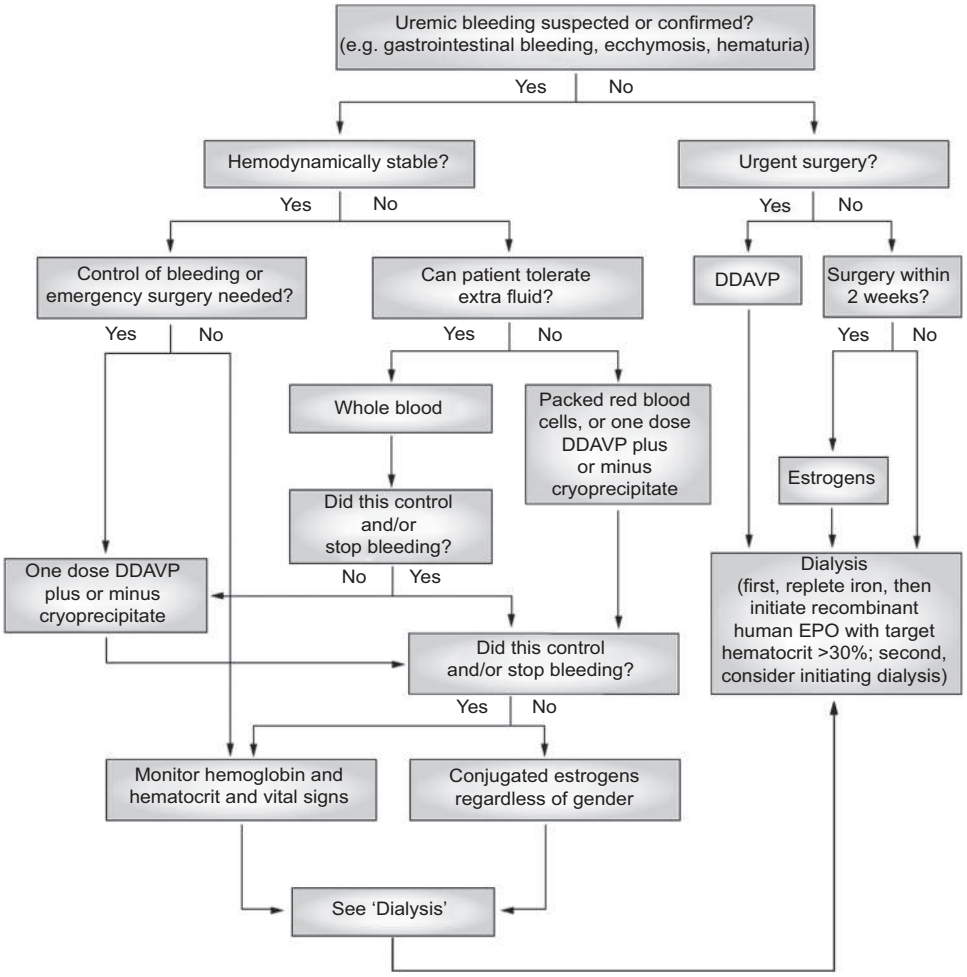


FIGURE 30.2 Suggested algorithm for management of patients with uremic platelet dysfunction and bleeding. *From reference 90.*

limited to assessments of its use with bleeding time or have been uncontrolled clinical observations.

Transfusion of RBCs to an Hb level of about 10 g/dL may also improve platelet dysfunction in patients with advanced CKD. It is thought that increasing the overall RBC supply in circulation will force platelets from the central location in the blood vessel to a more peripheral location, closer to the endothelium.[108] For chronic bleeding, an increase in the RBC supply can also be obtained with the use of ESAs.[127,128] ESAs also have direct effects on platelet number and platelet signaling, adhesion, and aggregation.[129,130] The elevated Hb concentration may also improve platelet function through enhanced binding of NO.[109]

Administration of cryoprecipitate may also have a role in the treatment of CKD patients with active bleeding who do not respond to local measures, DDVAP, and blood transfusions, or who are undergoing surgery.[131–133] Cryoprecipitate is enriched with vWF, factor VIII, and fibrinogen. Limited experience suggests that cryoprecipitate infusion can reduce the bleeding time in some patients and perhaps reduce operative blood loss. When effective in reducing the bleeding time, cryoprecipitate infusion does so within about an hour. Risks of cryoprecipitate administration include transmission of infectious agents and allergic reactions, including anaphylaxis.

Tranexamic acid is an inhibitor of fibrinolysis that reduces bleeding time and improves impaired platelet function in patients with advanced CKD.[134,135] Recombinant activated factor VII has also been reported to stop bleeding following a kidney biopsy that did not respond to DDAVP.[136] Further study will be needed to assess the role of both of these interventions.

For chronic bleeding, treatment with estrogens should be considered as conjugated estrogens reduce bleeding time. Effects on clinical bleeding or evidence that estrogens reduce bleeding risk following invasive procedures remains to be fully demonstrated, although estrogens have been reported to be useful in control of GI tract bleeding in patients with both acute and chronic renal failure.[107,137–143] Treatment with intravenous, oral, or transdermal estrogens reduces bleeding time within a day or two in some patients, with a lasting effect persisting for as long as 10–14 days after treatment is stopped. The mechanism of action is unknown, although effects of estrogen on NO have been postulated.[144] Estrogen-related side effects may limit its long-term use.

CONCLUSIONS

Anemia is a relatively common complication of CKD, particularly when the GFR declines to less than 30–40 mL/min. The most important factor contributing to this anemia is the relative deficiency of erythropoietin. Iron deficiency is also a common contributing factor. Erythrocytosis is a much less common occurrence in patients with CKD and is mostly seen in patients with polycystic kidney disease or following kidney transplantation. Defective platelet function occurs in some patients with advanced CKD but is not a common problem in those with mild to moderate CKD. Several treatments for platelet dysfunction in patients with CKD at risk for bleeding are available, but knowledge regarding their clinical efficacy is limited in the absence of appropriate well-designed randomized controlled clinical trials.

References

1. Hsu C, Bates D, Kuperman G, Curhan G. Relationship between hematocrit and renal function in men and women. *Kidney Int* 2001;**59**(2):725–31.
2. Cuijpers P, Reynolds 3rd C, Donker T, Li J, Andersson G, Beekman A. A personalized treatment of adult depression: medication, psychotherapy, or both? A systematic review. *Depress Anxiety* 2012;**29**(10):855–64.
3. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988–1994). *Arch Intern Med* 2002;**162**(12):1401–8.
4. Finkelstein F, Story K, Firanek C, et al. Health-related quality of life and hemoglobin levels in chronic kidney disease patients. *Clin J Am Soc Nephrol* 2009;**4**(1):33–8.
5. Regidor DL, Kopple JD, Kovesdy CP, et al. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. *J Am Soc Nephrol* 2006;**17**(4):1181–91.
6. KDOQI. Clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis* 2006;**47**(5 Suppl. 3):S11–145.
7. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2012;**2**:279–335.
8. Hsu C, McCulloch C, Curhan G. Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: results from the Third National Health and Nutrition Examination Survey. *J Am Soc Nephrol* 2002;**13**(2):504–10.
9. Clase C, Kiberd B, Garg A. Relationship between glomerular filtration rate and the prevalence of metabolic abnormalities: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Nephron Clin Pract* 2007;**105**(4):c178–84.
10. McFarlane S, Chen S, Whaley-Connell A, et al. Prevalence and associations of anemia of CKD: kidney early evaluation program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999–2004. *Am J Kidney Dis* 2008;**51**(4 Suppl. 2): S46–55.
11. Ibrahim H, Wang C, Ishani A, Collins A, Foley R. Screening for chronic kidney disease complications in US adults: racial implications of a single GFR threshold. *Clin J Am Soc Nephrol* 2008;**3**(6): 1792–9.
12. Ishimura E, Nishizawa Y, Okuno S, Matsumoto N, Emoto M, Inaba M, et al. Diabetes mellitus increases the severity of anemia in non-dialyzed patients with renal failure. *J Nephrol* 1998;**11**(2): 83–6.

13. El-Achkar T, Ohmit S, McCullough P, et al. Higher prevalence of anemia with diabetes mellitus in moderate kidney insufficiency: the kidney early evaluation program. *Kidney Int* 2005;**67**(4):1483–8.
14. Bosman D, Winkler A, Marsden J, Macdougall I, Watkins P. Anemia with erythropoietin deficiency occurs early in diabetic nephropathy. *Diabetes Care* 2001;**24**(3):495–9.
15. Koury S, Bondurant M, Koury M. Localization of erythropoietin synthesizing cells in murine kidneys by in situ hybridization. *Blood* 1988;**71**(2):524–7.
16. Koury S, Koury M, Bondurant M, Caro J, Graber S. Quantitation of erythropoietin-producing cells in kidneys of mice by in situ hybridization: correlation with hematocrit, renal erythropoietin mRNA, and serum erythropoietin concentration. *Blood* 1989; **74**(2):645–51.
17. Maxwell P, Osmond M, Pugh C, et al. Erythropoietin-producing cells in transgenic mice expressing SV40 large T antigen directed by erythropoietin control sequences. *Ann NY Acad Sci* 1994;**718**: 356–8.
18. Bachmann S, Le Hir M, Eckardt K. Co-localization of erythropoietin mRNA and ecto-5′-nucleotidase immunoreactivity in peritubular cells of rat renal cortex indicates that fibroblasts produce erythropoietin. *J Histochem Cytochem* 1993;**41**(3):335–41.
19. Bunn HF. Erythropoietin. *Cold Spring Harb Perspect Med* 2013;**3**(3): a011619.
20. Sasaki H, Bothner B, Dell A, Fukuda M. Carbohydrate structure of erythropoietin expressed in Chinese hamster ovary cells by a human erythropoietin cDNA. *J Biol Chem* 1987;**265**(25):12059–76.
21. Takeuchi M, Inoue N, Strickland T, et al. Relationship between sugar chain structure and biological activity of recombinant human erythropoietin produced in Chinese hamster ovary cells. *Proc Natl Acad Sci USA* 1989;**86**(20):7819–22.
22. Egrie J, Browne J. Development and characterization of novel erythropoiesis stimulating protein (NESP). *Nephrol Dial Transplant* 2001;**16**(Suppl. 3):3–13.
23. Haase VH. Hypoxic regulation of erythropoiesis and iron metabolism. *Am J Physiol Renal Physiol* 2010;**299**(1):F1–13.
24. Kapitsinou PP, Liu Q, Unger TL, et al. Hepatic HIF-2 regulates erythropoietic responses to hypoxia in renal anemia. *Blood* 2010; **116**(16):3039–48.
25. Wenger R, Hoogewijs D. Regulated oxygen sensing by protein hydroxylation in renal erythropoietin-producing cells. *Am J Physiol Renal Physiol* 2010;**298**(6):F1287–96.
26. Ivan M, Yang H, Kim W, et al. HIFalpha targeted for VHL-mediated destruction by proline hydroxylation: implications for O2 sensing. *Science* 2001;**292**(5516):464–8.
27. West J. Physiological effects of chronic hypoxia. *N Engl J Med* 2017; **376**:1965–71.
28. Zhu H, Bunn H. Oxygen sensing and signaling: impact on the regulation of physiologically important genes. *Respir Physiol* 1999;**115**(2):239–47.
29. Witthuhn B, Quelle F, Silvennoinen O, et al. JAK2 associates with the erythropoietin receptor and is tyrosine phosphorylated and activated following stimulation with erythropoietin. *Cell* 1993; **74**(2):227–36.
30. Remy I, Wilson I, Michnick S. Erythropoietin receptor activation by a ligand-induced conformation change. *Science* 1999;**283**(5404): 990–3.
31. Penta K, Sawyer S. Erythropoietin induces the tyrosine phosphorylation, nuclear translocation, and DNA binding of STAT1 and STAT5 in erythroid cells. *J Biol Chem* 1995;**270**(52):31282–7.
32. Koury MJ, Bondurant MC. Erythropoietin retards DNA breakdown and prevents programmed death in erythroid progenitor cells. *Science* 1990;**248**(4953):378–81.
33. Koury MJ, Bondurant MC. Control of red cell production: the roles of programmed cell death (apoptosis) and erythropoietin. *Transfusion* 1990;**30**(8):673–4.
34. Youssoufian H, Longmore G, Neumann D, Yoshimura A, Lodish H. Structure, function, and activation of the erythropoietin receptor. *Blood* 1993;**81**(9):2223–36.
35. Radtke H, Claussner A, Erbes P, Scheuermann E, Schoeppe W, Koch K. Serum erythropoietin concentration in chronic renal failure: relationship to degree of anemia and excretory renal function. *Blood* 1979;**54**(4):877–84.
36. Fehr T, Ammann P, Garzoni D, et al. Interpretation of erythropoietin levels in patients with various degrees of renal insufficiency and anemia. *Kidney Int* 2004;**66**(3):1206–11.
37. Maxwell P, Ferguson D, Nicholls L, Johnson M, Ratcliffe P. The interstitial response to renal injury: fibroblast-like cells show phenotypic changes and have reduced potential for erythropoietin gene expression. *Kidney Int* 1997;**52**(3):715–24.
38. Kaartinen K, Syrjanen J, Porsti I, et al. Insulin resistance and the progression of IgA nephropathy. *Nephrol Dial Transplant* 2007;**22**: 778–83.
39. Babitt J, Lin H. Molecular mechanisms of hepcidin regulation: implications for the anemia of CKD. *Am J Kidney Dis* 2010;**55**(4): 726–41.
40. Sangkhae V, Nemeth E. Regulation of the iron homeostatic hormone hepcidin. *Adv Nutr* 2017;**8**(1):126–36.
41. Ganz T, Nemeth E. Iron imports. IV. Hepcidin and regulation of body iron metabolism. *Am J Physiol Gastrointest Liver Physiol* 2006;**290**(2):G199–203.
42. Nemeth E, Ganz T. Regulation of iron metabolism by hepcidin. *Annu Rev Nutr* 2006;**26**:323–42.
43. Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science* 2004;**306**(5704):2090–3.
44. Camaschella C, Pagani A, Nai A, Silvestri L. The mutual control of iron and erythropoiesis. *Int J Lab Metabol* 2016;**38**(S1):20–6.
45. Nemeth E, Rivera S, Gabayan V, et al. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *J Clin Investig* 2004;**113**(9):1271–6.
46. Trombini P, Paolini V, Pelucchi S, et al. Hepcidin response to acute iron intake and chronic iron loading in dysmetabolic iron overload syndrome. *Liver Int* 2011;**31**(7):994–1000.
47. Nicolas G, Chauvet C, Viatte L, et al. The gene encoding the iron regulatory peptide hepcidin is regulated by anemia, hypoxia, and inflammation. *J Clin Investig* 2002;**110**(7):1037–44.
48. Andriopoulos JB, Gorradini E, Xia Y, et al. BMP6 is a key endogenous regulator of hepcidin expression and iron metabolism. *Nat Genet* 2009;**41**(4):482–7.
49. Babitt J, Huang F, Wrighting D, et al. Bone morphogenetic protein signaling by hemojuvelin regulates hepcidin expression. *Nat Genet* 2006;**38**(5):531–9.
50. Deira J, Martin M, Sanchez S, Garrido J, Nunez J, Tabernero J. Evaluation of intestinal iron absorption by indirect methods in patients on hemodialysis receiving oral iron and recombinant human erythropoietin. *Am J Kidney Dis* 2002;**39**(3):594–9.
51. Skikne B, Ahluwalia N, Fergusson B, Chonko A, Cook J. Effects of erythropoietin therapy on iron absorption in chronic renal failure. *J Lab Clin Med* 2000;**135**(6):452–8.

52. NKF-K/DOQI. Clinical practice guidelines for anemia of chronic kidney disease: update 2000. *Am J Kidney Dis* 2001;**37**(1 Suppl. 1): S182–238.
53. Ford B, Eby C, Scott M, Coyne D. Intra-individual variability in serum hepcidin precludes its use as a marker of iron status in hemodialysis patients. *Kidney Int* 2010;**78**(8):769–73.
54. Coyne D. Hepcidin: clinical utility as a diagnostic tool and therapeutic target. *Kidney Int* 2011;**80**(3):240–4.
55. Ferrari P, Kulkarni H, Dheda S, et al. Serum iron markers are inadequate for guiding iron repletion in chronic kidney disease. *Clin J Am Soc Nephrol* 2011;**6**(1):77–83.
56. Stancu S, Stanciu A, Zugravu A, et al. Bone marrow iron, iron indices, and the response to intravenous iron in patients with non-dialysis-dependent CKD. *Am J Kidney Dis* 2010;**55**(4): 639–47.
57. Stancu S, Barsan L, Stanciu A, Mircescu G. Can the response to iron therapy be predicted in anemic nondialysis patients with chronic kidney disease? *Clin J Am Soc Nephrol* 2010;**5**(3): 409–16.
58. Wu S, Jeng F, Wei S, et al. Red blood cell osmotic fragility in chronically hemodialyzed patients. *Nephron* 1998;**78**(1):28–32.
59. Ly J, Marticorena R, Donnelly S. Red blood cell survival in chronic renal failure. *Am J Kidney Dis* 2004;**44**(4):715–9.
60. Bonomini M, Zammit V, Pusey C, De Vecchi A, Arduini A. Pharmacological use of L-carnitine in uremic anemia: has its full potential been exploited? *Pharmacol Res* 2011;**63**(3):157–64.
61. Bonomini M, Sirolli V, Reale M, Arduini A. Involvement of phosphatidylserine exposure in the recognition and phagocytosis of uremic erythrocytes. *Am J Kidney Dis* 2001; **37**(4):807–14.
62. Brimble K, McFarlane A, Winegard N, Crowther M, Churchill D. Effect of chronic kidney disease on red blood cell rheology. *Clin Hemorheol Microcirc* 2006;**34**(3):411–20.
63. Golper T, Goral S, Becker B, Langman C. L-carnitine treatment of anemia. *Am J Kidney Dis* 2003;**41**(4 Suppl. 4):S27–34.
64. Ma J, Dou Y, Zhang H, et al. Correlation between inflammatory biomarkers and red blood cell life span in chronic hemodialysis patients. *Blood Purif* 2017;**43**:200–5.
65. Onoyama K, Sanai T, Motomura K, Fujishima M. Worsening of anemia by angiotensin converting enzyme inhibitors and its prevention by antiestrogenic steroid in chronic hemodialysis patients. *J Cardiovasc Pharmacol* 1989;**13**(Suppl. 3):S27–30.
66. Le Meur Y, Lorgeot V, Comte L, Szelag J, Aldigier J, Leroux-Robert C, et al. Plasma levels and metabolism of AcSDKP in patients with chronic renal failure: relationship with erythropoietin requirements. *Am J Kidney Dis* 2001;**38**(3):510–7.
67. Hirakata H, Onoyama K, Hori K, F M. Participation of the renin-angiotensin system in the captopril-induced worsening of anemia in chronic hemodialysis patients. *Clin Nephrol* 1986;**26**(1): 27–32.
68. Cruz D, Perazella M, Abu-Alfa A, Mahnensmith R. Angiotensin-converting enzyme inhibitor therapy in chronic hemodialysis patients: any evidence of erythropoietin resistance? *Am J Kidney Dis* 1996;**28**(4):535–40.
69. Keithi-Reddy S, Addabbo F, Patel T, Mittal B, Goligorsky M, Singh A. Association of anemia and erythropoiesis stimulating agents with inflammatory biomarkers in chronic kidney disease. *Kidney Int* 2008;**74**(6):782–90.
70. Goicoechea M, Martin J, de Sequera P, Quiroga J, Ortiz A, Carreno V, et al. Role of cytokines in the response to erythropoietin in hemodialysis patients. *Kidney Int* 1998;**54**(4):1337–43.
71. Wagner M, Alam A, Zimmermann J, Rauh K, Koljaja-Batzner A, Raff U, et al. Endogenous erythropoietin and the association with inflammation and mortality in diabetic chronic kidney disease. *Clin J Am Soc Nephrol* 2011;**6**(7):1573–9.
72. Inrig J, Bryskin S, Patel U, Arcasoy M, Szczech L. Association between high-dose erythropoiesis-stimulating agents, inflammatory biomarkers, and soluble erythropoietin receptors. *BMC Nephrol* 2011;**12**:67.
73. Adamson J. Hyporesponsiveness to erythropoiesis stimulating agents in chronic kidney disease: the many faces of inflammation. *Adv Chron Kidney Dis* 2009;**16**(2):76–82.
74. Chonchol M, Lippi G, Montagnana M, Muggeo M, Targher G. Association of inflammation with anaemia in patients with chronic kidney disease not requiring chronic dialysis. *Nephrol Dial Transplant* 2008;**23**(9):2879–83.
75. Macdougall I, Cooper A. Erythropoietin resistance: the role of inflammation and pro-inflammatory cytokines. *Nephrol Dial Transplant* 2002;**17**(Suppl. 11):39–43.
76. de Almeida EA, Alho I, Marques F, Thiran C, Bicho MP, Prata M. Haemoglobin and erythropoietin levels in polycystic kidney disease. *Nephrol Dial Transplant* 2008;**23**(1):412–3.
77. Eckardt K, Mollmann M, Neumann R, Brunkhorst R, Burger H, Lonnemann G, et al. Erythropoietin in polycystic kidneys. *J Clin Investig* 1989;**84**(4):1160–6.
78. Goldsmith H, Ahmad R, Raichura N, Lal S, McConnell C, Gould D, et al. Association between rising haemoglobin concentration and renal cyst formation in patients on long term regular haemodialysis treatment. *Proc Eur Dial Transpl Assoc* 1983;**19**: 313–8.
79. Wickre C, Norman D, Bennison A, Barry J, Bennett W. Postrenal transplant erythrocytosis: a review of 53 patients. *Kidney Int* 1983;**23**(5):731–7.
80. Vlahakos D, Marathias K, Agroyannis B, Madias N. Posttransplant erythrocytosis. *Kidney Int* 2003;**63**(4):1187–94.
81. Maktouf C, Yaich S, Aloui S, et al. Angiogenic activity in the sera of patients with post-kidney transplant erythrocytosis. *Saudi J Kidney Dis Transpl* 2014;**25**(5):1026–9.
82. Montanaro D, Gropuzzo M, Tulissi P, Boscutti G, Risaliti A, Baccarani U, et al. Angiotensin-converting enzyme inhibitors reduce hemoglobin concentrations, hematocrit, and serum erythropoietin levels in renal transplant recipients without posttransplant erythrocytosis. *Transplant Proc* 2001;**33**:1–2.
83. Navarro J, Garcia J, Macia M, Mora C, Chahin J, Gallego E, et al. Effects of losartan on the treatment of posttransplant erythrocytosis. *Clin Nephrol* 1998;**49**(6):370–2.
84. Perazella M, McPhedran P, Kliger A, Lorber M, Levy E, Bia M. Enalapril treatment of posttransplant erythrocytosis: efficacy independent of circulating erythropoietin levels. *Am J Kidney Dis* 1995;**26**(3):495–500.
85. Kujawa-Szewieczek A, Kolonko A, Kocierz M, Szotowska M, Trusolt W, Karkoszka H, et al. Association between gene polymorphisms of the components of the renin-angiotensin-aldosteron system, graft function, and the prevalence of hypertension, anemia, and erythrocytosis after kidney transplantation. *Transplant Proc* 2011;**43**(8):2957–63.
86. Ferguson J, Lewis J, Zucker M. Bleeding tendency in uremia. *Blood* 1956;**11**(12):1073–6.
87. Remuzzi G. Bleeding disorders in uremia: pathophysiology and treatment. *Adv Nephrol Necker Hosp* 1989;**18**:171–86.
88. Lambert M. Platelets in liver and renal disease. *Hematol Am Soc Hematol Educ Prog* 2016;**2016**(1):251–5.

89. Steiner R, Coggins C, Carvalho A. Bleeding time in uremia: a useful test to assess clinical bleeding. *Am J Hematol* 1979;**7**(2): 107–17.
90. Hedges SJ, Dehoney SB, Hooper JS, Amanzadeh J, Busti AJ. Evidence-based treatment recommendations for uremic bleeding. *Nat Clin Pract Nephrol* 2007;**3**(3):138–53.
91. Di Minno G, Martinez J, McKean M, De La Rosa J, Burke J, Murphy S. Platelet dysfunction in uremia. Multifaceted defect partially corrected by dialysis. *Am J Med* 1985;**79**(5):552–9.
92. Castaman G, Rodeghiero F, Lattuada A, La Greca G, Mannucci P. Multimeric pattern of plasma and platelet von Willebrand factor is normal in uremic patients. *Am J Hematol* 1993;**44**(4):266–9.
93. Sohal A, Gangji A, Crowther M, Treleaven D. Uremic bleeding: pathophysiology and clinical risk factors. *Thromb Res* 2006; **118**(3):417–22.
94. Warrell Jr R, Hultin M, Coller B. Increased factor VIII/von Willebrand factor antigen and von Willebrand factor activity in renal failure. *Am J Med* 1979;**66**(2):226–8.
95. Escolar G, Monteagudo J, Castillo R, Cases A, Garrido M, Ordinas A. Ultrastructural immunolocalization and morphometric quantification of platelet membrane GPIb and GPIIb-IIIa in uremic patients. *Prog Clin Biol Res* 1988;**283**:197–201.
96. Castillo R, Lozano T, Escolar G, Revert L, Lopez J, Ordinas A. Defective platelet adhesion on vessel subendothelium in uremic patients. *Blood* 1986;**68**(2):337–42.
97. Escolar G, Diaz-Ricart M, Cases A, Castillo R, Ordinas A, White J. Abnormal cytoskeletal assembly in platelets from uremic patients. *Am J Pathol* 1993;**143**(3):823–31.
98. Escolar G, Diaz-Ricart M, Cases A. Uremic platelet dysfunction: past and present. *Curr Hematol Rep* 2005;**4**(5):359–67.
99. Cases A, Escolar G, Reverter J, Ordinas A, Lopez-Pedret J, Revert L, et al. Recombinant human erythropoietin treatment improves platelet function in uremic patients. *Kidney Int* 1992; **42**(3):668–72.
100. Horowitz H, Stein I, Cohen B, White J. Further studies on the platelet-inhibitory effect of guanidinosuccinic acid and its role in uremic bleeding. *Am J Med* 1970;**49**(3):336–45.
101. Rabiner S. Bleeding in uremia. *Med Clin North Am* 1972;**56**(1): 221–33.
102. Rabiner S, Molinas F. The role of phenol and phenolic acids on the thrombocytopathy and defective platelet aggregation of patients with renal failure. *Am J Med* 1970;**49**(3):345–51.
103. Remuzzi G, Bertani T, Livio M, Cavenaghi A, Mysliwiec M, Marchesi D, et al. Vascular factors in the pathogenesis of uraemic bleeding. *Proc Eur Dial Transpl Assoc* 1978;**15**:449–55.
104. Noris M, Benigni A, Boccardo P, Aiello S, Gaspari F, Todeschini M, et al. Enhanced nitric oxide synthesis in uremia: implications for platelet dysfunction and dialysis hypotension. *Kidney Int* 1993; **44**(2):445–50.
105. Remuzzi G, Perico N, Zoja C, Corna D, Macconi D, Vigano G. Role of endothelium-derived nitric oxide in the bleeding tendency of uremia. *J Clin Investig* 1990;**86**(5):1768–71.
106. Remuzzi G, Marchesi D, Cavenaghi A, Livio M, Donati M, de Gaetanon G, et al. Bleeding in renal failure: a possible role of vascular prostacyclin (PGI2). *Clin Nephrol* 1979;**12**(3):127–31.
107. Livio M, Gotti E, Marchesi D, Mecca G, Remuzzi G, de Gaetano G. Uraemic bleeding: role of anaemia and beneficial effect of red cell transfusions. *Lancet* 1982;**2**(8306):1013–5.
108. Fernandez F, Goudable C, Sie P, Ton-That H, Durand D, Suc J, et al. Low haematocrit and prolonged bleeding time in uraemic patients: effect of red cell transfusions. *Br J Haematol* 1985;**59**(1): 139–48.
109. Martin W, Villani G, Jothianandan D, Furchgott R. Blockade of endothelium-dependent and glyceryl trinitrate-induced relaxation of rabbit aorta by certain ferrous hemoproteins. *J Pharmacol Exp Ther* 1985;**233**(3):679–85.
110. Cheung KL, Zakai NA, Folsom AR, Kurella Tamura M, Peralta CA, Judd SE, Callas PW, Cushman M. Measures of kidney disease and the risk of venous thromboembolism in the REGARDS (reasons for geographic and racial differences in stroke) study. *Am J Kidney Dis* 2017;**70**(2):182–90.
111. Rattazzi M, Villalta S, De Lucchi L, Sponchiado A, Galliazzo S, Faggin E, Pagliara V, Zilli C, Callegari E, Caberlotto L, Puato M, Pauletto P. Chronic kidney disease is associated with increased risk of venous thromboembolism recurrence. *Thromb Res* 2017; **160**:32–7.
112. Massicotte-Azarniouch D, Bader Eddeen A, Lazo-Langner A, Molnar AO, Lam NN, McCallum MK, Bota S, Zimmerman D, Garg AX, Harel Z, Perl J, Wald R, Sood MM. Risk of venous thromboembolism in patients by albuminuria and estimated GFR. *Am J Kidney Dis* 2017;**70**(6):826–33.
113. Cheung KL, Bouchard BA, Cushman M. Venous thromboembolism, factor VIII and chronic kidney disease. *Thromb Res* 2018; **170**:10–9.
114. Gäckler A, Rohn H, Lisman T, Benkö T, Witzke O, Kribben A, Saner FH. Evaluation of hemostasis in patients with end-stage renal disease. *PLoS One* 2019;**14**(2):e0212237.
115. Lindsay RM, Friesen M, Koens F, Linton AL, Oreopoulos D, de Veber G. Platelet function in patients on long term peritoneal dialysis. *Clin Nephrol* 1976;**6**(2):335–9.
116. Lindsay RM, Friesen M, Aronstam A, Andrus F, Clark WF, Linton A. Improvement of platelet function by increased frequency of hemodialysis. *Clin Nephrol* 1978;**10**(2):67–70.
117. Stewart JH, Castaldi PA. Uraemic bleeding: a reversible platelet defect corrected by dialysis. *Q J Med* 1967;**36**(143):409–23.
118. Rabiner SF. The effect of dialysis on platelet function of patients with renal failure. *Ann NY Acad Sci* 1972;**201**:234–42.
119. Nenci GG, Berrettini M, Agnelli G, Parise P, Buoncristiani U, Ballatori E. Effect of peritoneal dialysis, haemodialysis and kidney transplantation on blood platelet function. I. Platelet aggregation by ADP and epinephrine. *Nephron* 1979;**23**(6): 287–92.
120. Prowse CV, Sas G, Gader AM, Cort JH, Cash JD. Specificity in the factor VIII response to vasopressin infusion in man. *Br J Haematol* 1979;**41**(3):437–47.
121. Zeigler ZR, Megaludis A, Fraley D. Desmopressin (d-DAVP) effects on platelet rheology and von Willebrand factor activities in uremia. *Am J Hematol* 1992;**39**(2):90–5.
122. Canavese C, Salomone M, Pacitti A, Mangiarotti G, Calitri V. Reduced response of uraemic bleeding time to repeated doses of desmopressin. *Lancet* 1985;**1**(8433):867–8.
123. Mannucci P, Remuzzi G, Pusineri F, Lombardi R, Valsecchi C, Mecca G, et al. Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med* 1983;**308**(1):8–12.
124. Vigano G, Mannucci P, Lattuada A, Harris A, Remuzzi G. Subcutaneous desmopressin (DDAVP) shortens the bleeding time in uremia. *Am J Hematol* 1989;**31**(1):32–5.
125. Watson A, Keogh J. Effect of 1-deamino-8-D-arginine vasopressin on the prolonged bleeding time in chronic renal failure. *Nephron* 1982;**32**(1):49–52.
126. Kohler M, Hellstern P, Tarrach H, Bambauer R, Wenzel E, Jutzler G. Subcutaneous injection of desmopressin (DDAVP): evaluation of a new, more concentrated preparation. *Haemostasis* 1989;**19**(1):38–44.

127. Vigano G, Benigni A, Mendogni D, Mingardi G, Mecca G, Remuzzi G. Recombinant human erythropoietin to correct uremic bleeding. *Am J Kidney Dis* 1991;**18**(1):44−9.
128. Zwaginga J, Jsseldijk M, de Groot P, Kooistra K, Vos J, van Es A, et al. Treatment of uremic anemia with recombinant erythropoietin also reduces the defects in platelet adhesion and aggregation caused by uremic plasma. *Thromb Haemost* 1991;**66**(6):638−47.
129. Diaz-Ricart M, Etebanell E, Cases A, Lopez-Pedret J, Castillo R, Ordinas A, et al. Erythropoietin improves signaling through tyrosine phosphorylation in platelets from uremic patients. *Thromb Haemost* 1999;**82**(4):1312−7.
130. Tassies D, Reverter J, Cases A, Calls J, Escolar G, Ordinas A. Effect of recombinant human erythropoietin treatment on circulating reticulated platelets in uremic patients: association with early improvement in platelet function. *Am J Hematol* 1998;**59**(2):105−9.
131. Janson PA, Jubelirer SJ, Weinstein MJ, Deykin D. Treatment of the bleeding tendency in uremia with cryoprecipitate. *N Engl J Med* 1980;**303**(23):1318−22.
132. Triulzi D, Blumberg N. Variability in response to cryoprecipitate treatment for hemostatic defects in uremia. *Yale J Biol Med* 1990; **63**(1):1−7.
133. Davenport R. Cryoprecipitate for uremic bleeding. *Clin Pharm* 1991;**10**(6):429.
134. Sabovic M, Lavre J, Vujkovac B. Tranexamic acid is beneficial as adjunctive therapy in treating major upper gastrointestinal bleeding in dialysis patients. *Nephrol Dial Transplant* 2003;**18**(7): 1388−91.
135. Downey P, Tagle R, Pereira J, Mezzano D. Tranexamic acid and uremic bleeding: evidence-based treatment recommendations. *Nat Clin Pract Nephrol* 2007;**3**(6):E2.
136. Maksimovic B, Neretljak I, Vidas Z, Vojtusek I, Tomulic K, Knotek M. Treatment of bleeding after kidney biopsy with recombinant activated factor VII. *Blood Coagul Fibrinolysis* 2012;**23**(3): 241−3.
137. Liu Y, Kosfeld R, Marcum S. Treatment of uraemic bleeding with conjugated oestrogen. *Lancet* 1984;**2**(8408):887−90.
138. Vigano G, Gaspari F, Locatelli M, Pusineri F, Bonati M, Remuzzi G. Dose-effect and pharmacokinetics of estrogens given to correct bleeding time in uremia. *Kidney Int* 1988;**34**(6):853−8.
139. Sloand J, Schiff M. Beneficial effect of low-dose transdermal estrogen on bleeding time and clinical bleeding in uremia. *Am J Kidney Dis* 1995;**26**(1):22−6.
140. Heunisch C, Resnick D, Vitello J, Martin S. Conjugated estrogens for the management of gastrointestinal bleeding secondary to uremia of acute renal failure. *Pharmacotherapy* 1998;**18**(1): 210−7.
141. Heistinger M, Stockenhuber F, Schneider B, Pabinger I, Brenner B, Wagner B, et al. Effect of conjugated estrogens on platelet function and prostacyclin generation in CRF. *Kidney Int* 1990;**38**(6):1181−6.
142. Shemin D, Elnour M, Amarantes B, Abuelo J, Chazan J. Oral estrogens decrease bleeding time and improve clinical bleeding in patients with renal failure. *Am J Med* 1990;**89**(4):436−40.
143. Gonzalez J, Bryant S, Hermes-DeSantis E. Transdermal estradiol for the management of refractory uremic bleeding. *Am J Health Syst Pharm* 2018;**75**(9):e177−83.
144. Noris M, Todeschini M, Zappella S, Bonazzola S, Zoja C, Corna D, et al. 17beta-estradiol corrects hemostasis in uremic rats by limiting vascular expression of nitric oxide synthases. *Am J Physiol Renal Physiol* 2000;**279**(4):F626−35.

QUESTIONS AND ANSWERS

Question 1

A 51-year-old woman is referred to the nephrology clinic for management of CKD secondary to diabetic nephropathy. Serum creatinine (S[Cr]) is 2.1 mg/dL (eGFR 25 mL/min/1.73 m^2). She is taking lisinopril 40 mg daily and hydrochlorothiazide 25 mg daily. Her review of systems is completely negative. On examination, her blood pressure is 135/75 mm Hg. Her hemoglobin concentration is 11 g/dL, MCV 85 fL, serum ferritin 110 ng/mL, percent saturation of iron is 25%.

Which ONE of the following is NOT correct regarding her anemia?

A. Anemia is hypoproliferative with a low reticulocyte count
B. Anemia is associated with hospitalization risk, cognitive dysfunction and death
C. Anemia tends to develop at a higher level of GFR in diabetics vs. nondiabetics
D. She does not have anemia since her hemoglobin is greater than 10 g/dL

Answer: D

Answers A, B, C, are correct and answer D is not correct and therefore the answer to this question. **Answer D** is not correct because anemia is diagnosed when hemoglobin concentration is <13.0–13.5 g/dL in men and <12.0 g/dL in women.[6] **Answer A** is accurate as the anemia of CKD is hypoproliferative and associated with a low reticulocyte count. The primary cause is deficiency of erythropoietin. **Answer B** is accurate as evidenced by observational studies demonstrating an association between anemia in CKD and a higher risk of hospitalization, cognitive dysfunction, and death.[4,5] **Answer C** is accurate because anemia tends to develop at a higher level of GFR in diabetics than nondiabetics.[10–12] The exact reasons for this observation are not clear.

Question 2

A 67-year-old woman with membranous glomerulonephritis and an eGFR of 23 mL/min/1.73 m^2 presents with a hemoglobin of 11.5 g/dL.

Which of the following is NOT true regarding control of erythropoiesis in this patient:

A. The transcription factor HIF binds to a hypoxia response element in the erythropoietin gene to increase transcription of erythropoietin
B. An erythropoietin receptor is present on colony-forming units-erythroid (CFU-E) and other erythroid progenitor cells
C. In the presence of erythropoietin CFU-E develop into mature erythrocytes due to reduced apoptosis
D. Inflammatory cytokines such as TNF-α stimulate erythropoiesis

Answer: D

Answer D is the one answer that is NOT true. In CKD patients inflammatory cytokines such as TNF-α, interferon-γ, IL-6, and TGF-β inhibit erythropoiesis and contribute to anemia and erythropoietin resistance.[36–42] **Answer A** is accurate as the transcription factor HIF, a dimer comprised of HIFα and HIFβ subunits, binds to a hypoxia response element in the erythropoietin gene and other related hypoxia-responsive genes, increasing their transcription.[23,24] **Answer B** is accurate as an erythropoietin receptor is present on colony-forming units-erythroid (CFU-E) and other erythroid progenitor cells.[30] Binding of erythropoietin to its receptor results in a signaling cascade leading to increased numbers of CFU-E and other erythroid precursors. **Answer C** is correct because erythroid precursors, CFU-E in particular but others up to the stage of basophilic erythroblasts, are rapidly lost due to apoptosis in the absence of erythropoietin. In the presence of erythropoietin these cells develop into mature erythrocytes due to reduced apoptosis.[32,33]

Question 3

A 45-year-old man presents with hematemesis, a BP of 105/75 mm Hg, and a hemoglobin of 9 g/dL. He has a history of membranoproliferative glomerulonephritis secondary to hepatitis C virus infection and a baseline S[Cr] of 4.7 mg/dL and eGFR of 14 mL/min/1.73 m^2.

Which one of the following is TRUE regarding treatment directed at the uremic platelet defect?

A. No specific treatment for uremic bleeding is needed since patient is not yet on dialysis
B. The patient should be emergently started on hemodialysis
C. Desmopressin (DDAVP) should be started
D. Cryoprecipitate should not be used since it has been ineffective in correcting bleeding and carries the risk of transmission of infective agents

Answer: C

Answer C, use of DDAVP, is correct. DDAVP, a synthetic form of vasopressin, improves platelet function at least in part by stimulating release of large vWF multimers from endothelial cells.[115,116] DDAVP may also have direct effects on platelet aggregation and increase platelet surface GP Ib/IX and some circulating clotting factor concentrations such as factor VIII. DDAVP may be given intravenously or subcutaneously with

reduction in the bleeding time within 1−2 hours, an effect lasting up to 8 hours. Tachyphylaxis, presumably due to depletion of endothelial stores of vWF multimers, limits the effectiveness of DDAVP after the first or second dose.[117] **Answer A** is incorrect because DDAVP may be effective in this situation of active bleeding. **Answer B** is incorrect and will likely distract from the primary goal of diagnosing the source of bleeding. The extent to which dialysis actually improves clinically significant bleeding remains uncertain, because most studies have examined effects on bleeding time or *in vitro* tests of platelet function that may or may not correlate with clinical bleeding, rather than active, clinical bleeding directly.[110−114] **Answer D** is incorrect as cryoprecipitate is enriched with vWF, factor VIII, and fibrinogen and can reduce the bleeding time. Cryoprecipitate may have a role in patients with active bleeding that does not respond to local measures, DDAVP, and transfusion or who are undergoing surgery.[126−128] When effective in reducing the bleeding time, cryoprecipitate infusion does so within about an hour. Risks include transmission of infectious agents and allergic reactions, but in the correct situation should not preclude its use.

Question 4

A 37-yr-old man has CKD from IgA nephropathy. S[Cr] is 3.4 mg/dL and estimated GFR 20 mL/min/1.73 m^2. Hemoglobin concentration is 11.2 g/dL, MCV 86 fL, serum iron 148 μg/dL, percent saturation of iron is 29%, and serum ferritin 140 ng/dL.

Which ONE of the following contributes to the anemia of this patient?

A. Increased circulating hepcidin levels
B. Chronic ongoing blood loss
C. Iron deficiency
D. Vitamin B12 deficiency

Answer: A

Answer A is correct. Hepcidin is produced by the liver and plays an important role in systemic iron homeostasis. Hepcidin reduces intestinal iron absorption and hepatocyte and reticuloendothelial cell iron release by inducing internalization and degradation of an iron channel, ferroportin, which is present on the cell surface of duodenal enterocytes, hepatocytes, and macrophages.[41−43] Hepcidin levels are increased with inflammation and contribute to the functional iron deficiency seen in CKD patients. **Answer B,** ongoing blood loss, does not appear likely as there is no clinical reason for blood loss and iron deficiency would be expected to develop, which has not occurred. **Answer C**, iron deficiency, is incorrect because in the presence of true iron deficiency the percent saturation of iron is less than 20% and serum ferritin concentration is less than 100 ng/mL. **Answer D** is incorrect as vitamin B12 deficiency should lead to an increased MCV.

Question 5

Erythrocytosis can be seen in which ONE of the following conditions:

A. Diabetic nephropathy
B. Polycystic kidney disease
C. Focal and segmental glomerulosclerosis
D. Membranous glomerulonephritis

Answer: B

Answer B is correct as patients with ADPKD often have anemia that is less severe than expected for their level of GFR. Some ADPKD patients will have normal or even elevated Hb levels. Serum erythropoietin levels tend to be higher in patients with ADPKD compared to patients with other causes of CKD.[76,77] None of the other conditions is associated with erythrocytosis

Question 6

Which ONE of the following is true about the bleeding tendency seen in patients with advanced CKD?

A. Increased partial thromboplastin time is seen due to accumulation of uremic toxins
B. Primary defect is platelet dysfunction
C. Treatment with Factor V can decrease bleeding
D. Increased circulating levels of vWF interferes with endotheial function

Answer: B

Answer B is the correct answer. Levels of vWF are normal or at most minimally reduced in CKD. However, the functional interaction between platelets and vWF multimers is impaired, leading to platelet dysfunction.[88−90] **Answer A** is incorrect because partial thromboplastin time is normal in CKD patients. **Answer C** is incorrect because factor V levels are normal and treatment with factor V does not improve the uremic platelet defect. **Answer D** is incorrect because levels of vWF are normal, and it is the vWF−platelet interaction and not endothelial interaction that impairs platelet function.

CHAPTER

31

Hematologic and Infectious Complications of Chronic Kidney Disease

Jay I. Lakkis[a], *Matthew R. Weir*[b]

[a]University of Hawaii John A. Burns School of Medicine, Wailuku, HI, United States; [b]Division of Nephrology, University of Maryland School of Medicine, Baltimore, MD, United States

Abstract

Chronic kidney disease (CKD) is associated with an array of secondary abnormalities of blood cell lines: red blood cells, white blood cells, and platelets. Anemia in CKD becomes more common as CKD progresses and is associated with significant all-cause as well as cardiovascular morbidity and mortality. CKD also results in progressive platelet dysfunction and impaired primary hemostasis. Furthermore, CKD is associated with impaired immune homeostasis, with abnormalities in both innate and adaptive immunity, and their effector cells as well as humoral components, promoting infection and a state of chronic sterile inflammation. The latter is associated with increased risk of cardiovascular disease. We review the hematological and infectious complications of CKD, and their interconnectedness with cardiovascular disease and infection, the two major causes of mortality and morbidity in this patient population.

INTRODUCTION

Chronic kidney disease (CKD) affects 14.8% of the adult general population in the US and around 10% of adults worldwide.[1,2] The prevalence of CKD seems to have stabilized over the last decade after a persistent rise in the preceding two decades.[3]

CKD, whether a reduced estimated glomerular filtration rate (eGFR) and/or an increased urinary albumin excretion rate (UAER), carries an independent risk of cardiovascular and all-cause mortality.[4–10] The mortality rate more than doubles for Medicare patients with CKD aged 66 years or older,[1] and increases by a factor of 12 for CKD patients aged 50–64 and by a factor of 36 for CKD patients aged 16–49 years, when each subgroup is compared to age-matched subjects without CKD.[11] Seen in a different light, when comparing the life expectancy of an end-stage renal disease (ESRD) patient on renal replacement therapy (RRT) to that of a matched individual without ESRD, life expectancy is less than one-third for a person aged 80 years or less and around half for a patient aged 85 years or older.[1]

The two most common causes of mortality in the CKD population are cardiovascular disease (CVD) and infection.[1] Both burdens have strong links and associations rooted in dysregulation of immune homeostasis and chronic inflammation.

Furthermore, CKD results in significant morbidity. This chapter reviews the hematologic and infectious complications of CKD, focusing on the effects of CKD on erythrocytes and platelets, as well as its effects on leukocytes and immune homeostasis.

HEMATOLOGIC COMPLICATIONS OF CKD: RED BLOOD CELLS

Anemia in CKD: Introduction

Anemia is a relatively common complication of CKD that carries an increased risk of morbidity and mortality.[12,13] Analyses of adult (age >18 years) participant data from The National Health and Nutrition Examination Survey (NHANES) 2007–2008 and 2009–2010[14] estimate the prevalence of CKD at 14.0%, and the prevalence of anemia in patients with non–dialysis-dependent CKD (NDD-CKD) at 15.4%.

The prevalence of anemia increases in proportion with the National Kidney Foundation/Kidney Disease Outcomes Quality Initiative stage of CKD, with 17.4% of individuals with stage 3 CKD, 50.3% with stage 4 CKD, and 53.4% with stage 5 CKD having anemia. Similarly, a retrospective analysis of combined data from

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00031-0

non-Medicare patients aged 18–63 years and from Medicare patients aged 66–85 years estimated the prevalence of anemia at 28% in patients with stage 3–5 NDD-CKD,[15] with a prevalence of 22.4% in stage 3 CKD, 41.3% in stage 4 CKD, and 53.9% stage 5 CKD. In the older Medicare population, the prevalence of anemia in CKD (ACKD) was 50.1%, with a prevalence of 43.9% in stage 3 CKD, 64.0% in stage 4 CKD, and 72.8% stage 5 CKD. In patients with ESRD treated with hemodialysis (HD) for a period of 90 or more days, 80–83% had ACKD, which required erythropoiesis-stimulating agent (ESA) therapy.[1]

Anemia in CKD: Pathophysiology

CKD results in relative erythropoietin (Epo) deficiency, at times concomitant with Epo resistance, with a secondary decrease in red blood cell (RBC) production in the bone marrow. Up to 90% of human Epo is synthesized by renal interstitial fibroblasts,[16] with the remaining 10% in extra-renal tissues, mainly the liver. Hypoxia is the most potent stimulus for Epo production. Its effects are mediated by the inhibition of prolyl hydroxylase domain (PHD) proteins, which are responsible for the degradation of the alpha subunit of hypoxia-inducible factor (HIF) under normal oxygen conditions. The end result is an increase in HIF proteins with enhanced expression of hypoxia-induced genes (e.g. Epo).[17] Despite the chronic reduction in tissue oxygen tension linked to ACKD, Epo expression and production do not increase proportionately as expected, suggesting permanent loss of the fibroblasts' capacity to produce Epo. The relative Epo deficiency worsens with the severity of CKD, and no extra-renal compensatory corrective production has been described.

Dysregulation of iron homeostasis plays a pivotal role in the generation and maintenance of ACKD, as well as in resistance to ESA therapy,[18] especially in dialysis patients. Iron-restricted erythropoiesis is relatively common in patients with CKD. Iron-restricted erythropoiesis may have different phenotypes: iron deficiency, iron deficiency anemia, or functional iron deficiency (FID). Iron deficiency refers to diminished body iron stores with no anemia.[19] Iron deficiency anemia refers to depleted body iron stores with a secondary decrease in RBC mass. FID refers to iron-restricted erythropoiesis resulting from a failure to mobilize iron to the bone marrow for erythropoiesis despite apparent normal or increased iron body stores.[20]

In a normal steady state, oxygen is transported in humans by hemoglobin (Hb), a tetramer with two pairs of globin chains (α and β), with each chain bound to a heme group made of a porphyrin ring and an iron atom, which carries the oxygen. Thus, iron homeostasis (reduction, absorption, storage, transfer) is under strict control. The majority of iron in the human body is recycled from senescent cells (old RBCs phagocytized by macrophages or hepatocytes). A much smaller portion is absorbed daily to replace losses. Gastrointestinal dietary iron (Fe^{3+}) must be first reduced (Fe^{2+}) to be absorbed. The reduction is mediated by duodenal cytochrome B, a duodenal brush border ferric reductase enzyme. Following reduction of dietary iron, absorption takes place *via* the duodenal enterocyte luminal/apical divalent metal transporter 1 (DMT1). Thereafter intracellular iron is stored as ferritin, with subsequent regulated transfer to the blood *via* the basolateral transporter ferroportin,[21] where it is reoxidized (Fe^{3+}) and loaded to its carrier transferrin (known as apotransferrin when not carrying any iron). Transferrin delivers the iron to its target tissues for use (mainly in the bone marrow) or for storage (mainly by the liver), where it binds to its cell surface transferrin receptor (TfR) and is internalized and binds to intracellular ferritin. Transferrin exists predominantly in the monoferric form in a normal steady state, and in the diferric form in iron overload states.[18]

Ferroportin also mediates cellular iron efflux from other storage cells, mainly macrophages and hepatocytes,[22] and is feedback-regulated by hepcidin. Hepcidin is a 25-amino acid negative iron-regulatory hormone at the center of iron metabolism. Hepcidin is synthesized exclusively in the liver and binds ferroportin in response to an iron load or to inflammation. Then the hepcidin–ferroportin complex is endocytosed and broken down by lysosomes,[23] thus blocking any further rise in iron bioavailability and enhancing iron sequestration.

Hepcidin plays a key role in iron-restricted erythropoiesis, FID, and resistance to ESA therapy. CKD patients have increased plasma hepcidin levels, due to chronic inflammation and reduced renal clearance. They also have low ferroportin levels,[24,25] a combination that downregulates duodenal iron absorption[26] and interferes with the availability of stored iron for erythropoiesis.

Abnormal bone and mineral metabolism has also been associated with Epo resistance and iron-restricted erythropoiesis. Vitamin D is a potent inhibitor of hepcidin.[27] Vitamin D deficiency is a common finding in patients with CKD. As such, low vitamin D levels are associated with an increase in circulating hepcidin levels and FID. Furthermore, iron seems to play an important role in the regulation of fibroblast growth factor 23 (FGF-23) through mechanisms not yet fully elucidated.[28] Iron deficiency increases levels of FGF-23, a regulatory hormone secreted by osteocytes and osteoblasts with a crucial role in the maintenance of phosphorus homeostasis. This seems to be one of the mechanisms that

may explain the elevated levels of FGF-23 in CKD patients, in whom it promotes urinary phosphate excretion.

Patients with CKD, especially patients on RRT,[29] have diminished duodenal iron absorption as well as chronic blood loss due to relatively frequent phlebotomy, platelet dysfunction, and (in the case of HD patients) blood loss in the dialysis membrane and tubing.

ACKD may also result from other pathophysiological pathways such as inhibition of erythropoiesis by uremic toxins, Epo resistance due to a multitude of causes (such as chronic inflammation or secondary hyperparathyroidism, hemolysis, vitamin B12 [cobalamin], or folate deficiency) or shortened erythrocyte life span.[30–32] Finally, angiotensin II may play a minor physiological role in stimulating Epo production in humans.[33–35] Angiotensin-converting–enzyme inhibitor (ACEI) therapy may reduce the response to ESAs and contribute to ESA hyporesponsiveness or resistance.[16,36–38]

Anemia in CKD: Diagnosis

The severity of ACKD is proportional to the degree of reduction in eGFR (in mL/min/1.73 m^2 body surface area).[1] Anemia may become clinically evident when the eGFR decreases below 60 mL/min/1.73 m^2 but is most common in individuals with eGFR <30 mL/min/1.73 m^2. The most reliable biochemical marker for ACKD is the Hb concentration, rather than the hematocrit (Hct), because the latter may vary with extracellular fluid volume, measuring methods, and sample storage time.

The 2012 KDIGO (Kidney Disease: Improving Global Outcomes) Clinical Practice Guideline for Anemia in CKD adopted the 1968 World Health Organization definition of anemia as a hemoglobin concentration less than 12 g/dL in women and less than 13 g/dL in men.[39]

All best practice guidelines for the management of ACKD recommend periodic monitoring of the serum Hb in patients with CKD with and without anemia.[39–42] The 2012 KDIGO anemia guideline recommends, in the absence of anemia, a minimal Hb testing frequency of once every three months in patients with ESRD on RRT, once every six months in stage 4–5 CKD, and once a year in patients with stage 3 CKD.[39] In patients diagnosed with anemia not treated with ESA, the minimal frequency was once a month in patients with ESRD on RRT with HD, and every three months in all other CKD populations. In patients with ACKD receiving ESA therapy, Hb should be monitored at least once a month during the initiation phase, at least once every three months in NDD-CKD patients, and at least every month in dialysis patients during the maintenance phase.

An initial diagnostic workup for ACKD entails a strategy aimed at the exclusion of other potential causes of anemia in this patient population.[39–42] Age-appropriate screening for occult gastrointestinal blood loss is recommended. On peripheral blood smear and complete blood count, RBCs are typically normochromic, with a normal mean corpuscular hemoglobin, normocytic with a normal mean corpuscular volume, and have a normal RBC distribution width. Echinocytes or burr cells may be seen. The absolute and the corrected reticulocyte count confirm the hypoproliferative nature of this anemia.

Iron, transferrin saturation (TSat), and ferritin are essential to exclude concomitant iron deficiency and iron-restricted erythropoiesis. Most clinical practice guidelines would accept a transferrin saturation at 30% or less and a ferritin at 500 ng/mL or less as cutoffs that indicate iron deficiency and that warrant iron replacement therapy. The challenge arises with FID, where the iron parameters are discordant, with a transferrin saturation at 20% or less and a ferritin at 500 ng/mL or more and the safety of iron replacement therapy becomes questionable. Iron parameters should be evaluated at least once every three months in patients with ACKD on maintenance ESA therapy, and more often (e.g. every month) when ESA therapy is being initiated or adjusted, or when response to iron therapy is being evaluated.[39] However, the interpretation of these tests is fraught with complexities and may not always be straightforward. Neither the ferritin nor the transferrin saturation should be used alone to diagnose iron deficiency or to measure response to intravenous (IV) iron therapy.

Ferritin, a surrogate measure of total body iron stores, is an acute phase reactant that may be increased in patients with chronic inflammation.[18] Although a serum level of less than 100 mcg/L in NDD-CKD or less than 200 mcg/L in dialysis patients is desirable to diagnose iron deficiency with certainty, there is no evidence-based upper-limit ferritin cutoff above which FID can be excluded.

Other less available diagnostic tools for the evaluation of FID include the percentage of hypochromic red cells and the reticulocyte hemoglobin content.[20] Assessment of hepcidin levels is not currently recommended to evaluate iron status.

Evaluation of vitamin B12 (cobalamin) and RBC-folate levels should be performed.[39–42] Epo levels should not be part of a routine workup. The interpretation of Epo level is fraught with technical limitations and rarely adds to the evaluation and management plan. Epo levels are usually normal or slightly elevated in absolute terms.[32] They are, however, much lower than what would be expected for the degree of anemia, reflecting profound relative deficiency of Epo.

Anemia in CKD: Prognosis

ACKD is associated with increased mortality and morbidity.[13,43] ACKD has been associated with more frequent hospitalizations[44] and its severity with an increased length of hospital stay.[45] ACKD is also associated with a higher risk of left ventricular mass index (LVMI) and left ventricular hypertrophy (LVH), an independent predictor of increased mortality risk[46] and heart failure, new-onset atrial fibrillation,[47] increased CVD and mortality, impaired cognitive function, reduced functional status and exercise tolerance, decreased quality of life, and increased RBC transfusion requirements.

ACKD therapy, however, has not been reproducibly associated with reversal of mortality risk.[48] Similarly, there is conflicting evidence about the effect of ACKD therapy on associated morbidities such as health-related quality of life (HRQOL).[49,50] All evidence, however, points to a significant reduction in erythrocyte transfusion requirements.[31]

Anemia in CKD: Treatment

Treatment of ACKD focuses on minimizing blood loss, iron replacement therapy, and use of ESAs. If a patient requires both iron replacement and ESA therapy, then iron stores must be replenished first. Such a strategy is associated with a significantly lower ESA dose and prevents ESA resistance.[51]

Iron replacement therapy is one of the tenets of pharmacological therapy in patients with ACKD. Oral iron must be taken between meals and should not be combined with calcium-based phosphate-binders or foods. Absorption may be enhanced with concomitant administration of vitamin C. However, iron absorption in CKD is diminished, especially in ESRD patients. The excess hepcidin and low ferroportin downregulate duodenal iron absorption mediating FID. For these reasons, anemia management guidelines[39–42] in patients with ESRD recommend IV rather than oral iron therapy. Clinical trials and meta-analyses comparing the efficacy of oral vs. IV iron in the treatment of ACKD in patients with stage 3–5 CKD reached a similar conclusion.[52,53]

In patients with ESRD on RRT, in whom iron deficiency anemia is virtually ubiquitous and recurrent, the monthly dose of IV iron that can be administered safely is not well established. Some evidence indicates that a safe monthly dose is 100–200 mg per month and should not exceed 300 mg per month.[54] A higher monthly dose exceeding 400 mg is associated with increased mortality rate in HD patients.[55] However a meta-analysis of data from seven randomized controlled trials showed that higher dose iron (defined as >400 mg/month) was not associated with a higher risk of infection or all-cause mortality. Similarly the same meta-analysis analyzed data from fifteen observational trials and again higher dose iron (defined as >200 mg/month) was not associated with an increased risk of all-cause mortality, infection, cardiovascular events, or hospitalizations.[56]

The traditional oral iron formulations (e.g. ferrous sulfate, ferrous gluconate, ferrous fumarate) are relatively safe. Adverse reactions to oral iron therapy are mostly gastrointestinal, such as dark discoloration of stools, dyspepsia, and constipation. More recent additions to the pharmacopoeia of phosphate-binders, namely sucroferric oxyhydroxide and ferric citrate, are iron-based and serve dual roles as phosphate-binders and iron supplements. Administration of IV iron formulations (e.g. iron sucrose, ferric gluconate, ferumoxytol, ferric carboxymaltose, and iron dextran) can result in hypersensitivity reactions, including anaphylactic as well as anaphylactoid reactions. The highest risk of anaphylaxis on initial exposure has been associated with iron dextran, and the lowest with iron sucrose.[57] Evidence regarding safety of IV iron compared to oral iron is not uniform. Some studies reported a similar risk for infectious or cardiovascular events with oral and IV iron in patients with NDD-CKD and ESRD,[52,53] whereas others have shown an increased risk of infectious or cardiovascular events with administration of IV iron in patients with NDD-CKD, compared to the group treated with oral iron.[58,59] The mode of dosing IV iron has also been studied. Maintenance IV dosing is associated with a lower risk of infection than loading IV dosing.[60] All iron formulations may result in short- and long-term secondary iron overload. Immediately after IV iron is administered, the supra-physiologic iron load exceeds the capacity of a saturated iron homeostasis system, resulting in the generation of circulating free iron, which has been associated with enhanced bacterial growth *in vitro*,[61] impaired immune effector cell function, endothelial dysfunction, and increased oxidative stress.[62] Magnetic resonance imaging revealed evidence of hepatic iron overload in HD patients receiving IV iron replacement therapy, but the clinical significance of such a finding remains to be established.[63] Finally, detection of iron deposits in the microvasculature of patients with calcific uremic arteriolopathy raises concern about the role of iron administration in the pathogenesis of this serious disease.[64,65]

The Food and Drug Administration (FDA) approval of the first ESA, recombinant human Epo (rHuEPO), in 1989 for treatment of ACKD in dialysis patients and in 1993 for NDD-CKD patients heralded a new era in the treatment of ACKD. Pharmacological therapy of anemia decreases the need for RBC transfusions,[66] may cause partial regression of LVH,[67] may reverse clinical manifestations and symptomatology, may improve functional status, and some even report improved survival.

The benefits of treatment of anemia remain a topic of debate. For example, a systematic review of the effect of ESA therapy on HRQOL in CKD patients did not reveal any significant improvement.[49]

Currently available ESAs approved by the US FDA include:

(a) recombinant human Epo was approved for use in patients with ESRD on June 1, 1989, and for use in NDD-CKD patients on April 1, 1993?[68]
(b) darbepoetin alpha was approved for use in both dialysis and NDD-CKD patients on September 17, 2001,[69] and
(c) methoxy polyethylene glycol-epoetin beta, a continuous erythropoiesis receptor activator (CERA), was approved for use in all CKD patients on November 14, 2007.[70]
(d) On May 15, 2018, the first epoetin alpha biosimilar, epoetin alfa-epbx was approved by the FDA for treatment ACKD.[71]

ESA therapy is initiated, in the majority of patients, when he or she manifests clinical symptoms of anemia, or when Hb levels decline below 9 g/dL. Therapy should target a goal Hb of 10–11 g/dL. Levels higher than 12 g/dL must be avoided. Higher goals have been associated with poorer blood pressure (BP) control and increased risk of stroke and mortality.[66,72]

Most starting ESA doses are weight based. For example, epoetin alpha is usually started at 50–100 units/kg three times a week. Darbepoetin alpha is usually started at a dose of 0.45 mcg/kg once a week or 0.75 mcg/kg once every 2 weeks in dialysis patients, or at a dose of 0.45 mcg/kg every 4 weeks in NDD-CKD (usually 60–200 mcg every 2–4 weeks). Methoxy polyethylene glycol-epoetin beta is usually started at a dose of 0.6 mcg/kg once every 2 weeks (usually 25–75 mcg every 2–4 weeks). All ESA doses are titrated to achieve a goal Hb level of 10–11 g/dL in patients with ESRD. ESAs must be held if Hb level exceeds 11–11.5 g/dL, and the dose reduced before resumption of therapy. Targeting higher or gender-normal hemoglobin goals must be avoided.[72–76] Although the use of ESA and iron therapy confer a survival benefit in patients with lower hemoglobin levels, the benefit dissipates and mortality risk increases when therapy is administered in patients with higher hemoglobin levels.[77] Patients with a blunted initial Hb response to ESA carry a higher risk for development of CVD.[78] A higher ESA dose also conveys an increased risk for all-cause mortality as well as cardiovascular mortality.[79]

There is no evidence that one ESA, e.g. CERA, is superior in efficacy or safety to another.[31,80] A systematic review showed higher doses of short-acting ESA (epoetin alpha) over a longer time frame are noninferior to lower doses with more frequent administration in NDD-CKD patients.[81] Subcutaneous administration of epoetin is less costly than use of the IV route.[82] ESA therapy does not slow progression of CKD.[83,84]

Adverse effects of ESAs include an increase in BP, mediated by a direct systemic vasoconstrictive effect of ESAs.[16,85,86] Other risks associated with ESA administration include pure red cell aplasia, seizure activity,[80,87] thrombotic events, including stroke[88] and enhanced arteriovenous dialysis access thrombosis, and promotion of tumor growth. In patients with ACKD and cancer, ESAs are relatively contraindicated due to evidence pointing to enhancement of tumor growth and increased mortality in the cancer patient population.[89,90] Risks and benefits of ESA therapy and alternative options must be discussed with the patient and care coordinated with an oncologist.

Novel therapies for ACKD include inhibitors of HIF-PHDs,[17,91–98] non-ESA therapies that simulate hypoxic conditions and are currently in phase 3 clinical trials. PHD inhibitors stop the degradation of the alpha subunit of HIF, levels of which are normally regulated by oxygen tension. This results in the increased concentration and stabilization of the heterodimer HIF (α and β subunits, the beta subunit of which is under constitutive expression). In turn, HIF upregulates the expression of hypoxia-induced genes, including Epo and DMT1. Phase 2a and 3 trials with four different agents (GSK-1278863/daprodustat, FG-4592/roxadustat, AKB-6548/vadadustat, and BAY-85-3934/molidustat) have shown that HIF–prolyl hydroxylase inhibitors offer an additional form of treatment in patients with ACKD and NDD-CKD as well as ESRD, through the induction of endogenous Epo production and promotion of more favorable iron homoeostasis (e.g. improved intestinal iron absorption and decreased circulating hepcidin levels). No serious adverse reactions have been reported so far, although theoretical concerns over promotion of tumor growth and pulmonary arterial hypertension remain.

Anemia in CKD: Conclusions

Anemia is a common complication of CKD and is associated with increased morbidity and mortality, including cardiovascular morbidity and mortality (Figure 31.1). ACKD is primarily mediated by relative Epo deficiency, Epo hyporesponsiveness or resistance, and iron-restricted erythropoiesis, which may take the form of true iron deficiency anemia or FID. Treatment of ACKD is focused on achieving a goal Hb that alleviates any existing symptoms, reverses the high mortality rate associated with very low Hb, minimizes transfusion-dependence, and avoids the thrombotic complications of correction to normal Hb levels. A level of 10 g/dL is

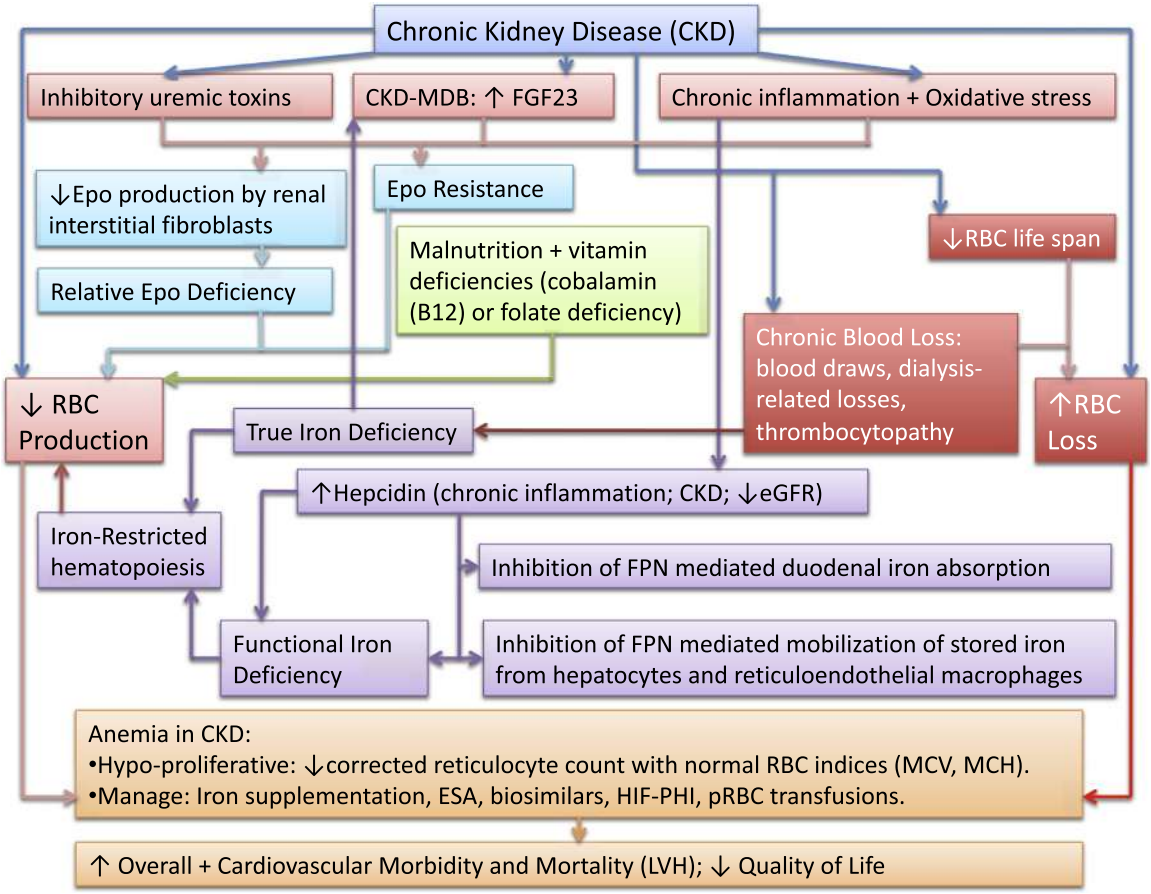


FIGURE 31.1 The pathophysiology and management of anemia in chronic kidney disease. Many processes increase the risk of cardiovascular disease in the patient with chronic kidney disease. *eGFR*, estimated glomerular filtration rate; *ESA*, erythropoiesis-stimulating agent.

acceptable for most CKD patient populations. Pharmacological therapy consists of ESAs and iron supplementation, but both therapies are associated with risks that must be weighed carefully against the benefits.

Erythrocytosis/Polycythemia

Erythrocytosis can be seen in patients with CKD in two settings: cystic kidney disease (mostly autosomal dominant polycystic kidney disease [ADPKD]), and following kidney transplantation. In ADPKD, erythrocytosis is thought to be due to pericystic local tissue hypoxia and dysregulated HIF proteins, with a secondary increase in Epo production.[99] In ESRD patients treated with HD and not on Epo therapy, an elevated Hb concentration was not associated with increased risk of mortality.[100] Erythrocytosis in this patient population may be associated with cystic kidney disease, chronic hypoxia due to pulmonary or CVD, and tobacco use.

Erythrocytosis after transplantation complicates around 8–15% of kidney transplants and occurs 8–24 months after transplantation with a spontaneous remission rate of 25% at 2 years.[101] This is clinically relevant because 10–30% of polycythemic patients develop arterial or venous thrombotic complications (including cerebrovascular accident and pulmonary embolism) with a 1–2% mortality rate.

Treatment with an ACEI or an angiotensin receptor blocker (ARB) is preferred.[101] Angiotensin II (AII) is a direct stimulus to Epo production. Increased AII production may be encountered in patients with renal hypoperfusion and tissue hypoxia, such as those with transplant renal artery stenosis or native renovascular disease, who develop erythrocytosis, which improves with ACEI or ARB therapy.[16]

HEMATOLOGIC COMPLICATIONS OF CKD: PLATELETS

Platelet Dysfunction: Introduction

Patients with CKD are at increased risk of hemorrhage[102–104] as well as thrombosis.[105] Both risks increase progressively with worsening CKD.

Abnormalities in either eGFR or UAER (urine albumin:creatinine ratio [UACR] in mg albumin per gram creatinine) have been associated with increased risk of hemorrhage.[106] For instance, a patient with an eGFR of <15 mL/min/1.73 m^2, and an UACR >300 mg/g has an adjusted relative risk of all-cause major hemorrhage of 5.5 compared to one with an eGFR ≥ 90 mL/min/1.73 m^2, and an UACR <30 mg/g. It is estimated that one in seven patients will develop a major hemorrhagic event for ESRD patients within three years after initiating dialysis.

Similar results are also seen in more specific CKD subpopulations. Patients with CKD and high CVD risk have a 1.5-fold increased risk of bleeding compared to matched subjects with no CKD.[107] This risk is increased with albuminuria as well as decreased eGFR, although the risk association is stronger with albuminuria. For example, the risk is 3.5-fold in a patient with an eGFR <45 mL/min/1.73 m^2 and albuminuria compared to a patient with eGFR above 45 mL/min/1.73 m^2 and no albuminuria. Similarly, in patients with non−ST-elevation myocardial infarction or unstable angina who had percutaneous coronary intervention and received anticoagulant therapy, CKD was associated with a higher risk of major and minor bleeding as well as restenosis at 30 days and 180 days. The risk increased progressively with the severity of CKD.[108] NDD-CKD adult patients aged 66 years or more who were treated with warfarin for atrial fibrillation had an increased risk of major hemorrhage.[109] The risk is also higher in dialysis patients. Finally, the risk of gastrointestinal hemorrhage was significantly higher in NDD-CKD patients depending on the eGFR. In a patient with eGFR <30 mL/min/1.73 m^2, the hazard ratio was 7.06 compared to a patient with eGFR ≥ 90 mL/min/1.73 m^2.[110] The risk of hemorrhage is also approximately five times higher in dialysis patients compared to patients without CKD.[111]

Acquired platelet dysfunction or uremic thrombocytopathy plays a key role in the increased risk of bleeding seen in the CKD population. Below, we will review normal platelet function and summarize alterations triggered by CKD.

Platelet Dysfunction: Pathophysiology

Platelets originate from bone marrow megakaryocytes and migrate to the circulation, where they are responsible for primary hemostasis during their seven day lifetime. Structurally, a platelet has heterogeneous components.[112] First, a peripheral zone composed of a plasma membrane glycocalyx that houses the surface glycoporteins (GPs), which are essential for platelet activation and adhesion and aggregation; a lipid bilayer, which contains tissue factor (coagulation factor III) that plays a key role in binding coagulation factors after platelet activation; and a submembrane area with a membrane contractile cytoskeleton made of actin filaments that determine platelet morphology and mediate receptor translocation to the surface and regulate platelet activation signal systems. Secondly, a sol−gel zone consists of an organized matrix of circumferential micrtotubules and microfilaments that make up the cytoplasmic contractile cytoskeleton, a system designed to contribute to platelet morphology and keep secretory organelles apart from each other and from other structures, and which on platelet activation constricts to reposition organelles in the platelet center, where they release their contents through a surface-connected canalicular system. Third, an Organelle Zone consists of alpha-granules where von Willebrand factor (VWF) can be found, dense granules that contain serotonin (5-hydroxytryptamine, 5HT) and adenosine diphosphate (ADP), and lysosomes.

In the event of endothelial injury, circulating platelets are mobilized to the site of injury, where platelet adhesion to the injured blood vessel takes place. Adhesion is mediated by the binding of exposed subendothelial extracellular matrix collagen to platelet surface GPVI and integrin $\alpha 2\beta 1$, and in conditions of high shear, the binding of GPIbα-IX-V complex to VWF.[113] Platelet activation occurs when platelet thrombin receptors, protease-activated receptors PAR1 and PAR4, interact with thrombin (byproduct of prothrombin, coagulation factor II).[114] An activation signal may be amplified *via* a positive feedback loop generated by the interaction of ADP and 5HT (released by platelet dense granules) with platelet receptors $P2Y_1$, $P2Y_{12}$, and $5HT_{2A}$, or by the interaction of thromboxane A2 (the product of arachidonic acid metabolism *via* the cyclooxygenase 1 pathway) with its thromboxane prostanoid receptor on the platelet surface. Platelet aggregation is mediated by fibrinogen (coagulation factor I) and by the binding of VWF to activated platelet surface GP integrin αIIbβ3 (previously known as GPIIb/IIIa).[115] The aggregation reaction may also be amplified by other mediators. Platelet adhesion, activation, and aggregation result in the formation of a platelet plug, which is solidified as a thrombus by secondary hemostasis and formation of a fibrin clot. On their natural end of life or on completion of their role in primary hemostasis, platelets are cleared from the circulation by phagocytes, and taken up by the spleen, where they are destroyed.

The mechanisms by which CKD promotes risk of bleeding are not completely understood. CKD impairs platelet adhesion, activation, and aggregation.[116] CKD has been associated with dysfunctional platelet interaction and adhesion to injured blood vessel walls, a paucity in the content of the dense granule including

decreased content of ADP and serotonin/5HT, defective release of the alpha granule, altered VWF function, abnormal cytoskeletal structures, impaired platelet intracellular signaling, increased platelet cyclic adenosine monophosphate and cyclic guanosine monophosphate (cGMP), abnormal vascular endothelium, and increased synthesis of nitric oxide (NO; endothelium-derived relaxing factor, EDRF), which exerts direct and indirect inhibitory effects on platelet aggregation. The latter are mediated by an NO-driven rise in cGMP and a secondary decline in ADP and thromboxane A2, both of which amplify the signal for platelet aggregation. Finally uremia is hypothesized to generate and retain incompletely identified circulating "uremic" toxins and inhibitors detrimental to platelet function (such as guanidino compounds).[117–119] These findings are best illustrated by experiments showing that the addition of normal plasma to a uremic milieu improves platelet function and *vice versa*.

Anemia also plays a role in the pathogenesis of thrombocytopathy in CKD patients.[120,121] Anemia alters the flow pattern of platelets in the blood vessels, shifting them into a central position and away from the endothelial surface. Hemoglobin binds NO. Therefore a decrease in hemoglobin results in increased bioavailability of NO and secondary direct and indirect inhibitory effects on platelet aggregation. Finally, a decrease in RBC mass is associated with a further decrease in availability of ADP and thromboxane A2, both of which are also produced by RBCs.

Platelet Dysfunction: Diagnosis

The diagnosis of platelet dysfunction is often made by the clinical presentation and rarely by specific diagnostic testing. Clinical manifestations of acquired platelet dysfunction may be minor or major and involve cutaneous, mucosal, and serosal tissues. Minor bleeding events involve the skin, with oozing from sites of previous venipunctures, easy bruising, ecchymoses or purpura, or the mucosa with epistaxis, gingival hemorrhage, menorrhagia, or hematuria.[122] Major bleeding events include intracranial, gastrointestinal, and retroperitoneal hemorrhage. Bleeding may be spontaneous, but more often is provoked (e.g. associated with procedures or trauma). Bleeding is more pronounced in patients with ESRD who are receiving inadequate or no dialysis.

Platelet count is usually normal, as are the prothrombin time (PT) and the activated partial thromboplastin time (aPTT).[103] Levels of coagulation factors are normal to increased. Neither serum blood urea nitrogen nor serum creatinine concentration (S[Cr]) levels accurately predict bleeding risk.

Bleeding time (BT) increases with declining eGFR or worsening UACR.[104] BT may play a role in the evaluation of platelet function before surgical or invasive procedures in patients with ESRD with inadequate or no dialysis.[123] The BT, however, is insensitive and nonspecific. Its interpretation is marred by severe technical and other limitations. Therefore the BT is rarely used clinically.

Platelet adhesion and aggregation are impaired in CKD patients. Ristocetin-induced platelet aggregation (RIPA), a diagnostic tool to assess platelet aggregation and the intact functionality of the interaction of GPIbα-IX-V with its ligand (VWF), is diminished in uremic patients.[124,125] Similarly, platelet VWF multimer pattern is abnormal and the mean platelet VWF antigen and activity are reduced, whereas the mean plasma VWF antigen and activity are increased. However, these diagnostic tools are not routinely available for clinicians and are mainly used in research settings.

Platelet Dysfunction: Prognosis

Acquired platelet dysfunction in CKD cannot be fully and permanently reversed. A thorough and preventive approach may decrease risks of bleeding and/or thrombosis. For example, in ESRD patients, it is essential to ensure prescription and delivery of adequate dialysis. Correcting ACKD may help decrease the degree of platelet dysfunction. Patients with CKD may have indications for anticoagulant therapy, and risks and benefits must be assessed carefully and discussed with the patient.

Platelet Dysfunction: Treatment

Several strategies have been evaluated in the management of uremic thrombocytopathy.[117] Initiation of RRT or ensuring the adequacy of dialysis in the ESRD patients improves platelet function, albeit not fully.[103,126–130] Provision of adequate dialysis without anticoagulation is specifically recommended before any invasive or surgical procedures.

Correction of anemia to goal hemoglobin of 10 g/dL in the CKD patient reduces BT and may improve platelet function and primary hemostasis.[120,121,131] Correction of anemia may be achieved by ESA and/or iron therapy or by red blood cell transfusions. ESA therapy may have a direct salutary effect on platelet function in ESRD patients.[132–134]

Desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP), whether used at 0.3 mcg per kg IV or subcutaneously, or at 3 mcg per kg intranasally, shortens BT and restores hemostasis temporarily, and slows or stops bleeding. Its effects last up to 4–8 hours.[135–138] DDAVP appears to replenish a large

VWF multimer pattern *via* endothelial cell stimulation and promote platelet glycocalyx glycoprotein expression. It is one of the safest pharmacological therapies available, but its drawbacks include short duration of action and tachyphylaxis.

Cryoprecipitate also improves BT and reduces or corrects major bleeding for a period lasting less than 24–36 hours.[139–141] Cryoprecipitate is rich in VWF, factor VIII, and fibrinogen. Its major drawbacks, infections, and transfusion reactions, limit its use to clinical scenarios where other measures have failed or in the perioperative setting. Conjugated estrogens, whether administered orally or intravenously, also reduce BT in uremic patients and improve hemorrhage during active bleeding.[142–144] The major drawbacks are estrogen-related side effects, including hot flashes. Low-dose transdermal estradiol at 50–100 mcg twice weekly provides a mode of sustained long-term estrogen therapy that is best suited for refractory uremic bleeding. Transdermal estradiol may have the additional benefit of a lower risk of thrombotic events compared to oral estrogen.[145,146] Tranexamic acid, a synthetic antifibrinolytic agent, has been used to treat uremic thrombocytopathy.[147,148]

Platelet Dysfunction: Conclusions

Platelet dysfunction and secondary abnormal primary hemostasis and bleeding diathesis are relatively common complications of CKD and carry an increased risk of mortality and morbidity (Figure 31.2). Such abnormalities become more prevalent with declining eGFR or worsening UACR and are most pronounced in patients with advanced CKD or ESRD. The mechanisms underlying platelet dysfunction have not been fully explained, but a multitude of abnormalities have been described. Therapy is usually reserved for patients with active bleeding or in the perioperative setting. Therapy is only successful at partial and temporary reversal of the bleeding problem and consists of

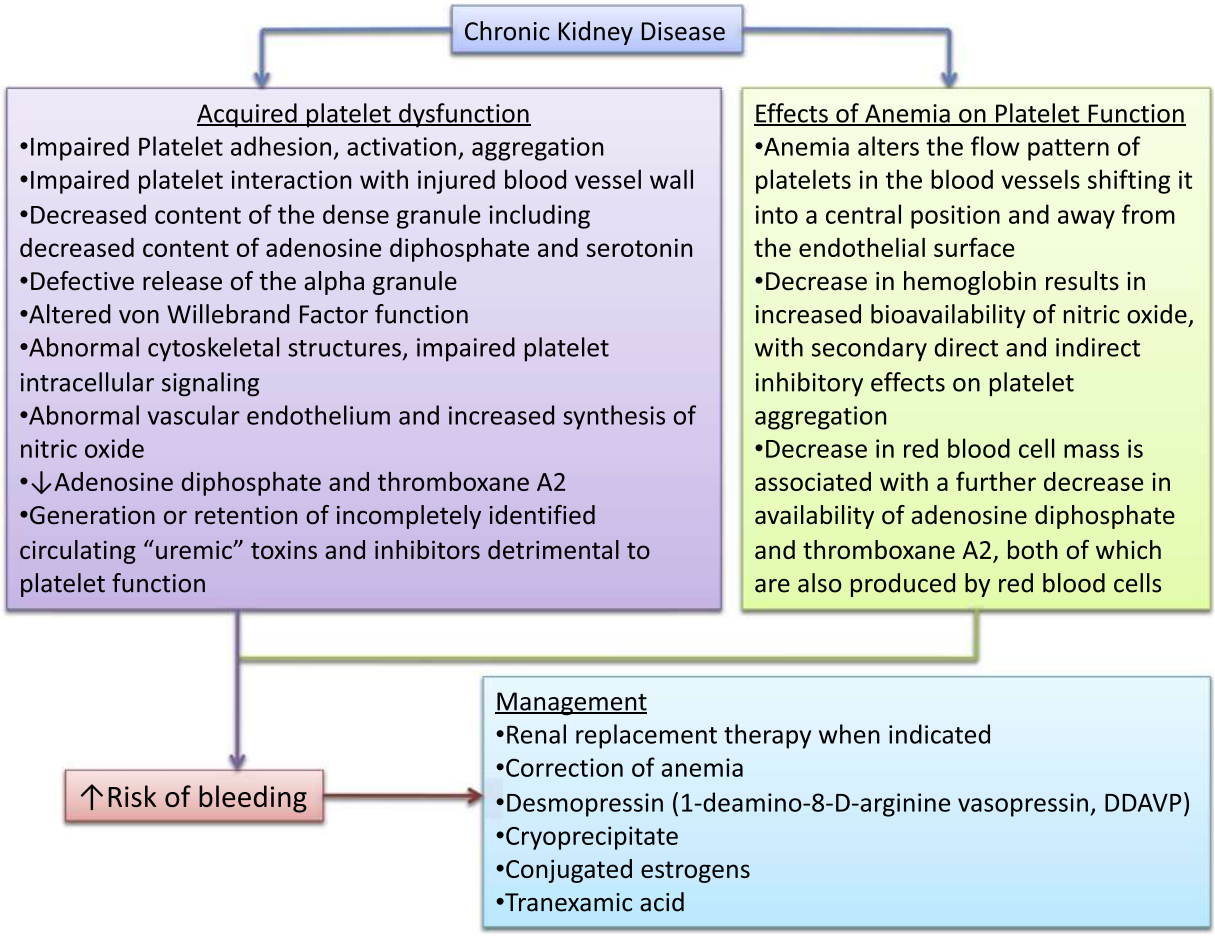


FIGURE 31.2 Platelet dysfunction in chronic kidney disease and its management.

emphasizing the adequacy of dialysis in the ESRD population, correction of anemia, and use of selected pharmacological agents. Evidence from randomized control trials to guide therapy is lacking.

INFECTIOUS COMPLICATIONS OF CKD: LEUKOCYTES AND IMMUNE HOMEOSTASIS

Introduction: Leukocyte and Immune Dysfunction in CKD

Kidney injury triggers injury in distant organs *via* organ cross-talk. CKD affects multiple organ systems, including the immune system. Immune dysfunction in this patient population may manifest as a higher rate of infections as well as a state of chronic sterile inflammation, lower rates of response to vaccinations, and a higher rate of neoplastic diseases.

Infection is the second most common cause of mortality (after CVD) in patients with ESRD on RRT,[1] with a mortality rate of 11%. Septicemia accounts for 8% and other infections for 3% of deaths. Similarly reduction in eGFR and/or albuminuria is associated with an increased risk of infection and infection-related mortality.[149,150] The increased risk of infection applies to community-acquired infections[151] as well as infection-related hospitalizations.[152] Furthermore, in NDD-CKD patients, an infectious event is independently associated with an increased rate of adverse cardiovascular outcomes, progression to ESRD and mortality.[153]

In addition to infection, CKD has been associated with a state of chronic sterile inflammation, which promotes atherosclerosis, cardiovascular morbidity, and mortality. CKD is also associated with increased rates of nonresponse to immunizations.

To understand the full complexity of the effects of CKD on leukocytes and their place in immune homeostasis, it is essential to highlight relevant components of the immune system and summarize the effects of CKD on these components.

The human immune system serves to recognize, defend against, and eliminate a potential source of danger (microbes, tumor cells) and to assist in recovery and tissue repair, all while maintaining a set of checks and balances to avoid mounting a response to self-antigens or to the ubiquitous human microbiome.[154,155] The immune system infrastructure is the sum total of the coordinated efforts of innate immunity and adaptive immunity, both of which have cellular and humoral components, as well as a complex network of cell-to-cell signaling and communication in different tissues and organ systems.

Pathophysiology: the Immune System in Health and in CKD

Types of Cellular Immunity

Cellular immunity, whether innate or adaptive, may be classified into three types[156]:

Type 1 immunity defends against intracellular infections. Its effector cells include the mononuclear phagocyte system (circulating monocytes and tissue-resident macrophages, as well as tissue dendritic cells [DCs]), natural killer (NK) cells, and other group 1 innate lymphoid cells (ILC1s). ILC groups[157] are lymphoid cell groups that do not express antigen-specific receptors and are either classified as cytotoxic or helper, cytotoxic (TC1), and helper (Th1) T lymphocytes.
Type 2 immunity defends against helminths and venoms. Its effector cells include basophils and mast cells, eosinophils, group 2 innate lymphoid cells (ILC2s), cytotoxic (TC2) and helper (Th2) T lymphocytes.
Type 3 immunity protects against extracellular bacterial and mycotic infections. Its effector cells include neutrophils and mononuclear phagocytes, group 3 innate lymphoid cells (e.g. ILC3s), cytotoxic (TC17) and helper (Th17) T lymphocytes, and epithelial cells.

Innate Cellular Immunity: An Overview

Innate immunity is elicited by several first line general defense mechanisms, written in one's genetic code, and may be cellular or humoral. Innate immunity entails a swift response within minutes of exposure to a threat, with nonspecific, general pathogen recognition, phagocytosis, and antigen presentation. Innate immunity has no immunologic memory. In the short-term, this defense strategy is desirable to contain and neutralize any potential threat. If innate nonspecific activity lasts for longer times, however, then responses can cause extensive damage to host tissue. Therefore, the innate immune system also works in tandem with, induces, and regulates elements of the slower and more specific adaptive immune system, which ultimately accomplishes the task of accurate and precise neutralization of the threat.

Cellular innate defenses include nonprofessional physical or anatomical barriers such as surface epithelia and mucous membranes (skin, respiratory, gastrointestinal and genitourinary systems), and secretions with soluble antimicrobial products such as tears and saliva.

Innate Cellular Immunity: Pattern Recognition Receptors

Innate cellular immunity includes multiple professional effector cells equipped with pattern recognition receptors (PRRs).[158] PRRs are instrumental in the recognition of characteristic conserved motifs found on the surface of various pathogens, known as pathogen-associated molecular patterns (PAMPs). PRRs also recognize and respond to damage-associated molecular patterns (DAMPs), molecules released by cells in distress. Functionally, PRR-mediated innate immune response activation may follow one of two pathways: signaling PRRs that activate immune effector cells, or endocytotic receptors and soluble PRRs that phagocytose and internalize pathogens.[159]

PRRs may be classified functionally into three categories: secreted (e.g. mannose-binding lectin family), endocytic (e.g. macrophage scavenger receptor), and signaling (e.g. toll-like receptors [TLRs]).[160] There are different families of PRRs. Four have been characterized, including two trans-membrane and two cytosolic families.[161,162]

Trans-membrane—TLRs

The TLR family includes 13 members.[163,164] TLRs are found either on the surface of the cell membrane (TLR1, TLR2, TLR2, TLR4, TLR5, TLR6) or in the membrane of endosomes and lysosomes (TLR3, TL7, TLR8, TLR9). One example is TLR4, a cell-membrane PRR, which recognizes and binds the gram-negative bacterial lipopolysaccharide (LPS).

Compared to controls, CKD patients have a higher level of TLR4 activity.[165] The activity level rises with declining eGFR. For example, there was higher TLR4 expression in neutrophils in HD patients and higher TLR4 expression in monocytes in stage 3−4 CKD patients compared to patients with eGFR greater than 60 mL/min/1.73 m^2.[166] This increase may play a proinflammatory role and promote muscle wasting in CKD, as well as progression of CKD and renal fibrosis.[167,168]

Trans-membrane—C-type Lectin Receptors

One example is DC-specific receptor-1, which is expressed in DCs, monocytes and macrophages, as well as polymorphonucelar cells (PMNs), and binds to carbohydrate-rich PAMPs in the fungal cell wall.[169]

Cytosolic—Retinoic acid-inducible gene I−like receptors).

Cytosolic retinoic acid-inducible gene I−like receptors identify intracellular viral RNA PAMPs and trigger an innate immune response including the release of type I interferons (IFNs).[170]

Cytosolic—Nucleotide-binding oligomerization domain-like receptors

Cytosolic nucleotide-binding oligomerization domain−like receptors serve as continuous patrols to recognize and respond to PAMPs or DAMPs.[171,172]

Innate Cellular Immunity: Effector Cells: An Overview

Innate effector cells initiate and regulate the inflammatory response, help contain and eliminate potential threats, and assist in the repair of tissue damage. Many are professional antigen-presenting cells (APCs) such as monocytes/macrophages and DCs. Neutrophils/granulocytes have also been described to acquire and play a role in antigen presentation to CD4+ memory T cells.[173,174]

Antigens are presented to T cells *via* cell a surface tetramer known as the major histocompatibility complex (MHC). MHC class I molecules (HLA-A, B, and C) are expressed on the surface of all nucleated cells and process endogenous or intracellular peptide antigens such as viral antigens. Expression of MHC class II molecules (HLA-DP, DQ, and DR) are unique to APCs only and process exogenous or extracellular peptide antigens. After an APC engulfs and degrades a pathogen, MHC class II binds with a pathogen-derived peptide and moves to the cell surface where it presents its antigen to T cells.

Innate Effector Cells Include Phagocytes, Granulocytes and Natural Killer Cells

Innate Cellular Immunity: Effector Cells: Phagocytes

Phagocytes function as continuous sensors and monitors for pathogens in the circulation as well as in tissues. Phagocytes include neutrophils (granulocytes [WBC]/PMNs), and cells of the mononuclear phagocyte system, including circulating monocytes and their derivative tissue-resident macrophages, as well as tissue-resident DCs. Their defining feature is phagocytosis. Phagocytosis may be a direct process of engulfing the pathogen, or an indirect process where the pathogen is premodified by antibodies or complement (opsonization) for more effective phagocyte identification and recognition, before phagocytosis.

Neutrophils are products of myeloid progenitor cells and are the most abundant granulocytes. Neutrophils are among the first cells to migrate to the site of infection in response to chemotactic stimuli produced by cells in distress or by tissue-resident immune cells. Responding neutrophils switch on nicotinamide adenine dinucleotide phosphate oxidase (NOX2) and produce superoxide, the precursor for reactive oxygen species (ROS) through the enzymatic activity of intracellular myeloperoxidase. Neutrophils may directly engulf,

phagocytose, and kill pathogens through PRR–PAMP interaction or may indirectly recognize a complement-opsonized or antibody-opsonized pathogen and internalize it into a phagosome and kill it. The phagosome then merges with the PMN granules, resulting in degranulation, with the release of preformed antimicrobial factors as well as toxic ROS, in addition to the formation of neutrophil extracellular traps (NETs) and ectosomes.[175,176] NETs consist of antimicrobial proteins and enzymes embedded in a matrix of chromatin fibers and histones released by neutrophils. NETs trap and destroy pathogens,[177,178] but in certain disease states, NETs promote chronic inflammation and atherosclerosis, and sometimes they play the role of an autoamplifying loop of cell death, a process known as necroinflammation.

CKD results in a spontaneous chronic activation[178] of the neutrophil and impairs its primary functions.[179] These dysregulated functions include its ability to respond to a stimulus due to impaired chemotaxis and adhesion, the magnitude and efficacy of its response with impaired production and release of ROS and cytokines and lytic enzymes, as well as its ability to ingest and kill a pathogen and to undergo apoptosis afterward, as well as its ability to recruit other immune cells to the site of an infection. For example, in ESRD patients, *in vitro* studies show altered neutrophil function, with diminished chemotactic response, as well as oxidative metabolic response to chemotactic stimuli, and downregulation of C5a receptors.[180] Similarly, in CKD patients, there is also downregulation of the expression of superoxide dismutase 2,[181] an enzyme crucial for the oxidative burst, as well as blunted or downregulated cytokine gene expression. Expression and activity of TLR-4 in neutrophils is increased in HD patients.[182] FGF-23 (increased in CKD to maintain phosphate homeostasis) impedes neutrophil activation, chemotaxis, and function.[183]

CKD is associated with enhanced neutrophil priming and activation, decreased responsiveness to stimuli, increased myeloperoxidase activity and increased oxidative stress, and an overall increase in PMN apoptosis.[184] These effects were related to the severity of CKD and most prominent in ESRD patients treated with dialysis. Uremic toxins enhance neutrophil activation, with a resultant increase in NET and ROS formation, and impair PMN programmed cell death and clearance at the conclusion of an immune response, promoting a state of chronic sterile inflammation,[178,184,185] which in turn increases the risk of atherosclerosis and CVD.

Circulating or peripheral monocytes are a heterogeneous cell population of the myeloid lineage. They migrate to different organs and differentiate into specialized tissue-resident macrophages. For example, in the kidneys there are kidney macrophages, in the liver Kupffer cells, in the brain microglia, and in the lungs alveolar macrophages. Macrophages serve patrolling functions, recognizing pathogens directly through PRR (e.g. TLR) or indirectly through opsonization. Macrophages phagocytize and destroy potential threats including microbes, recruit other immune cells to the site of infection, and release inflammatory cytokines and ROS. Macrophages also function as APCs to adaptive immune effector cells.

In vitro studies in ESRD patients show altered monocyte function, with diminished oxidative metabolic response to chemotactic stimuli, and downregulation of C5a receptors.[180] Other studies show impaired phagocytosis,[186] increased cytokine[187] and ROS production, and increased TLR-2 expression and TLR-4 expression and activity[182] in dialysis patients.

Some subsets of circulating or peripheral monocytes in CKD patients manifest a phenotype of persistent proinflammatory activation,[188–191] and these subsets increase in number as CKD stage progresses. One subset, $CD40^{+}$ monocytes, increases with severity of CKD, an increase mediated by hyperhomocysteinemia.[190,192] $CD40^{+}$ monocytes are associated with a proinflammatory state and CVD. These altered monocyte subsets, other examples of which include $CD14^{++}$ $CD16^{+}$ intermediate monocytes, promote the CKD chronic inflammatory state in various ways (e.g. secrete proinflammatory cytokines) and cause damage to host (self) tissues such as vascular endothelial cells, increasing risk of developing CVD and atherosclerosis.[190,193–195] Chronic inflammation has been associated with increased foam cell formation, atherosclerosis, and enhanced macrophage infiltration of radial artery samples collected from patients with ESRD undergoing surgery for arteriovenous access.[196] Tissues show increased expression of tumor necrosis factor alpha (TNFα) and monocyte chemotactic protein-1 (MCP-1). Elevated MCP1 plasma levels correlate with the severity of coronary in CKD patients.[197]

In vitro studies show patients with NDD-CKD have decreased monocyte TL4 expression and a blunted response of $CD14^{+}$ monocytes to LPS, with diminished production of cytokines TNFα, interleukin (IL) 1β, IL6 and IL8, compared to controls.[198,199]

A higher absolute blood monocyte count has been associated with a higher risk of incident CKD, as well as progression of CKD,[200] and a higher risk of the combined endpoint of ESRD and death.[201]

DCs are another heterogeneous subset of phagocytes derived from bone marrow myeloid leukocyte precursors. They move as immature cells to nonlymphoid tissues, such as the kidney (cortex, medulla, or

tubulointerstitium), where they continuously monitor for pathogens. When a DC-PRR identifies a PAMP, the DC begins migration to secondary lymphoid tissue (lymph nodes, spleen, mucosal lymphoid tissues), during which it matures *via* TLR-mediated expression of key surface markers, and plays a salient role as the most powerful APC to naïve T cells, resulting in T-lymphocyte activation as well as regulation.

In vitro studies show that normal DCs fail to differentiate and exhibit decreased ability to endocytose in a uremic milieu, while enhancing T-cell proliferation.[186]

In the CKD population, DC play a proinflammatory role in stimulation of T cells[202] *via* supply of costimulatory signaling molecules (e.g. CD80, CD86, B7) and release of proinflammatory cytokines, promoting fibrosis and progression of CKD. Furthermore, DCs may be implicated in the etiology of hypertension.[203] DCs also play role in the progression of several primary kidney diseases, such as T-cell mediated glomerular injury, antiphospholipid disease, and lupus nephritis.[202,204–206]

Differentiation lines are often blurred between tissue-resident macrophages and tissue-resident DCs. There is no consensus at this time, regarding which establishes unique identity or roles, between these two components of the mononuclear phagocyte system.[207]

Innate Cellular Immunity: Effector Cells: Natural Killer Cells

NK cells also have heterogeneous subsets of cells: regulatory NK cells, tolerant NK cells, and cytotoxic NK cells.[208] The latter subset of cells are cytotoxic group 1 ILCs, which have the ability to recognize infected cells or tumor cells, through loss of cell surface MHC class I. NK cells lyse target cells *via* cytotoxic granules (perforin, granzymes) on first encounter without any prerequisite activation. Cytotoxic NK cells may also perform their role *via* antibody-dependent cellular cytotoxicity. They also secrete cytokines (such as IFNγ, TNFα), which activate other effector cells, resulting in phagocytosis and destruction of the pathogen.

In CKD patients, activated NK cells are thought to play a role in progression of CKD and renal fibrosis.[209] In ESRD patients, the activity of NK cells is downregulated,[210] possibly as a result of the chronic inflammatory state and increased levels of proinflammatory mediators.

Innate Cellular Immunity: Effector Cells: Granulocytes (Other than Neutrophils)

Circulating basophils (granulocyte WBCs)[211] and tissue-resident mast cells[212] play a major role in eliciting immediate and late-phase hypersensitivity/allergic reactions, as well as in the defense against parasitic infections. Basophil activation may be IgE-dependent. In this case, IgE-dependent cross-linking results in cell degranulation, with release of preformed mediators (mainly histamine and leukotriene C4 [LT-C4]), and *de novo* synthesis and secretion of cytokines (IL-4 and IL-13). Basophil activation may also be IgE-independent in response to PAMPs recognition by TLR-2/TLR-4 ligands, interaction with complement component 5a receptor (C5aR) or helper T cells (TH2) cytokines. The end result is cytokine synthesis and release.

Similar to tissue-resident macrophages, mast cells function as quite effective sentinels for immediate detection of pathogen exposure. In addition to their role as effector cells, basophils and mast cells also play an immunomodulatory role.[212,213] In patients with ESRD, basophil function is impaired with impaired adhesion and degranulation.[214] CKD patients have an increased kidney mast cell population. Mast cells have been associated with chronic local inflammation, progression of CKD, and renal fibrosis.[215]

The activation of eosinophils (granulocyte WBCs),[216] with or without degranulation is essential in the defense against parasitic infections, leading to the release of preformed cytotoxic proteins, lyzoymes, cytokines, chemokines, and leukotrienes. Eosinophils also play a key role in immunoregulation. Patients with CKD tend to have a higher blood eosinophil count,[201] and a spike in blood eosinophil count is an independent predictor of increased risk of ESRD and death.

Innate Humoral Immunity

Humoral innate defenses include additional physiological barriers such as proteins with immune function, such as antimicrobial peptides and acute phase proteins and cytokines, as well as complement proteins from any of the three complement activation pathways: the classical pathway, the alternative pathway, and the mannose-binding lectin (MBL) pathway.

The complement system plays a major role in opsonization of pathogens. It incorporates a large number of circulating proteins, which on recognition of a pathogen component, trigger one of the three series of activation reactions. Antibody–antigen complexes bind C1 to activate the classical pathway, pathogen cell surface proteins bind C3b to activate the alternative pathway, and mannose residues on pathogen surfaces bind MBL, activating the MBL pathway. All three activated complement pathways converge to form C3-convertase, which activates C3 and the lytic pathway with the production of C5b-9 or the membrane attack complex (MAC), while producing byproducts. These byproducts include C3b, which serves the role of opsonin, C3a, which activates

mast cells, and C5a that also activates mast cells and in addition chemotactically recruits neutrophils and macrophages. The MAC binds the pathogen's cell surface, resulting in lytic cell death.

In CKD patients, the cytokine response to pathogen exposure is impaired, whereas basal proinflammatory cytokine levels are elevated.[160,166,217,218] The basal elevation may be due to primed effector cells as well as decreased renal clearance. The latter seems to affect the balance in favor of proinflammatory cytokines. For example, TNFα levels are elevated in uremic patients and promote oxidative stress and chronic inflammation.[219]

In patients with proteinuria, loss of proteins with immune functions may also increase risk of infection. A multiplex proteomics assay identified 28 proteins whose levels were associated with the annual change in eGFR. Eleven of these predicted the incidence of CKD. Proteins linked to inflammation included TNF-related apoptosis-inducing ligand receptor 2, TNF receptor 1, TNF receptor 2, CD40L receptor, FGF-23, macrophage colony-stimulating factor 1, and MCP-1.[220] ESRD patients have a significant increase in MBL levels. During an infection a low level predicts higher mortality rate.[160,221] Endotoxin tolerance has also been hypothesized.

Adaptive Cellular Immunity: an Overview

Adaptive immunity is antigen-specific and is elicited by T cells and B cells. Adaptive immunity is mounted over days by acquired cellular and humoral responses, with the development of lasting immunologic memory.

Adaptive Cellular Immunity: T Cells

The champion effectors of adaptive cellular immunity are the T lymphocytes, which mature in the thymus into naive T cells and eventually become either CD4+ helper T cells (subtypes include Th1, Th2, and Th17), CD8+ cytotoxic T cells, or natural regulatory T cells (Tregs: CD4+ CD25+) in secondary lymphoid tissues (lymph nodes, spleen, mucosa-associated lymphoid tissue [MALT]).

T cell activation and proliferation follows a three-signal model. The first signal to trigger T cell activation is specific, occurring when a T cell receptor (TCR) binds to a non-self antigen scavenged by an APC. For the antigen to be recognized by the T cell, it has to be loaded to the MHC class II receptor on the surface of APCs. The TCR-MHCII complex is further stabilized by the T cell CD4 or CD8 coreceptor. A second general (nonspecific) signal, mediated by the interaction of APC costimulatory receptors with T-cell ligands, is required to trigger full T-cell activation and proliferation. Exposure to a pathogen activates helper T cell CD28, which binds to APC surface molecule CD80 (B7.1) or CD86 (B7.2), triggering T cell proliferation as well as the production of CD152 (CTLA-4), which competes with CD28 for the binding of CD80/CD86, regulating the degree of T cell activation and proliferation. A third signal, in the form of cytokines, helps T cells differentiate and mature into what is needed in the tissue to conquer and degrade the pathogen.

When CD4+ helper T cells are activated *via* the MHC class II three-signal model, they induce and regulate the adaptive immune response. Th1 cells synthesize and release IL2 and IFNγ; recruit macrophages, neutrophils, and cytotoxic T cells; and play a major role in neutralizing intracellular pathogens (such as viruses and bacteria). Th2 cells synthesize and release IL4, IL5, IL6, IL10, and IL13; recruit eosinophils and mast cells; stimulate B-cell antibody production; and play a major role in neutralizing extracellular pathogens (such as helminths and bacteria). Th17 cells synthesize and release IL17, in response to APC secretion of IL23, and play a role in instigating an inflammatory response and recruiting Th2 and NK cells.

CD8+ cytotoxic T cells are serial killers. They may also be activated following recognition and binding of the TCR to antigenic peptides presented by MHC class I molecules and play a major role in destruction of cells infected with intracellular pathogens or invaded by tumor cells. Their cytotoxicty pathways may be cytokine mediated (IFNγ, TNFα), or involve targeted cytotoxic granules (such as perforin and granzymes), or *via* the binding of CD8+ T cell Fas ligand to fas receptor on the surface of the target cell, thus activating the caspase cascade, resulting in cell death. Because CD8+ T cells can express both Fas and Fas ligand, this last mechanism is used to shape and downregulate the immune response *via* CD8+ T cell fratricide.

Helper T-cell activation and proliferation in response to a pathogen is decreased in CKD.[222–225] This is characterized by a dysfunctional second signal (the APC-costimulation signal), which is believed to be due to decreased expression of costimulatory surface molecules on the APC surface. The chronic priming or activation of APCs and the hypercytokinemia also blunt T-cell activation. Finally, cytokines seem to shift helper T-cell differentiation in favor of Th1 rather than Th2, with a subsequent decline in B-cell activation and antibody production.

Furthermore, CKD patients have an abnormal ratio of CD4+/CD8+ cells in favor of an excess of cytotoxic T cells and manifest overexpression of CD8+ T cell Fas ligand. Their T-cell lines, including naïve and memory

T cells, have accelerated apoptosis.[223,226,227] The Treg population is also decreased in CKD[228–230] and manifests increased susceptibility to apoptosis, a process mediated by oxidized low-density lipoprotein.

Adaptive Humoral Immunity: B Cells

The proponent effectors of adaptive humoral immunity are the B lymphocytes, which mature in the bone marrow (the other primary lymphoid tissue) and produce immunoglobulins (Ig). B cell activation occurs on the binding of a B cell receptor to a circulating free or membrane-bound antigen, triggering a chain of bidirectional activation signals between B cells and Th2 Cells. B cells then can differentiate into short-lived plasma cells that secrete antibodies, providing a rapid response. Alternatively B cells can establish a germline center in secondary lymphoid tissue for B cell maturation and proliferation, resulting in memory B cells and long-lived plasma cells. These cells capable of Ig class switch recombination and can produce high-affinity antigen-specific antibodies.

CKD is associated with a reduction in B-cell activation, proliferation, immunoregulation, and antibody production.[231,232] In ESRD patients, all subpopulations of B cells were reduced resulting in B-cell lymphopenia.[187] This may be mediated by a diminished Th1 cell population and increased apoptosis.[233–235]

The Aftermath of an Immune Response to a Pathogen Exposure

After immune activation and containment of a pathogen, not only is it paramount for the immune response to be proportionate and measured, but it is also important for it to dissipate and be part of the healing and repair process to restore a healthy and steady-state immune homeostasis. An intact immune system is essential to "clean up" after infection, to avoid a residual chronic inflammatory state. Apoptosis (programmed cell death) is a physiologic process, which occurs in the maintenance of tissue homeostasis. Apoptotic cells express unique characteristics, which assist phagocytes to target and kill them with little if any immune reaction. Apoptosis of immune effector cells has to occur at the right moment in the timeline of an immune reaction to pathogen exposure. If the timeline occurs early, due to enhanced immune effector cell apoptosis, this will result in an attenuated immune response and inability to control infection. If timeline occurs late, due to delayed apoptosis or impaired clearance of apoptotic PMNs by macrophages, then a persistent inflammatory state may ensue. The most proapoptotic stimuli studied, which might be affected in CKD, are TNF-α and Fas ligand. Immunoglobulin light chains have been found to have antiapoptotic effects.

Chronic Inflammation and Immune Dysfunction in CKD

Chronic inflammation is a risk factor for cardiovascular mortality in patients with CKD. The relationship between CKD and chronic inflammation is complex, multifaceted, and not completely understood. Both eGFR reduction and glomerular podocyte injury manifested as microalbuminuria or macroalbuminuria promote a proinflammatory state and tubulointerstitial disease.[236,237]

The pathophysiology of the chronic inflammation is multifactorial. CKD is associated with chronic stimulation of the renin–angiotensin–aldosterone system (RAAS). Both angiotensin II and aldosterone promote oxidative stress and chronic inflammation. Acidosis and use of less biocompatible membranes or venous catheters for access in HD patients have also been shown to promote inflammation.[238]

In addition, there is growing evidence that CKD patients have altered gut microbiota (intestinal dysbiosis), and intestinal inflammation with significant disruptions in the functional integrity of the intestinal epithelial barrier,[239–241] resulting in a "leaky gut" and translocation of bacterial deoxyribonucleic acid (DNA) and endotoxins into the systemic circulation. The endotoxemia plays an important role in generating or maintaining the inflammatory state in CKD. Blood endotoxin levels correlate with severity of CKD, predict the severity of inflammation, and correlate with atherosclerosis risk.

Dietary restrictions imposed on patients with advanced CKD (especially low potassium and low phosphorus diets) dictate a low plant fiber intake. This diet results in a secondary change in the gut microbiome. Epidemiologic studies suggest that a high-fiber diet promotes the growth of endosymbiotic bacteria, preventing gram-negative bacterial overgrowth and the production of endotoxins and gut-derived uremic toxins, and thereby minimizing these triggers of systemic inflammation. Similarly, some observational studies suggest a beneficial role of prebiotics (ingested nondigestible compounds, which enhance bacterial growth and activity, e.g. chicory), and probiotics (ingested live organisms, such as yogurts). Finally, many CKD patients have comorbidities, such as diabetes mellitus, which are a significant source of inflammation and infection.

Diagnosis: Infectious Complications of CKD

CKD patients may have a blunted immune response to infection. The classical signs and symptoms of infection, such as fever or leukocytosis, therefore may not always be present. Patients with ESRD may present with nonspecific symptoms. Diagnosis is usually based on a focused history and physical examination. Additional

diagnostic tools, such as cultures and or imaging studies, may be ordered when indicated.

Prognosis: Infectious Complications of CKD

CKD patients have an increase in the rate and in the severity of infections, with a secondary increase in all-cause mortality as well as cardiovascular mortality. Infection is the second most common cause of death, after CVD, in the ESRD population.

The basal chronic inflammatory state not only potentiates but is sometimes also enhanced by other complications of CKD, such as atherogenesis and CVD,[242,243] ACKD,[32] mineral and bone disorder (MBD),[183,244–247] protein energy wasting (PEW) and protein-calorie malnutrition, and secondary muscle wasting and cachexia.[248–250] Thus, a thorough strategy to mitigate inflammation and potential sources of infection is essential.

Treatment: Infectious Complications of CKD

Infections should be treated with targeted empirical antimicrobial therapy, and in a timely fashion in CKD patients, due to their acquired immunodeficiency and concerns regarding potentially increased severity. Dosing of antimicrobial therapy must be adjusted to the eGFR as needed. At the conclusion of the diagnostic evaluation, the antimicrobial regimen may be modified based on pathogen identification and susceptibility.

Prevention may play a key role in decreasing infection and inflammation in CKD patients. Avoidance or expedited removal of venous catheters as accesses for dialysis is imperative. Treatment and correction of metabolic acidosis and MBD, regular foot examinations in diabetic patients, evidence-based use of renin–angiotensin–aldosterone blockers in patients with proteinuria (where therapy may minimize loss of proteins with immune functions), physical activity, and dietary interventions, which may help restore the gut microbiota and treat PEW may all prove helpful.

Suboptimal response to immunizations, due to acquired impairment in T-cell dependent immunity, has been well described in CKD patients.[232,251] The rate of nonresponders is relatively high especially with advanced CKD and ESRD. The response of tuberculosis skin testing is impaired in ESRD patients, reducing its utility to diagnose latent tuberculosis.

Both the CDC and the 2012 KDIGO clinical practice guideline recommend that all patients with CKD, regardless of stage, receive the annual age-appropriate inactivated influenza vaccine.[252] Pneumococcal vaccination, ideally pneumococcal conjugate vaccine (PCV13) followed by pneumococcal polysaccharide vaccine (PPSV23), and a booster offered every five years, is advised for patients aged 65 years or older, or with stage 4–5 CKD (eGFR $<30\,mL/min/1.73\,m^2$) and ESRD. Tetanus, diphtheria, and pertussis vaccination should be offered every ten years after initial dose. Zoster recombinant zoster vaccine is recommended in a series of two doses, two to six months apart, for CKD patients aged 50 years or older. Finally, hepatitis B vaccination series at 0, 1, and 6 months is advised for all patients with ESRD who are susceptible (especially the HD population, and preferably in stage 4–5 CKD) as this approach has been associated with a higher rate of responsiveness to the vaccine.

Conclusions: Infectious Complications of CKD

CKD is associated with a state of immune deficiency on exposure to pathogens, increasing the risk and severity of infections in this population, with secondary risk of morbidity and mortality (Figure 31.3). This state of immune incompetence is mediated by dysfunctional innate immunity in response to pathogens, with diminished PRR expression and blunted phagocyte function, affecting adhesion, chemotaxis, cytokine and ROS production, signaling, endocytosis, proteolytic activity, and antigen-presentation capacity. Adaptive immunity is also affected, with a decrease in T cell activation and proliferation, with disruption of the ratio of Th1/Th2 cells in favor of Th1 cells, and in the ratio of CD4+/CD8+ T cells in favor of CD8+ T cells, as well as increased susceptibility to early and accelerated apoptosis. Similarly B-cell activation and proliferation is decreased, as is immunoglobulin production, while apoptosis is increased.

On the other hand, CKD is associated with a state of basal immune activation, oxidative stress and chronic sterile inflammation, also associated with an increase in morbidity and mortality (Figure 31.3). This state of basal immune activation may be in response to a multitude of factors (such as altered gut microbiota and low level endotoxemia, acidosis, RAAS activation, dialysis membrane characteristics, and dialysis water quality). Immune activation is mainly mediated by primed or preactivated neutrophils and monocytes, increased levels of proinflammatory cytokines, and an aberrant complement system activity. Chronic inflammation and oxidative stress are interlinked with other undesirable outcomes such as enhanced atherosclerosis, PEW, MBD, obesity, and insulin resistance.

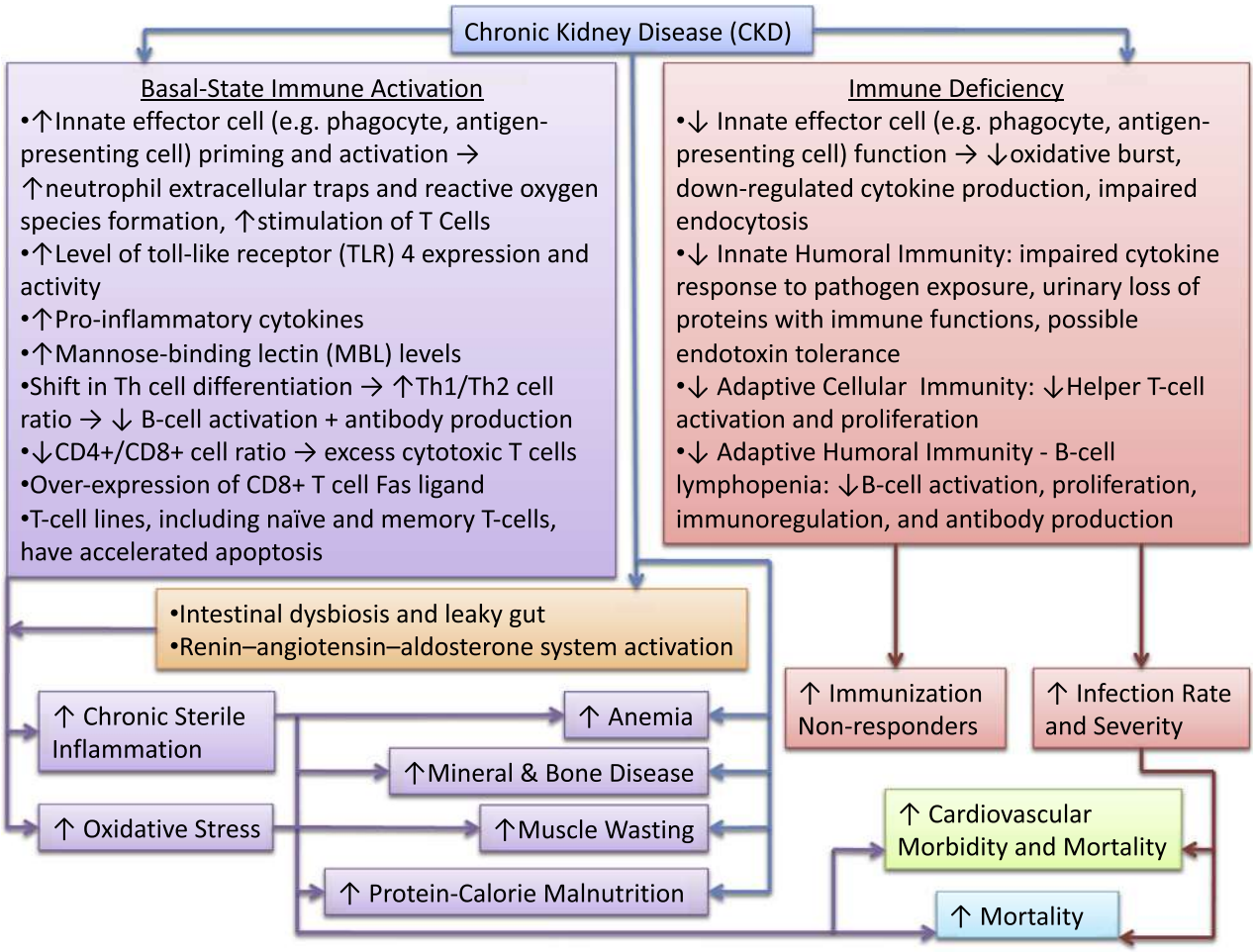


FIGURE 31.3 Immune dysfunction in chronic kidney disease, and how it may lead to increased risk for infection and cardiovascular disease.

COI/Disclosures

Jay I. Lakkis: Dialysis Medical Director in Maui, Hawaii for Fresenius Medical Care North America.
Matthew R. Weir: Scientific Advisor: Amgen, Akebia, AstraZeneca, and Vifor. Grant support: R01DK066013, U01DK106102, U01DK116095, R01HL127422, and R01HL132372.

References

1. Saran R, Robinson B, Abbott KC, Agodoa LYC, Bhave N, Bragg-Gresham J, et al. US renal data system 2017 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2018;**71**(3S1):A7.
2. Schiller JS, Clark TC, Norris T. *Early release of selected estimates based on data from the January–September 2017 National Health Interview Survey. Leisure-time physical activity.* Centers for Disease Control and Prevention. Chronic Kidney Disease Surveillance System—United States. website: http://www.cdc.gov/ckd. Available from: https://nccd.cdc.gov/ckd/.
3. Murphy D, McCulloch CE, Lin F, Banerjee T, Bragg-Gresham JL, Eberhardt MS, et al. Trends in prevalence of chronic kidney disease in the United States. *Ann Intern Med* 2016;**165**(7):473–81.
4. Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol* 2006;**17**(8):2275–84.
5. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet Lond Engl* 2010;**375**(9731):2073–81.
6. Hillege HL, Fidler V, Diercks GFH, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002;**106**(14):1777–82.
7. Tanaka F, Komi R, Makita S, Onoda T, Tanno K, Ohsawa M, et al. Low-grade albuminuria and incidence of cardiovascular disease and all-cause mortality in nondiabetic and normotensive individuals. *J Hypertens* 2016;**34**(3):506–12. discussion 512.
8. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**(13):1296–305.
9. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease,

High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003;**108**(17):2154–69.
10. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006;**17**(7):2034–47.
11. Drey N, Roderick P, Mullee M, Rogerson M. A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. *Am J Kidney Dis* 2003;**42**(4):677–84.
12. Stirnadel-Farrant HA, Luo J, Kler L, Cizman B, Jones D, Brunelli SM, et al. Anemia and mortality in patients with nondialysis-dependent chronic kidney disease. *BMC Nephrol* 2018;**19**(1):135.
13. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The impact of anemia on cardiomyopathy, morbidity, and and mortality in end-stage renal disease. *Am J Kidney Dis* 1996;**28**(1): 53–61.
14. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PLoS One* 2014;**9**(1):e84943.
15. St Peter WL, Guo H, Kabadi S, Gilbertson DT, Peng Y, Pendergraft T, et al. Prevalence, treatment patterns, and healthcare resource utilization in Medicare and commercially insured non-dialysis-dependent chronic kidney disease patients with and without anemia in the United States. *BMC Nephrol* 2018; **19**(1):67.
16. Zeisberg M, Kalluri R. Physiology of the renal interstitium. *Clin J Am Soc Nephrol* 2015;**10**(10):1831–40.
17. Haase VH. HIF-prolyl hydroxylases as therapeutic targets in erythropoiesis and iron metabolism. *Hemodial Int* 2017; **21**(Suppl. 1):S110–24.
18. Panwar B, Gutiérrez OM. Disorders of iron metabolism and anemia in chronic kidney disease. *Semin Nephrol* 2016;**36**(4):252–61.
19. Camaschella C. Iron-deficiency anemia. *N Engl J Med* 2015; **372**(19):1832–43.
20. Thomas DW, Hinchliffe RF, Briggs C, Macdougall IC, Littlewood T, Cavill I, et al. Guideline for the laboratory diagnosis of functional iron deficiency. *Br J Haematol* 2013;**161**(5):639–48.
21. Fleming RE, Ponka P. Iron overload in human disease. *N Engl J Med* 2012;**366**(4):348–59.
22. Drakesmith H, Nemeth E, Ganz T. Ironing out ferroportin. *Cell Metabol* 2015;**22**(5):777–87.
23. Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science* 2004; **306**(5704):2090–3.
24. Langer AL, Ginzburg YZ. Role of hepcidin-ferroportin axis in the pathophysiology, diagnosis, and treatment of anemia of chronic inflammation. *Hemodial Int* 2017;**21**(Suppl. 1):S37–46.
25. Bârsan L, Stanciu A, Stancu S, Căpusă C, Brătescu L, Mandache E, et al. Bone marrow iron distribution, hepcidin, and ferroportin expression in renal anemia. *Hematol Amst Neth* 2015;**20**(9):543–52.
26. Ganz T, Nemeth E. Iron balance and the role of hepcidin in chronic kidney disease. *Semin Nephrol* 2016;**36**(2):87–93.
27. Bacchetta J, Zaritsky JJ, Sea JL, Chun RF, Lisse TS, Zavala K, et al. Suppression of iron-regulatory hepcidin by vitamin D. *J Am Soc Nephrol* 2014;**25**(3):564–72.
28. David V, Martin A, Isakova T, Spaulding C, Qi L, Ramirez V, et al. Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production. *Kidney Int* 2016;**89**(1):135–46.
29. KDOQI, National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis* 2006;**47**(5 Suppl. 3): S11–145.
30. Coronado Daza J, Martí-Carvajal AJ, Ariza García A, Rodelo Ceballos J, Yomayusa González N, Páez-Canro C, et al. Early versus delayed erythropoietin for the anaemia of end-stage kidney disease. *Cochrane Database Syst Rev* 2015;(12):CD011122.
31. Palmer SC, Saglimbene V, Mavridis D, Salanti G, Craig JC, Tonelli M, et al. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. *Cochrane Database Syst Rev* 2014;**12**:CD010590.
32. Babitt JL, Lin HY. Mechanisms of anemia in CKD. *J Am Soc Nephrol* 2012;**23**(10):1631–4.
33. Gossmann J, Burkhardt R, Harder S, Lenz T, Sedlmeyer A, Klinkhardt U, et al. Angiotensin II infusion increases plasma erythropoietin levels via an angiotensin II type 1 receptor-dependent pathway. *Kidney Int* 2001;**60**(1):83–6.
34. Freudenthaler SM, Schenck T, Lucht I, Gleiter CH. Fenoterol stimulates human erythropoietin production via activation of the renin angiotensin system. *Br J Clin Pharmacol* 1999;**48**(4):631–4.
35. Freudenthaler S, Benöhr P, Grenz A, Selzer T, Schmidt T, Mörike K, et al. Do alterations of endogenous angiotensin II levels regulate erythropoietin production in humans? *Br J Clin Pharmacol* 2003;**56**(4):378–87.
36. Matsumura M, Nomura H, Koni I, Mabuchi H. Angiotensin-converting enzyme inhibitors are associated with the need for increased recombinant human erythropoietin maintenance doses in hemodialysis patients. Risks of Cardiac Disease in Dialysis Patients Study Group. *Nephron* 1997;**77**(2):164–8.
37. Navarro JF, Mora C, Rivero A. Effect of angiotensin-converting enzyme inhibitors on hematological parameters and recombinant human erythropoietin doses in peritoneal dialysis patients. *Nephron* 1998;**80**(2):239.
38. Cheungpasitporn W, Thongprayoon C, Chiasakul T, Korpaisarn S, Erickson SB. Renin-angiotensin system inhibitors linked to anemia: a systematic review and meta-analysis. *QJM* 2015;**108**(11):879–84.
39. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2012;(2):279–335.
40. Mikhail A, Brown C, Williams JA, Mathrani V, Shrivastava R, Evans J, et al. Renal association clinical practice guideline on anaemia of chronic kidney disease. *BMC Nephrol* 2017;**18**(1):345.
41. National Clinical Guideline Centre (UK). *Anaemia management in chronic kidney disease: partial update 2015*. London: Royal College of Physicians (UK); 2015 (National Institute for Health and Care Excellence: Clinical Guidelines). Available from: http://www.ncbi.nlm.nih.gov/books/NBK299242/.
42. Kliger AS, Foley RN, Goldfarb DS, Goldstein SL, Johansen K, Singh A, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for anemia in CKD. *Am J Kidney Dis* 2013; **62**(5):849–59.
43. Locatelli F, Pisoni RL, Combe C, Bommer J, Andreucci VE, Piera L, et al. Anaemia in haemodialysis patients of five European countries: association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2004;**19**(1):121–32.
44. Portolés J, Gorriz JL, Rubio E, de Alvaro F, García F, Alvarez-Chivas V, et al. The development of anemia is associated to poor prognosis in NKF/KDOQI stage 3 chronic kidney disease. *BMC Nephrol* 2013;**14**:2.
45. Garlo K, Williams D, Lucas L, Wong R, Botler J, Abramson S, et al. Severity of anemia predicts hospital length of stay but not readmission in patients with chronic kidney disease: a retrospective cohort study. *Medicine (Baltim)* 2015;**94**(25):e964.
46. Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* 1999;**34**(1):125–34.
47. Xu D, Murakoshi N, Sairenchi T, Irie F, Igarashi M, Nogami A, et al. Anemia and reduced kidney function as risk factors for new onset of atrial fibrillation (from the Ibaraki prefectural health study). *Am J Cardiol* 2015;**115**(3):328–33.

48. Vinhas J, Barreto C, Assunção J, Parreira L, Vaz A. Treatment of anaemia with erythropoiesis-stimulating agents in patients with chronic kidney disease does not lower mortality and may increase cardiovascular risk: a meta-analysis. *Nephron Clin Pract* 2012; **121**(3–4):c95–101.
49. Collister D, Komenda P, Hiebert B, Gunasekara R, Xu Y, Eng F, et al. The effect of erythropoietin-stimulating agents on health-related quality of life in anemia of chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2016;**164**(7):472–8.
50. Cody JD, Hodson EM. Recombinant human erythropoietin versus placebo or no treatment for the anaemia of chronic kidney disease in people not requiring dialysis. *Cochrane Database Syst Rev* 2016; (1):CD003266.
51. Roger SD, Tio M, Park H-C, Choong HL, Goh B, Cushway TR, et al. Intravenous iron and erythropoiesis-stimulating agents in haemodialysis: a systematic review and meta-analysis. *Nephrol Carlton Vic* 2017;**22**(12):969–76.
52. Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: an updated systematic review and meta-analysis. *Am J Kidney Dis* 2016;**68**(5):677–90.
53. Macdougall IC, Bock AH, Carrera F, Eckardt K-U, Gaillard C, Van Wyck D, et al. FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia. *Nephrol Dial Transplant* 2014;**29**(11):2075–84.
54. Robinson BM, Larkina M, Bieber B, Kleophas W, Li Y, Locatelli F, et al. Evaluating the effectiveness of IV iron dosing for anemia management in common clinical practice: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *BMC Nephrol* 2017;**18**(1):330.
55. Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG. Time-dependent associations between iron and mortality in hemodialysis patients. *J Am Soc Nephrol* 2005;**16**(10): 3070–80.
56. Hougen I, Collister D, Bourrier M, Ferguson T, Hochheim L, Komenda P, et al. Safety of intravenous iron in dialysis: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2018;**13**(3): 457–67.
57. Wang C, Graham DJ, Kane RC, Xie D, Wernecke M, Levenson M, et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. *J Am Med Assoc* 2015;**314**(19):2062–8.
58. Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. *Kidney Int* 2015;**88**(4): 905–14.
59. Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. *BMJ* 2013;**347**:f4822.
60. Brookhart MA, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Kshirsagar AV. Infection risk with bolus versus maintenance iron supplementation in hemodialysis patients. *J Am Soc Nephrol* 2013; **24**(7):1151–8.
61. Parkkinen J, von Bonsdorff L, Peltonen S, Grönhagen-Riska C, Rosenlöf K. Catalytically active iron and bacterial growth in serum of haemodialysis patients after i.v. iron-saccharate administration. *Nephrol Dial Transplant* 2000;**15**(11):1827–34.
62. Vaziri ND. Understanding iron: promoting its safe use in patients with chronic kidney failure treated by hemodialysis. *Am J Kidney Dis* 2013;**61**(6):992–1000.
63. Rostoker G, Griuncelli M, Loridon C, Couprie R, Benmaadi A, Bounhiol C, et al. Hemodialysis-associated hemosiderosis in the era of erythropoiesis-stimulating agents: a MRI study. *Am J Med* 2012;**125**(10):991–9. e1.
64. Farah M, Crawford RI, Levin A, Chan Yan C. Calciphylaxis in the current era: emerging "ironic" features? *Nephrol Dial Transplant* 2011;**26**(1):191–5.
65. Patterson DS, Allen WM. Calcium mobilisation and calciphylaxis in piglets induced by iron injections. *Vet Rec* 1970;**86**(26):791.
66. Pfeffer MA, Burdmann EA, Chen C-Y, Cooper ME, de Zeeuw D, Eckardt K-U, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;**361**(21):2019–32.
67. Glassock RJ, Pecoits-Filho R, Barberato SH. Left ventricular mass in chronic kidney disease and ESRD. *Clin J Am Soc Nephrol* 2009; **4**(Suppl. 1):S79–91.
68. Research C for DE and. *Postmarket drug safety information for patients and providers - information for Epogen/Procrit (epoetin alfa)*. Available from: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm541173.htm.
69. Research C for DE and. *Postmarket drug safety information for patients and providers - information for Aranesp (darbepoetin alfa)*. Available from: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm541148.htm.
70. *Drug approval package: Mircera (methoxy polyethylene glycol-epoetin beta) NDA #125164*. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/125164TOC.cfm.
71. Research C for DE and. *Approved drugs - FDA approves Retacrit as a biosimilar to Epogen/Procrit*. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm607723.htm.
72. Phrommintikul A, Haas SJ, Elsik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. *Lancet Lond Engl* 2007;**369**(9559):381–8.
73. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;**355**(20):2085–98.
74. Inrig JK, Sapp S, Barnhart H, Patel UD, Reddan D, Singh A, et al. Impact of higher hemoglobin targets on blood pressure and clinical outcomes: a secondary analysis of CHOIR. *Nephrol Dial Transplant* 2012;**27**(9):3606–14.
75. Drüeke TB, Locatelli F, Clyne N, Eckardt K-U, Macdougall IC, Tsakiris D, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; **355**(20):2071–84.
76. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;**339**(9): 584–90.
77. Brookhart MA, Schneeweiss S, Avorn J, Bradbury BD, Liu J, Winkelmayer WC. Comparative mortality risk of anemia management practices in incident hemodialysis patients. *J Am Med Assoc* 2010;**303**(9):857–64.
78. Solomon SD, Uno H, Lewis EF, Eckardt K-U, Lin J, Burdmann EA, et al. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. *N Engl J Med* 2010;**363**(12):1146–55.
79. Koulouridis I, Alfayez M, Trikalinos TA, Balk EM, Jaber BL. Dose of erythropoiesis-stimulating agents and adverse outcomes in CKD: a metaregression analysis. *Am J Kidney Dis* 2013;**61**(1):44–56.
80. Saglimbene VM, Palmer SC, Ruospo M, Natale P, Craig JC, Strippoli GF. Continuous erythropoiesis receptor activator (CERA) for the anaemia of chronic kidney disease. *Cochrane Database Syst Rev* 2017 07;**8**:CD009904.
81. Hahn D, Esezobor CI, Elserafy N, Webster AC, Hodson EM. Short-acting erythropoiesis-stimulating agents for anaemia in predialysis patients. *Cochrane Database Syst Rev* 2017 09;**1**:CD011690.

82. Besarab A, Reyes CM, Hornberger J. Meta-analysis of subcutaneous versus intravenous epoetin in maintenance treatment of anemia in hemodialysis patients. *Am J Kidney Dis* 2002;**40**(3):439–46.
83. Elliott S, Tomita D, Endre Z. Erythropoiesis stimulating agents and reno-protection: a meta-analysis. *BMC Nephrol* 2017;**18**(1):14.
84. Covic A, Nistor I, Donciu M-D, Dumea R, Bolignano D, Goldsmith D. Erythropoiesis-stimulating agents (ESA) for preventing the progression of chronic kidney disease: a meta-analysis of 19 studies. *Am J Nephrol* 2014;**40**(3):263–79.
85. Eckardt KU. Cardiovascular consequences of renal anaemia and erythropoietin therapy. *Nephrol Dial Transplant* 1999;**14**(5): 1317–23.
86. Krapf R, Hulter HN. Arterial hypertension induced by erythropoietin and erythropoiesis-stimulating agents (ESA). *Clin J Am Soc Nephrol* 2009;**4**(2):470–80.
87. Robles NR. The safety of erythropoiesis-stimulating agents for the treatment of anemia resulting from chronic kidney disease. *Clin Drug Investig* 2016;**36**(6):421–31.
88. Seliger SL, Zhang AD, Weir MR, Walker L, Hsu VD, Parsa A, et al. Erythropoiesis-stimulating agents increase the risk of acute stroke in patients with chronic kidney disease. *Kidney Int* 2011;**80**(3): 288–94.
89. Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. *Lancet Lond Engl* 2009; **373**(9674):1532–42.
90. Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, et al. Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev* 2012;**12**:CD003407.
91. Holdstock L, Meadowcroft AM, Maier R, Johnson BM, Jones D, Rastogi A, et al. Four-week studies of oral hypoxia-inducible factor-prolyl hydroxylase inhibitor GSK1278863 for treatment of anemia. *J Am Soc Nephrol* 2016;**27**(4):1234–44.
92. Ariazi JL, Duffy KJ, Adams DF, Fitch DM, Luo L, Pappalardi M, et al. Discovery and preclinical characterization of GSK1278863 (daprodustat), a small molecule hypoxia inducible factor-prolyl hydroxylase inhibitor for anemia. *J Pharmacol Exp Ther* 2017; **363**(3):336–47.
93. Brigandi RA, Johnson B, Oei C, Westerman M, Olbina G, de Zoysa J, et al. A novel hypoxia-inducible factor-prolyl hydroxylase inhibitor (GSK1278863) for anemia in CKD: a 28-day, phase 2A randomized trial. *Am J Kidney Dis* 2016;**67**(6):861–71.
94. Sugahara M, Tanaka T, Nangaku M. Prolyl hydroxylase domain inhibitors as a novel therapeutic approach against anemia in chronic kidney disease. *Kidney Int* 2017;**92**(2):306–12.
95. Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: a potential new treatment for anemia in patients with CKD. *Am J Kidney Dis* 2017;**69**(6):815–26.
96. Besarab A, Chernyavskaya E, Motylev I, Shutov E, Kumbar LM, Gurevich K, et al. Roxadustat (FG-4592): correction of anemia in incident dialysis patients. *J Am Soc Nephrol* 2016;**27**(4):1225–33.
97. Pergola PE, Spinowitz BS, Hartman CS, Maroni BJ, Haase VH. Vadadustat, a novel oral HIF stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease. *Kidney Int* 2016;**90**(5):1115–22.
98. Flamme I, Oehme F, Ellinghaus P, Jeske M, Keldenich J, Thuss U. Mimicking hypoxia to treat anemia: HIF-stabilizer BAY 85-3934 (Molidustat) stimulates erythropoietin production without hypertensive effects. *PLoS One* 2014;**9**(11):e111838.
99. Eckardt KU, Möllmann M, Neumann R, Brunkhorst R, Burger HU, Lonnemann G, et al. Erythropoietin in polycystic kidneys. *J Clin Investig* 1989;**84**(4):1160–6.
100. Goodkin DA, Fuller DS, Robinson BM, Combe C, Fluck R, Mendelssohn D, et al. Naturally occurring higher hemoglobin concentration does not increase mortality among hemodialysis patients. *J Am Soc Nephrol* 2011;**22**(2):358–65.
101. Vlahakos DV, Marathias KP, Agroyannis B, Madias NE. Posttransplant erythrocytosis. *Kidney Int* 2003;**63**(4):1187–94.
102. Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. *Semin Thromb Hemost* 2010; **36**(1):34–40.
103. Galbusera M, Remuzzi G, Boccardo P. Treatment of bleeding in dialysis patients. *Semin Dial* 2009;**22**(3):279–86.
104. Kim HY, Oak CY, Kim MJ, Kim CS, Choi JS, Bae EH, et al. Prevalence and associations for abnormal bleeding times in patients with renal insufficiency. *Platelets* 2013;**24**(3):213–8.
105. Mahmoodi BK, Gansevoort RT, Næss IA, Lutsey PL, Brækkan SK, Veeger NJGM, et al. Association of mild to moderate chronic kidney disease with venous thromboembolism: pooled analysis of five prospective general population cohorts. *Circulation* 2012; **126**(16):1964–71.
106. Molnar AO, Bota SE, Garg AX, Harel Z, Lam N, McArthur E, et al. The risk of major hemorrhage with CKD. *J Am Soc Nephrol* 2016; **27**(9):2825–32.
107. Ocak G, Rookmaaker MB, Algra A, de Borst GJ, Doevendans PA, Kappelle LJ, et al. Chronic kidney disease and bleeding risk in patients at high cardiovascular risk: a cohort study. *J Thromb Haemost* 2018;**16**(1):65–73.
108. Attallah N, Yassine L, Fisher K, Yee J. Risk of bleeding and restenosis among chronic kidney disease patients undergoing percutaneous coronary intervention. *Clin Nephrol* 2005;**64**(6):412–8.
109. Jun M, James MT, Manns BJ, Quinn RR, Ravani P, Tonelli M, et al. The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study. *BMJ* 2015;**350**:h246.
110. Ishigami J, Grams ME, Naik RP, Coresh J, Matsushita K. Chronic kidney disease and risk for gastrointestinal bleeding in the community: the atherosclerosis risk in communities (ARIC) study. *Clin J Am Soc Nephrol* 2016 07;**11**(10):1735–43.
111. Luo J-C, Leu H-B, Hou M-C, Huang K-W, Lin H-C, Lee F-Y, et al. Nonpeptic ulcer, nonvariceal gastrointestinal bleeding in hemodialysis patients. *Am J Med* 2013;**126**(3):264. e25-32.
112. Gremmel T, Frelinger AL, Michelson AD. Platelet physiology. *Semin Thromb Hemost* 2016;**42**(3):191–204.
113. Nuyttens BP, Thijs T, Deckmyn H, Broos K. Platelet adhesion to collagen. *Thromb Res* 2011;**127**(Suppl. 2):S26–29.
114. De Candia E. Mechanisms of platelet activation by thrombin: a short history. *Thromb Res* 2012;**129**(3):250–6.
115. Jackson SP. The growing complexity of platelet aggregation. *Blood* 2007;**109**(12):5087–95.
116. Boccardo P, Remuzzi G, Galbusera M. Platelet dysfunction in renal failure. *Semin Thromb Hemost* 2004;**30**(5):579–89.
117. Hedges SJ, Dehoney SB, Hooper JS, Amanzadeh J, Busti AJ. Evidence-based treatment recommendations for uremic bleeding. *Nat Clin Pract Nephrol* 2007;**3**(3):138–53.
118. Noris M, Remuzzi G. Uremic bleeding: closing the circle after 30 years of controversies? *Blood* 1999;**94**(8):2569–74.
119. Maejima M, Takahashi S, Hatano M. Platelet aggregation in chronic renal failure–whole blood aggregation and effect of guanidino compounds. *Nihon Jinzo Gakkai Shi* 1991;**33**(2):201–12.
120. Livio M, Gotti E, Marchesi D, Mecca G, Remuzzi G, de Gaetano G. Uraemic bleeding: role of anaemia and beneficial effect of red cell transfusions. *Lancet Lond Engl* 1982;**2**(8306):1013–5.
121. Fernandez F, Goudable C, Sie P, Ton-That H, Durand D, Suc JM, et al. Low haematocrit and prolonged bleeding time in uraemic patients: effect of red cell transfusions. *Br J Haematol* 1985;**59**(1):139–48.
122. Escolar G, Díaz-Ricart M, Cases A. Uremic platelet dysfunction: past and present. *Curr Hematol Rep* 2005;**4**(5):359–67.
123. Soyoral YU, Demir C, Begenik H, Esen R, Kucukoglu ME, Aldemir MN, et al. Skin bleeding time for the evaluation of

uremic platelet dysfunction and effect of dialysis. *Clin Appl Thromb* 2012;**18**(2):185–8.
124. Gralnick HR, McKeown LP, Williams SB, Shafer BC, Pierce L. Plasma and platelet von Willebrand factor defects in uremia. *Am J Med* 1988;**85**(6):806–10.
125. Casonato A, Pontara E, Vertolli UP, Steffan A, Durante C, De Marco L, et al. Plasma and platelet von Willebrand factor abnormalities in patients with uremia: lack of correlation with uremic bleeding. *Clin Appl Thromb* 2001;**7**(2):81–6.
126. Kaw D, Malhotra D. Platelet dysfunction and end-stage renal disease. *Semin Dial* 2006;**19**(4):317–22.
127. Stewart JH, Castaldi PA. Uraemic bleeding: a reversible platelet defect corrected by dialysis. *Q J Med* 1967;**36**(143):409–23.
128. Nenci GG, Berrettini M, Agnelli G, Parise P, Buoncristiani U, Ballatori E. Effect of peritoneal dialysis, haemodialysis and kidney transplantation on blood platelet function. I. Platelet aggregation by ADP and epinephrine. *Nephron* 1979;**23**(6): 287–92.
129. Lindsay RM, Friesen M, Aronstam A, Andrus F, Clark WF, Linton AL. Improvement of platelet function by increased frequency of hemodialysis. *Clin Nephrol* 1978;**10**(2):67–70.
130. Di Minno G, Martinez J, McKean ML, De La Rosa J, Burke JF, Murphy S. Platelet dysfunction in uremia. Multifaceted defect partially corrected by dialysis. *Am J Med* 1985;**79**(5):552–9.
131. Cases A, Escolar G, Reverter JC, Ordinas A, Lopez-Pedret J, Revert L, et al. Recombinant human erythropoietin treatment improves platelet function in uremic patients. *Kidney Int* 1992;**42**(3): 668–72.
132. Diaz-Ricart M, Etebanell E, Cases A, López-Pedret J, Castillo R, Ordinas A, et al. Erythropoietin improves signaling through tyrosine phosphorylation in platelets from uremic patients. *Thromb Haemostasis* 1999;**82**(4):1312–7.
133. van Geet C, Hauglustaine D, Verresen L, Vanrusselt M, Vermylen J. Haemostatic effects of recombinant human erythropoietin in chronic haemodialysis patients. *Thromb Haemostasis* 1989;**61**(1):117–21.
134. Zhou XJ, Vaziri ND. Defective calcium signalling in uraemic platelets and its amelioration with long-term erythropoietin therapy. *Nephrol Dial Transplant* 2002;**17**(6):992–7.
135. Viganò GL, Mannucci PM, Lattuada A, Harris A, Remuzzi G. Subcutaneous desmopressin (DDAVP) shortens the bleeding time in uremia. *Am J Hematol* 1989;**31**(1):32–5.
136. Rydzewski A, Rowiński M, Myśliwiec M. Shortening of bleeding time after intranasal administration of 1-deamino-8-D-arginine vasopressin to patients with chronic uremia. *Folia Haematol Leipz Ger 1928* 1986;**113**(6):823–30.
137. Shapiro MD, Kelleher SP. Intranasal deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *Am J Nephrol* 1984; **4**(4):260–1.
138. Mannucci PM, Remuzzi G, Pusineri F, Lombardi R, Valsecchi C, Mecca G, et al. Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med* 1983;**308**(1):8–12.
139. Janson PA, Jubelirer SJ, Weinstein MJ, Deykin D. Treatment of the bleeding tendency in uremia with cryoprecipitate. *N Engl J Med* 1980;**303**(23):1318–22.
140. Jubelirer SJ, Janson PA, Weinstein MJ, Deykin D. Cryoprecipitate shortens the bleeding time and reduces bleeding complications in patients with uremia. *Trans Assoc Am Phys* 1980;**93**:182–91.
141. Maierhoter W, Adams MB, Kleinman JG, Roth DA. Treatment of the bleeding tendency in uremia with cryoprecipitate. *N Engl J Med* 1981;**305**(11):645.
142. Heunisch C, Resnick DJ, Vitello JM, Martin SJ. Conjugated estrogens for the management of gastrointestinal bleeding secondary to uremia of acute renal failure. *Pharmacotherapy* 1998;**18**(1): 210–7.
143. Sloand JA, Schiff MJ. Beneficial effect of low-dose transdermal estrogen on bleeding time and clinical bleeding in uremia. *Am J Kidney Dis* 1995;**26**(1):22–6.
144. Viganò G, Gaspari F, Locatelli M, Pusineri F, Bonati M, Remuzzi G. Dose-effect and pharmacokinetics of estrogens given to correct bleeding time in uremia. *Kidney Int* 1988;**34**(6):853–8.
145. Gonzalez J, Bryant S, Hermes-DeSantis ER. Transdermal estradiol for the management of refractory uremic bleeding. *Am J Health-Syst Pharm* 2018;**75**(9):e177–83.
146. Bali A, Hix JK, Kouides P. Safe and effective use of chronic transdermal estradiol for life-threatening uremic bleeding in a patient with coronary artery disease. *Nephron Extra* 2014;**4**(2):134–7.
147. Mezzano D, Muñoz B, Pais E, Downey P, Pereira J. Fast decrease of bleeding time by tranexamic acid in uremia. *Thromb Haemostasis* 2000;**83**(5):785.
148. Downey P, Tagle R, Pereira J, Mezzano D. Tranexamic acid and uremic bleeding: evidence-based treatment recommendations. *Nat Clin Pract Nephrol* 2007;**3**(6):E2. author reply E3.
149. Wang HE, Gamboa C, Warnock DG, Muntner P. Chronic kidney disease and risk of death from infection. *Am J Nephrol* 2011; **34**(4):330–6.
150. James MT, Laupland KB, Tonelli M, Manns BJ, Culleton BF, Hemmelgarn BR, et al. Risk of bloodstream infection in patients with chronic kidney disease not treated with dialysis. *Arch Intern Med* 2008;**168**(21):2333–9.
151. McDonald HI, Thomas SL, Nitsch D. Chronic kidney disease as a risk factor for acute community-acquired infections in high-income countries: a systematic review. *BMJ Open* 2014;**4**(4): e004100.
152. Viasus D, Garcia-Vidal C, Cruzado JM, Adamuz J, Verdaguer R, Manresa F, et al. Epidemiology, clinical features and outcomes of pneumonia in patients with chronic kidney disease. *Nephrol Dial Transplant* 2011;**26**(9):2899–906.
153. Cheikh Hassan HI, Tang M, Djurdjev O, Langsford D, Sood MM, Levin A. Infection in advanced chronic kidney disease leads to increased risk of cardiovascular events, end-stage kidney disease and mortality. *Kidney Int* 2016;**90**(4):897–904.
154. Rankin LC, Artis D. Beyond host defense: emerging functions of the immune system in regulating complex tissue physiology. *Cell* 2018;**173**(3):554–67.
155. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science* 2012;**336**(6086): 1268–73.
156. Annunziato F, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. *J Allergy Clin Immunol* 2015;**135**(3):626–35.
157. Ebbo M, Crinier A, Vély F, Vivier E. Innate lymphoid cells: major players in inflammatory diseases. *Nat Rev Immunol* 2017;**17**(11): 665–78.
158. Cao X. Self-regulation and cross-regulation of pattern-recognition receptor signalling in health and disease. *Nat Rev Immunol* 2016; **16**(1):35–50.
159. Jeannin P, Jaillon S, Delneste Y. Pattern recognition receptors in the immune response against dying cells. *Curr Opin Immunol* 2008;**20**(5):530–7.
160. Kato S, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, et al. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol* 2008;**3**(5):1526–33.
161. Dowling JK, Mansell A. Toll-like receptors: the swiss army knife of immunity and vaccine development. *Clin Transl Immunol* 2016;**5**(5):e85.
162. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell* 2010;**140**(6):805–20.
163. Akira S, Takeda K. Toll-like receptor signalling. *Nat Rev Immunol* 2004;**4**(7):499–511.

164. Takeda K, Akira S. Toll-like receptors. *Curr Protoc Immunol* 2015; **109**. 14.12.1-14.1210.
165. Verzola D, Bonanni A, Sofia A, Montecucco F, D'Amato E, Cademartori V, et al. Toll-like receptor 4 signalling mediates inflammation in skeletal muscle of patients with chronic kidney disease. *J Cachexia Sarcopenia Muscle* 2017;**8**(1):131–44.
166. Grabulosa CC, Manfredi SR, Canziani ME, Quinto BMR, Barbosa RB, Rebello JF, et al. Chronic kidney disease induces inflammation by increasing Toll-like receptor-4, cytokine and cathelicidin expression in neutrophils and monocytes. *Exp Cell Res* 2018;**365**(2):157–62.
167. Zager RA. "Biologic memory" in response to acute kidney injury: cytoresistance, toll-like receptor hyper-responsiveness and the onset of progressive renal disease. *Nephrol Dial Transplant* 2013; **28**(8):1985–93.
168. Yiu WH, Lin M, Tang SCW. Toll-like receptor activation: from renal inflammation to fibrosis. *Kidney Int Suppl* 2014;**4**(1):20–5.
169. Hoving JC, Wilson GJ, Brown GD. Signalling C-type lectin receptors, microbial recognition and immunity. *Cell Microbiol* 2014; **16**(2):185–94.
170. Yoneyama M, Onomoto K, Jogi M, Akaboshi T, Fujita T. Viral RNA detection by RIG-I-like receptors. *Curr Opin Immunol* 2015; **32**:48–53.
171. Caruso R, Warner N, Inohara N, Núñez G. NOD1 and NOD2: signaling, host defense, and inflammatory disease. *Immunity* 2014;**41**(6):898–908.
172. Griebel T, Maekawa T, Parker JE. NOD-like receptor cooperativity in effector-triggered immunity. *Trends Immunol* 2014;**35**(11): 562–70.
173. Vono M, Lin A, Norrby-Teglund A, Koup RA, Liang F, Loré K. Neutrophils acquire the capacity for antigen presentation to memory CD4+ T cells in vitro and ex vivo. *Blood* 2017 06; **129**(14):1991–2001.
174. Lin A, Loré K. Granulocytes: new members of the antigen-presenting cell family. *Front Immunol* 2017;**8**:1781.
175. Winterbourn CC, Kettle AJ, Hampton MB. Reactive oxygen species and neutrophil function. *Annu Rev Biochem* 2016;**85**:765–92.
176. Nauseef WM, Borregaard N. Neutrophils at work. *Nat Immunol* 2014;**15**(7):602–11.
177. Pallet N. Neutrophil extracellular traps orchestrate necroinflammation. *J Am Soc Nephrol* 2017;**28**(6):1670–2.
178. Kim J-K, Hong C-W, Park MJ, Song YR, Kim HJ, Kim SG. Increased neutrophil extracellular trap formation in uremia is associated with chronic inflammation and prevalent coronary artery disease. *J Immunol Res* 2017;**2017**:8415179.
179. Haag-Weber M, Hörl WH. Dysfunction of polymorphonuclear leukocytes in uremia. *Semin Nephrol* 1996;**16**(3):192–201.
180. Lewis SL, Van Epps DE. Neutrophil and monocyte alterations in chronic dialysis patients. *Am J Kidney Dis* 1987;**9**(5):381–95.
181. Olsson J, Jacobson TAS, Paulsson JM, Dadfar E, Moshfegh A, Jacobson SH, et al. Expression of neutrophil SOD2 is reduced after lipopolysaccharide stimulation: a potential cause of neutrophil dysfunction in chronic kidney disease. *Nephrol Dial Transplant* 2011;**26**(7):2195–201.
182. Gollapudi P, Yoon J-W, Gollapudi S, Pahl MV, Vaziri ND. Leukocyte toll-like receptor expression in end-stage kidney disease. *Am J Nephrol* 2010;**31**(3):247–54.
183. Rossaint J, Unruh M, Zarbock A. Fibroblast growth factor 23 actions in inflammation: a key factor in CKD outcomes. *Nephrol Dial Transplant* 2017;**32**(9):1448–53.
184. Sela S, Shurtz-Swirski R, Cohen-Mazor M, Mazor R, Chezar J, Shapiro G, et al. Primed peripheral polymorphonuclear leukocyte: a culprit underlying chronic low-grade inflammation and systemic oxidative stress in chronic kidney disease. *J Am Soc Nephrol* 2005;**16**(8):2431–8.
185. Cohen G, Raupachova J, Hörl WH. The uraemic toxin phenylacetic acid contributes to inflammation by priming polymorphonuclear leucocytes. *Nephrol Dial Transplant* 2013;**28**(2):421–9.
186. Lim WH, Kireta S, Leedham E, Russ GR, Coates PT. Uremia impairs monocyte and monocyte-derived dendritic cell function in hemodialysis patients. *Kidney Int* 2007;**72**(9):1138–48.
187. Pahl MV, Vaziri ND, Yuan J, Adler SG. Upregulation of monocyte/macrophage HGFIN (Gpnmb/Osteoactivin) expression in end-stage renal disease. *Clin J Am Soc Nephrol* 2010;**5**(1):56–61.
188. Laudański K, Nowak Z. Aberrant function and differentiation of monocytes in end stage renal disease. *Arch Immunol Ther Exp* 2012; **60**(6):453–9.
189. Scherberich JE. Proinflammatory blood monocytes: main effector and target cells in systemic and renal disease; background and therapeutic implications. *Int J Clin Pharmacol Ther* 2003;**41**(10): 459–64.
190. Yang J, Fang P, Yu D, Zhang L, Zhang D, Jiang X, et al. Chronic kidney disease induces inflammatory CD40+ monocyte differentiation via homocysteine elevation and DNA hypomethylation. *Circ Res* 2016;**119**(11):1226–41.
191. Wallquist C, Paulson JM, Hylander B, Lundahl J, Jacobson SH. Increased accumulation of CD16+ monocytes at local sites of inflammation in patients with chronic kidney disease. *Scand J Immunol* 2013;**78**(6):538–44.
192. Dai J, Fang P, Saredy J, Xi H, Ramon C, Yang W, et al. Metabolism-associated danger signal-induced immune response and reverse immune checkpoint-activated CD40+ monocyte differentiation. *J Hematol OncolJ Hematol Oncol* 2017;**10**(1):141.
193. Ramírez R, Carracedo J, Merino A, Soriano S, Ojeda R, Alvarez-Lara MA, et al. CD14+CD16+ monocytes from chronic kidney disease patients exhibit increased adhesion ability to endothelial cells. *Contrib Nephrol* 2011;**171**:57–61.
194. Heine GH, Ortiz A, Massy ZA, Lindholm B, Wiecek A, Martínez-Castelao A, et al. Monocyte subpopulations and cardiovascular risk in chronic kidney disease. *Nat Rev Nephrol* 2012;**8**(6):362–9.
195. Scherberich JE, Nockher WA. Blood monocyte phenotypes and soluble endotoxin receptor CD14 in systemic inflammatory diseases and patients with chronic renal failure. *Nephrol Dial Transplant* 2000;**15**(5):574–8.
196. Hu ZB, Chen Y, Gong YX, Gao M, Zhang Y, Wang GH, et al. Activation of the CXCL16/CXCR6 pathway by inflammation contributes to atherosclerosis in patients with end-stage renal disease. *Int J Med Sci* 2016;**13**(11):858–67.
197. Akdoğan MF, Azak A, Denizli N, Huddam B, Koçak G, Gücün M, et al. MCP-1 and soluble TWEAK levels are independently associated with coronary artery disease severity in patients with chronic kidney disease. *Ren Fail* 2015;**37**(8):1297–302.
198. Ando M, Shibuya A, Tsuchiya K, Akiba T, Nitta K. Reduced expression of Toll-like receptor 4 contributes to impaired cytokine response of monocytes in uremic patients. *Kidney Int* 2006;**70**(2): 358–62.
199. Liu Z, Kan Y-H, Wei Y-D, Li X-J, Yang F, Hou Y, et al. Decreased number of CD14+TLR4+ monocytes and their impaired cytokine responses to lipopolysaccharide in patients with chronic kidney disease. *J Huazhong Univ Sci Technol Med Sci* 2015;**35**(2):206–11.
200. Bowe B, Xie Y, Xian H, Li T, Al-Aly Z. Association between monocyte count and risk of incident CKD and progression to ESRD. *Clin J Am Soc Nephrol* 2017;**12**(4):603–13.
201. Agarwal R, Light RP. Patterns and prognostic value of total and differential leukocyte count in chronic kidney disease. *Clin J Am Soc Nephrol* 2011;**6**(6):1393–9.
202. Teteris SA, Engel DR, Kurts C. Homeostatic and pathogenic role of renal dendritic cells. *Kidney Int* 2011;**80**(2):139–45.
203. Dixon KB, Davies SS, Kirabo A. Dendritic cells and isolevuglandins in immunity, inflammation, and hypertension. *Am J Physiol Heart Circ Physiol* 2017;**312**(3):H368–74.

204. Broder A, Chan JJ, Putterman C. Dendritic cells: an important link between antiphospholipid antibodies, endothelial dysfunction, and atherosclerosis in autoimmune and non-autoimmune diseases. *Clin Immunol Orlando Fla* 2013;**146**(3):197–206.
205. Panzer U, Kurts C. T cell cross-talk with kidney dendritic cells in glomerulonephritis. *J Mol Med Berl Ger* 2010;**88**(1):19–26.
206. Sung S-S, Bolton WK. T cells and dendritic cells in glomerular disease: the new glomerulotubular feedback loop. *Kidney Int* 2010; **77**(5):393–9.
207. Gottschalk C, Kurts C. The debate about dendritic cells and macrophages in the kidney. *Front Immunol* 2015;**6**:435.
208. Fu B, Tian Z, Wei H. Subsets of human natural killer cells and their regulatory effects. *Immunology* 2014;**141**(4):483–9.
209. Law BMP, Wilkinson R, Wang X, Kildey K, Lindner M, Rist MJ, et al. Interferon-γ production by tubulointerstitial human CD56bright natural killer cells contributes to renal fibrosis and chronic kidney disease progression. *Kidney Int* 2017;**92**(1):79–88.
210. Lonnemann G. Impaired NK cell function in ESRD patients. *Blood Purif* 2008;**26**(4):315–6.
211. Cromheecke JL, Nguyen KT, Huston DP. Emerging role of human basophil biology in health and disease. *Curr Allergy Asthma Rep* 2014;**14**(1):408.
212. Cardamone C, Parente R, Feo GD, Triggiani M. Mast cells as effector cells of innate immunity and regulators of adaptive immunity. *Immunol Lett* 2016;**178**:10–4.
213. Chirumbolo S, Bjørklund G, Sboarina A, Vella A. The role of basophils as innate immune regulatory cells in allergy and immunotherapy. *Hum Vaccines Immunother* 2018;**14**(4):815–31.
214. Aljadi Z, Nopp A, Winqvist O, Russom A, Hylander B, Jacobson SH, et al. Altered basophil function in patients with chronic kidney disease on hemodialysis. *Clin Nephrol* 2017;**88**(8):86–96.
215. Holdsworth SR, Summers SA. Role of mast cells in progressive renal diseases. *J Am Soc Nephrol* 2008;**19**(12):2254–61.
216. Davoine F, Lacy P. Eosinophil cytokines, chemokines, and growth factors: emerging roles in immunity. *Front Immunol* 2014;**5**:570.
217. Mihai S, Codrici E, Popescu ID, Enciu A-M, Albulescu L, Necula LG, et al. Inflammation-related mechanisms in chronic kidney disease prediction, progression, and outcome. *J Immunol Res* 2018;**2018**:2180373.
218. Andres-Hernando A, Dursun B, Altmann C, Ahuja N, He Z, Bhargava R, et al. Cytokine production increases and cytokine clearance decreases in mice with bilateral nephrectomy. *Nephrol Dial Transplant* 2012;**27**(12):4339–47.
219. Neirynck N, Glorieux G, Schepers E, Dhondt A, Verbeke F, Vanholder R. Pro-inflammatory cytokines and leukocyte oxidative burst in chronic kidney disease: culprits or innocent bystanders? *Nephrol Dial Transplant* 2015;**30**(6):943–51.
220. Carlsson AC, Ingelsson E, Sundström J, Carrero JJ, Gustafsson S, Feldreich T, et al. Use of proteomics to investigate kidney function decline over 5 years. *Clin J Am Soc Nephrol* 2017 07;**12**(8): 1226–35.
221. Satomura A, Endo M, Ohi H, Sudo S, Ohsawa I, Fujita T, et al. Significant elevations in serum mannose-binding lectin levels in patients with chronic renal failure. *Nephron* 2002;**92**(3):702–4.
222. Girndt M, Sester M, Sester U, Kaul H, Köhler H. Molecular aspects of T- and B-cell function in uremia. *Kidney Int Suppl* 2001; **78**:S206–211.
223. Moser B, Roth G, Brunner M, Lilaj T, Deicher R, Wolner E, et al. Aberrant T cell activation and heightened apoptotic turnover in end-stage renal failure patients: a comparative evaluation between non-dialysis, haemodialysis, and peritoneal dialysis. *Biochem Biophys Res Commun* 2003;**308**(3):581–5.
224. Stachowski J, Pollok M, Burrichter H, Spithaler C, Baldamus CA. Signalling via the TCR/CD3 antigen receptor complex in uremia is limited by the receptors number. *Nephron* 1993;**64**(3):369–75.
225. Meuer SC, Hauer M, Kurz P, Meyer zum Büschenfelde KH, Köhler H. Selective blockade of the antigen-receptor-mediated pathway of T cell activation in patients with impaired primary immune responses. *J Clin Investig* 1987;**80**(3):743–9.
226. Matsumoto Y, Shinzato T, Amano I, Takai I, Kimura Y, Morita H, et al. Relationship between susceptibility to apoptosis and Fas expression in peripheral blood T cells from uremic patients: a possible mechanism for lymphopenia in chronic renal failure. *Biochem Biophys Res Commun* 1995;**215**(1):98–105.
227. Yoon J-W, Gollapudi S, Pahl MV, Vaziri ND. Naïve and central memory T-cell lymphopenia in end-stage renal disease. *Kidney Int* 2006;**70**(2):371–6.
228. Vaziri ND, Pahl MV, Crum A, Norris K. Effect of uremia on structure and function of immune system. *J Ren Nutr* 2012;**22**(1): 149–56.
229. Hendrikx TK, van Gurp EAFJ, Mol WM, Schoordijk W, Sewgobind VDKD, Ijzermans JNM, et al. End-stage renal failure and regulatory activities of CD4+CD25bright+FoxP3+ T-cells. *Nephrol Dial Transplant* 2009;**24**(6):1969–78.
230. Meier P, Golshayan D, Blanc E, Pascual M, Burnier M. Oxidized LDL modulates apoptosis of regulatory T cells in patients with ESRD. *J Am Soc Nephrol* 2009;**20**(6):1368–84.
231. Smogorzewski M, Massry SG. Defects in B-cell function and metabolism in uremia: role of parathyroid hormone. *Kidney Int Suppl* 2001;**78**:S186–189.
232. Beaman M, Michael J, MacLennan IC, Adu D. T-cell-independent and T-cell-dependent antibody responses in patients with chronic renal failure. *Nephrol Dial Transplant* 1989;**4**(3):216–21.
233. Degiannis D, Mowat AM, Galloway E, Tsakiris D, Briggs JD, Junor BJ, et al. In vitro analysis of B lymphocyte function in uraemia. *Clin Exp Immunol* 1987;**70**(2):463–70.
234. Raskova J, Ghobrial I, Czerwinski DK, Shea SM, Eisinger RP, Raska K. B-cell activation and immunoregulation in end-stage renal disease patients receiving hemodialysis. *Arch Intern Med* 1987;**147**(1):89–93.
235. Fernández-Fresnedo G, Ramos MA, González-Pardo MC, de Francisco AL, López-Hoyos M, Arias M. B lymphopenia in uremia is related to an accelerated in vitro apoptosis and dysregulation of Bcl-2. *Nephrol Dial Transplant* 2000;**15**(4):502–10.
236. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. *N Engl J Med* 1998;**339**(20):1448–56.
237. Remuzzi G, Ruggenenti P, Perico N. Chronic renal diseases: renoprotective benefits of renin-angiotensin system inhibition. *Ann Intern Med* 2002;**136**(8):604–15.
238. Akchurin OM, Kaskel F. Update on inflammation in chronic kidney disease. *Blood Purif* 2015;**39**(1–3):84–92.
239. Slavin JL. Position of the American Dietetic Association: health implications of dietary fiber. *J Am Diet Assoc* 2008;**108**(10): 1716–31.
240. Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. *J Am Soc Nephrol* 2014;**25**(4):657–70.
241. Lau WL, Kalantar-Zadeh K, Vaziri ND. The gut as a source of inflammation in chronic kidney disease. *Nephron* 2015;**130**(2): 92–8.
242. Jovanovich A, Isakova T, Stubbs J. Microbiome and cardiovascular disease in CKD. *Clin J Am Soc Nephrol* 2018;**13**(10):1598–604.
243. Dai L, Golembiewska E, Lindholm B, Stenvinkel P. End-stage renal disease, inflammation and cardiovascular outcomes. *Contrib Nephrol* 2017;**191**:32–43.
244. Hénaut L, Chillon J-M, Kamel S, Massy ZA. Updates on the mechanisms and the care of cardiovascular calcification in chronic kidney disease. *Semin Nephrol* 2018;**38**(3):233–50.
245. David V, Francis C, Babitt JL. Ironing out the cross talk between FGF23 and inflammation. *Am J Physiol Renal Physiol* 2017 01; **312**(1):F1–8.

246. Gal-Moscovici A, Sprague SM. Use of vitamin D in chronic kidney disease patients. *Kidney Int* 2010;**78**(2):146–51.
247. Benz K, Hilgers K-F, Daniel C, Amann K. Vascular calcification in chronic kidney disease: the role of inflammation. *Internet J Nephrol* 2018;**2018**:4310379.
248. Obi Y, Qader H, Kovesdy CP, Kalantar-Zadeh K. Latest consensus and update on protein-energy wasting in chronic kidney disease. *Curr Opin Clin Nutr Metab Care* 2015;**18**(3):254–62.
249. Ikizler TA, Cano NJ, Franch H, Fouque D, Himmelfarb J, Kalantar-Zadeh K, et al. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. *Kidney Int* 2013;**84**(6):1096–107.
250. Fouque D, Pelletier S, Mafra D, Chauveau P. Nutrition and chronic kidney disease. *Kidney Int* 2011;**80**(4):348–57.
251. Eleftheriadis T, Antoniadi G, Liakopoulos V, Kartsios C, Stefanidis I. Disturbances of acquired immunity in hemodialysis patients. *Semin Dial* 2007;**20**(5):440–51.
252. KDIGO. Clinical practice guideline for the evaluation and management of chronic kidney disease: summary of recommendation statements. *Kidney Int Suppl* 2012;**3**(1):5–14.

QUESTIONS AND ANSWERS

Question 1

The anemia seen in patients with CKD is, in part, related to all of the following except:

A. Chronic inflammation
B. Relative erythropoietin deficiency
C. FID
D. Abnormal mineral and bone metabolism
E. Hepcidin deficiency

Answer: E

Hepcidin levels are increased in CKD and play a role in iron restricted erythropoiesis, FID, and resistance to erythropoietin therapy.

Question 2

The diagnostic workup for anemia in patients with CKD should include all of the following except:

A. Age appropriate screening for gastrointestinal blood loss
B. Evaluation of red blood cell morphology
C. Transferrin saturation and ferritin
D. Hepcidin level
E. Erythropoietin level

Answer: D and E

Neither measurement of hepcidin or erythropoietin levels are recommended as part of the evaluation. These tests may be less available and have substantial technical limitations and rarely add to the evaluation.

Question 3

The treatment of anemia in patients with dialysis-dependent or non−dialysis-dependent CKD with ESAs may be associated with all of the following except:

A. Diminished need for red blood cell transfusion
B. Increased BP
C. Increased risk of cardiovascular thrombotic events
D. Improved cardiovascular outcomes in patients with heart failure
E. Enhanced quality of life

Answer: D

There are no studies demonstrating improved cardiovascular outcomes with correction of anemia in patients with dialysis-dependent or nondialysis-dependent CKD.

Question 4

All of the following factors are mechanistically related to the thrombocytopathy seen in patients with CKD except:

A. Anemia
B. Dysfunctional platelet adhesion, activation, and aggregation
C. Increased content in the platelet dense granules of ADP and serotonin
D. Impaired intracellular signaling in the platelet
E. Increased vascular endothelial production of nitric oxide

Answer: C

There is a paucity in the content (ADP and serotonin) of platelet dense granules and their release in the patient with CKD.

Question 5

Which of the following statements are false about monitoring bleeding risk in patients with reduced kidney function:

A. Platelet count is usually normal
B. PT and aPTT are usually normal or increased
C. BT is reasonably accurate and commonly available
D. The RIPA is diminished
E. Serum blood urea nitrogen and creatinine levels may be used as an assessment tool to predict bleeding risk

Answer: C and E

Serum blood urea nitrogen and creatinine do not accurately predict bleeding risk. The BT is nonsensitive and nonspecific and fraught with technical and interpretation limitations.

Question 6

Which of the following statements are false about the effects of CKD on immune function:

A. CKD is associated with decreased baseline neutrophil and activation
B. FGF-23 has been shown to impede neutrophil activation, chemotaxis, and function
C. CKD is associated with an overall increase in neutrophil apoptosis

D. CKD is associated with decreased monocyte TL4 expression and a blunted response to LPS exposure, as well as a diminished production of TNFα, IL-1β, and IL-6

E. Cytokine responses to pathogen exposure is impaired

Answer: A

CKD is associated with spontaneous chronic activation of neutrophils, which impairs its primary functions of chemotaxis, adhesion, and production and release of ROS and cytokines as well as its ability to ingest and kill a pathogen.

CHAPTER

32

Immune Function in Chronic Kidney Disease

Madeleine V. Pahl, Nosratola D. Vaziri

Division of Nephrology and Hypertension, UCI Medical Center, Orange, CA, United States

Abstract

Chronic Kidney Disease (CKD) is simultaneously associated with immune activation, marked by systemic inflammation, and immune deficiency. Systemic inflammation contributes to the development of atherosclerosis, cardiovascular disease, cachexia, and anemia, while immune deficiency leads to impaired response to vaccination, and increased incidence and severity of microbial infections. CKD-associated inflammation and immune deficiency are associated with (a) general expansion of monocytes and elevations of their basal integrin, Toll-like receptor expression, cytokine production, and reactive oxygen species (ROS) generation and reduced phagocytic capacity, (b) depletion and impaired inhibitory activity of regulatory T cells, (c) spontaneous activation, degranulation, increased basal ROS production, decreased phagocytic capacity, and increased apoptosis of circulating polymorphonuclear leukocytes, (d) upregulation of ROS production machinery and chemokine expression in the cellular constituents of various tissues, highlighting participation of nonimmune cells in the prevailing inflammatory state, (e) depletion of the antigen-presenting dendritic cells, (f) reduced CD4/CD8 T cell ratio and depletion of naïve and central memory T cells, and (g) diffuse B cell lymphopenia leading to impaired humoral immunity. Thus, CKD-associated inflammation is due to activation of the innate immune system, orchestrated by monocytes, macrophages, granulocytes, and cellular constituents of other organs/tissues. This is coupled with immune deficiency caused by depletion of dendritic cells, naïve and central memory T cells and B cells, and impaired phagocytic function of polymorphonuclear leukocytes and monocytes.

EPIDEMIOLOGY AND BACKGROUND

Chronic kidney disease (CKD) is simultaneously associated with immune activation that is characterized by systemic inflammation and immune deficiency.[1,2] The systemic inflammation contributes to many comorbidities, including atherosclerosis, cardiovascular disease, cachexia, malnutrition, and anemia,[1] whereas the immune deficiency leads to impaired response to vaccination and increased incidence, severity, and poor outcome of microbial infections (Figure 32.1).[1–3] High failure rates for vaccinations against hepatitis B virus, influenza, *Clostridium tetani*, and *Corynebacterium diphtheriae* are well known.[4] Reports from the Hemodialysis (HEMO) study note annual infection rates as high as 35%.[5] Mortality rates are increased 10-fold for pneumonia and 100-fold for sepsis in hemodialysis (HD) patients, compared with the general population.[6]

Before describing CKD-associated immunological disorders, a brief overview of the structure and function of the immune system is provided.

STRUCTURE AND FUNCTION OF THE IMMUNE SYSTEM

The immune system comprises a complex set of interactions between soluble factors and cells designed to protect against various diseases, by detecting and destroying invading microbes and cancer cells, and identifying, removing, and helping to repair damaged tissues. Inflammation is the critical step in the immune response to infection and tissue damage.[7]

The body's immune defense is accomplished by the innate and adaptive immune systems. The innate immune system comprises cells and processes that culminate in a prompt and nonspecific response to infection and tissue injury. Activation of the innate immune system is orchestrated by neutrophils, monocytes, macrophages, platelets, natural killer cells (NK cells), innate lymphoid cells, and other cellular constituents such as epithelial and mast cells. These cells use pattern recognition receptors (PRRs), which recognize pathogen-associated molecular patterns (PAMPs) on microorganisms, and communicate through various cytokines. The PRRs exist as either secreted circulating proteins or membrane-bound receptors. The secreted proteins, which include defensin, cathelicidin (induced by vitamin D), collectins, lectins, and pentraxins

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00032-2

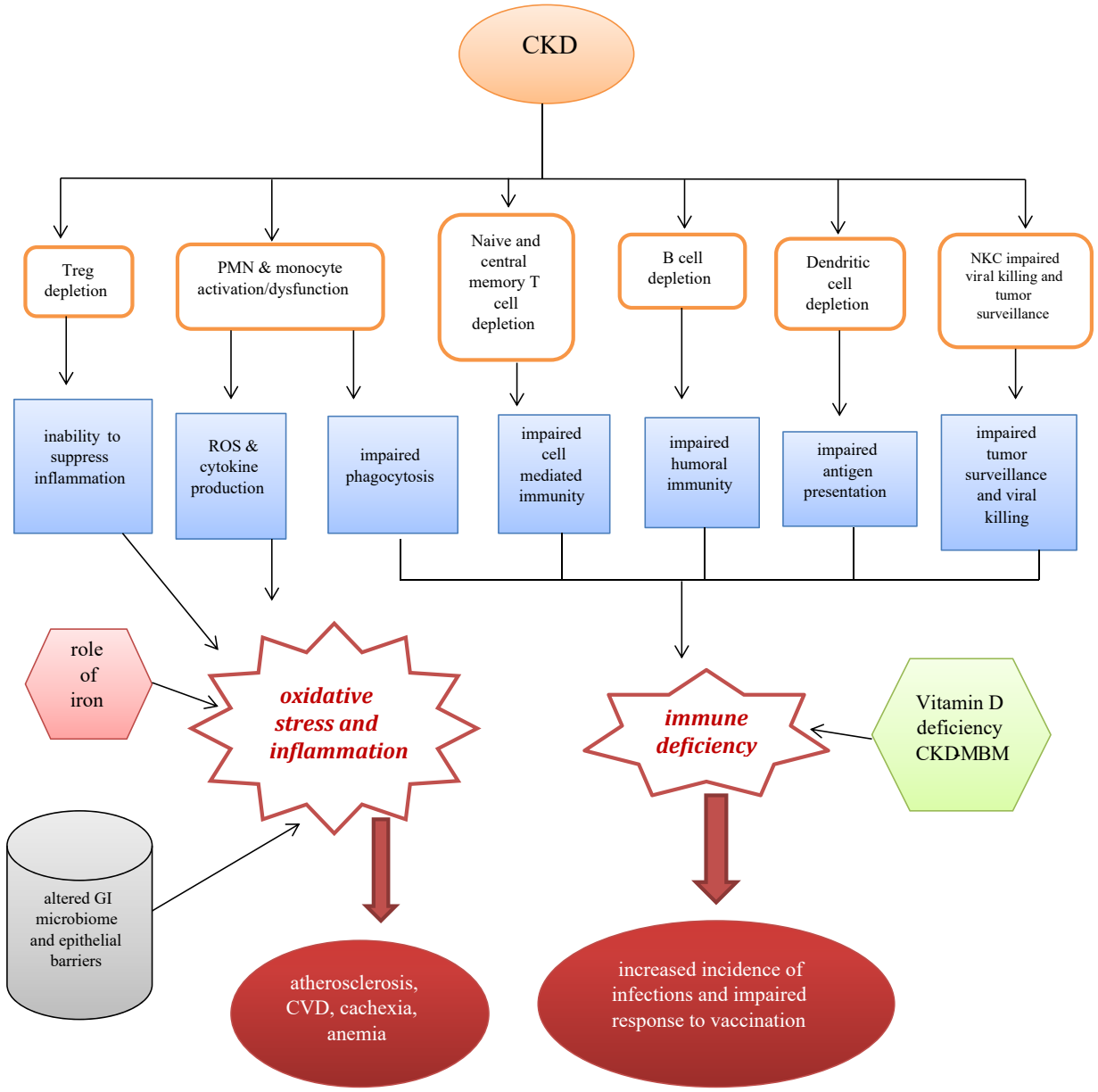


FIGURE 32.1 Summary of the impact of chronic kidney disease (CKD) on innate and adaptive immunity and their adverse consequences.

(including CRP) mediate direct microbial killing, act as helper proteins for transmembrane receptors, or opsonins. Membrane-bound PRRs are expressed constitutively on many innate immune cells and the antigen-presenting cells (APCs). They include the membrane-bound and intracellular Toll-like receptors (TLRs) and their associated detection-enhancing proteins (LPS-binding protein, CD14, and MD2), nucleotide-binding oligomerization domain–like receptors, RIG-1-like receptors, and C-type lectin receptors on macrophages and dendritic cells. Activation of the innate immune system begins with the resident cells at the site of infection or injury (macrophages, epithelial cells, mast cells) followed by recruitment of circulating neutrophils, NK cells, dendritic cells, monocytes, and platelets if needed.

The adaptive immune response enables the host to recognize, remember, and mount stronger attacks on reencounter with the same pathogen. Adaptive immune cells include T and B lymphocytes that express cell-specific receptors (T cell receptors [TCR] and B cell receptors [BCR]) with which they recognize their cognate antigens.

T cells recognize their cognate antigen in a processed form as a peptide in the context of a major histocompatibility complex (MHC) molecule. APCs take up,

degrade, and load antigens onto the MHC for presentation to T cells. Dendritc cells (DCs) are the predominant APC, but monocytes/macrophages also act as APC and can differentiate into DCs.[8] After exposure to antigen DCs migrate to lymphoid tissues where they come into contact with the naïve T cells. This interaction results in a complex cascade of membrane glycoprotein contacts, intracellular signaling, and cytokine secretion leading to activation of T cells. Activated T cells that express CD 4 (helper T cells) play a role in activation of cytotoxic effector T cells (CD8+ lymphocytes) and the differentiation of B cells. They are subdivided into distinct categories (i.e. Th1, Th2, Th17, and regulatory [Treg] T cells) based on their cytokine production profile.[9] After activation some naïve T cells become short-lived effector T cells, while others become long-lived memory T-cells to provide a more rapid and effective response to a recurrent insult.[10] Effector T cells migrate into the peripheral tissues to combat the injury or interact with other lymphocytes, such as B cells.

B lymphocytes are the precursors of plasma cells that produce antibodies. B cells are produced in the bone marrow. After an initial differentiation they migrate to the spleen as transitional B cells, where they differentiate into mature long-lived lymphocytes.[11] The diversity of the B lymphocyte pool determines the individual's capacity to mount a protective immune response. Innate B cells produce mainly IgM antibodies that have low-affinity and high cross-reactivity. They constitute a readily available immunoglobulin pool that fights various infections before high-affinity specific antibodies are produced by conventional B cells.[12] Primed B cells express a unique BCR made of an immobilized antibody that recognizes and binds only one particular antigen. Unlike T cells, which require processed antigen presentation, B cells recognize antigens in their native forms. Once encountering their cognate antigen and receiving signals from the helper T cells (predominately Th2 type), B cells differentiate into short-lived antibody-producing plasma cells and long-lived memory B cells. Memory cells lodge in lymph nodes and mucosal tissues, and on subsequent encounter with the antigen, rapidly proliferate and produce high affinity, antigen-specific immunoglobulins.[13] A brief overview of the immune system is depicted in Figure 32.2.

CKD-ASSOCIATED IMMUNE DEFICIENCY

Although bacterial infections have diminished as a cause of death in the general population, they remain a common cause of death in patients with advanced CKD, particularly those maintained on renal replacement therapy.[2,3] This is due to the impaired immune response in uremia[2] that is caused by: (a) decreased granulocyte and monocyte/macrophage phagocytic function[14,15]; (b) defective antigen-presenting capacity of APC[8,9]; (c) depletion of dendritic cells[16]; (d) reduced numbers and antibody-producing capacity of B lymphocytes[17,18]; (e) increased T cell apoptosis causing depletion of naïve and central memory CD 4+ and CD8+ T lymphocytes[19,20]; and (f) impaired cell-mediated immunity.[19] The exact mechanisms underlying these derangements are not fully understood, but signs of activation and/or loss of function have been found.

Patients with advanced CKD develop anemia, due to diminished erythropoietin production, erythropoietin resistance, shortened erythrocyte life span, and impaired intestinal absorption and defective release of iron from storage sites. Indiscriminate use of intravenous iron preparations to treat anemia has resulted in an epidemic of iron overload and elevated levels of non−transferrin bound iron in the dialysis population.[21−23] The poorly liganded iron compounds are taken up by lymphocytes whose capacity to safely store iron in catalytically inactive form is limited. This results in iron-catalyzed oxidative stress and death or dysfunction of lymphocytes, which can contribute to immune deficiency.[24,25] In addition, iron overload impairs microbial killing and phagocytic capacities of macrophages and neutrophilic granulocytes and simultaneously heightens proliferation and virulence of pathogenic microorganisms. Together these abnormalities increase the incidence, severity, and poor outcome of microbial infections in iron-overloaded CKD patients.[26]

CKD-ASSOCIATED INFLAMMATION

CKD is associated with systemic inflammation and oxidative stress, which contribute to progression of CKD, atherosclerosis, cardiovascular disease, cachexia, and anemia, among other comorbidities.[1,27] CKD-associated inflammation is due to the activation of the innate immune system, orchestrated by monocytes, macrophages, granulocytes, and nonimmune cells. It is associated with: (a) general expansion of monocytes and elevations of their basal integrin, Toll-like receptor (TLR)-2, and TLR-4 expression, cytokine production, and reactive oxygen species (ROS) generation[28,29]; (b) depletion and impaired inhibitory activity of Treg cells[30,31]; (c) polymorphonuclear leukocyte (PMN) activation, degranulation, and basal ROS production[28]; (d) upregulation of ROS production machinery and chemokine expression in the cellular constituents of various tissues, highlighting participation of nonimmune cells in the inflammatory state[32]; (e) increased proinflammatory activity of low density lipoprotein

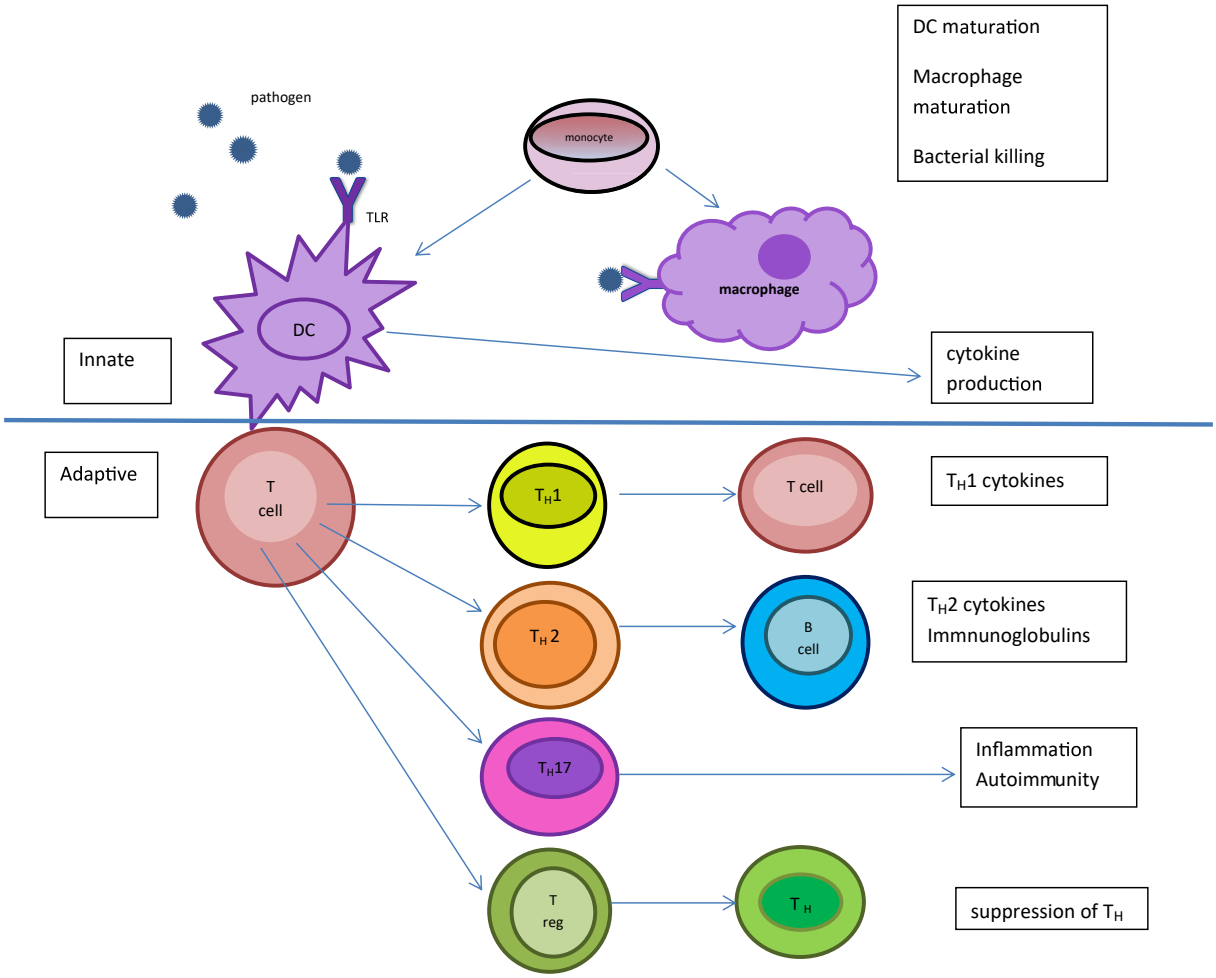


FIGURE 32.2 Overview of innate and adaptive immune system.

(LDL) and reduced antiinflammatory capacity of high density lipoprotein (HDL)[33,34]; (f) paralysis of the endogenous antioxidant, anti-inflammatory, and cytoprotective defense systems due to impaired activation of Nrf2, the master regulator of genes encoding numerous antioxidant and cytoprotective enzymes and related proteins[35–37]; (g) comorbid conditions such as diabetes and autoimmune disorders; (h) impaired intestinal epithelial barrier structure and function, which by enabling influx of endotoxin and other noxious luminal contents into the systemic circulation results in endotoxemia and systemic inflammation[38]; (i) uremic toxins; (j) blood exposure to dialyzer membranes and dialysate impurities; (k) hypervolemia and hypertension; (l) as well as other factors.

The majority of the available data on the effects of CKD on the immune system are derived from studies in patients with end-stage renal disease (ESRD) on renal replacement therapy. There are little available data from individuals with early stage CKD, but where available this information will be highlighted. Further studies are needed to explore the effects of mild to moderate CKD on the structure and function of the immune system in humans.

EFFECTS OF CKD ON COMPONENTS OF INNATE IMMUNITY

Monocyte and Macrophage Abnormalities in CKD

Monocytes are produced by the bone marrow, stored in the spleen, and distributed in all tissues as macrophages. Monocytes/macrophages play a key role in defense against microbial infections, participate in tissue healing, and contribute to the pathogenesis of inflammation and atherosclerosis. They engulf microbes, infected cells, and tissue debris directly or *via* intermediary proteins such as antibodies or complement components. These functions are essential in the

defense against microbial infections and healing of injured tissues. However, uptake of oxidized LDL *via* scavenger receptors by macrophages in the artery wall and glomerular mesangium results in the development and progression of atherosclerosis and glomerulosclerosis. Finally by producing cytokines and ROS, and releasing growth factors, metalloproteinases, and tissue factor, macrophages participate in the healing of damaged tissues, and the development of local and systemic inflammation, oxidative stress, and rupture of atheromatous plaques.[39]

Monocytes are classified based on expressions of CD14 (PRR) and CD16 (Fc gamma III receptor) into CD14++/CD16− (classical), CD14++/CD16+ (intermediate), and CD14+/CD16+ (proinflammatory) subtypes. CD14+CD16+ monocytes have a high capacity to produce inflammatory cytokines (TNF-α, IL-6, and IFN-α) and promote inflammation.[39] ESRD is associated with a general expansion of circulating monocytes, particularly of the proinflammatory CD14+CD16+ subtype.[29] The increase in circulating CD16+ monocytes has been reported in patients with CKD stage 2−5 and appears to be exacerbated by the initiation of HD.[40] Additionally, expression of purigenic receptors (P2X7)[41] and TLR-4 has been shown to be increased in circulating monocytes in those with early stage CKD, and to be associated with elevated levels of IL-6 and MCP-1.[42] In HD patients, monocytes show elevated basal toll-like receptor TLR-2 and TLR-4 expression, upregulation of cell surface integrin expression, increased basal cytokine and ROS production, and exaggerated response to lipopolysaccharide.[28,29,43] The modality of renal replacement therapy appears to play a role in the level of proinflammatory monocytes as patients treated with peritoneal dialysis have lower levels compared with those maintained on HD.[44] These abnormalities point to spontaneous activation of monocytes and their contribution to the prevailing oxidative stress, systemic inflammation, and atherosclerosis in CKD. Uremic plasma triggers production of osteoactivin by monocytes and macrophages, which can contribute to vascular calcification.[45] Moreover uremic plasma stimulates adhesion and infiltration of normal monocytes−macrophages in cultured human endothelial monolayers used to simulate an arterial wall *in vitro*[46] and to increase the expression of scavenger receptors, SR-A and CD36.[47,48] Epidemiologic studies have identified the association of increased intermediate monocytes (CD14++/CD16+) with adverse cardiovascular outcomes in nondialysis CKD stage 2−5 patients, as is the case in the general population,[39] and higher monocyte counts with increased incident kidney disease and progression of CKD.[49]

The mechanisms responsible for the increased numbers of proinflammatory monocytes in CKD are unknown. It has been speculated that oxidative stress, which increases generation of TLR ligands (such as oxidized phospholipids), may stimulate release of CD14+/CD16+ monocytes from the bone marrow.[50] Increased angiotensin converting enzyme (ACE) mRNA levels, decreased ACE2 levels, and upregulation of angiotensin II levels have recently been described in both subjects with CKD stage 2−5 and HD patients, and noted to be associated with increased monocyte−endothelial cell adhesion.[51] Additionally, both uremic serum with elevated levels of homocysteine and exogenous homocysteine have been shown to induce CD40 expression in CD14+/CD16− monocytes, suggesting homocysteine may play a role in the CKD-associated increase of proinflammatory monocytes.[52] Exposure to uremic toxins may also play a role. Exposure to p-cresyl sulfate has been shown to result in increased monocyte nitrous oxide (NO) production and macrophage activation.[53] Moderate increases of indoxyl sulfate result in promotion of monocyte-derived profibrotic macrophages that may contribute to maladaptive vascular remodeling and sustain a level of chronic inflammation.[54]

The spontaneous activation of monocytes in uremia is accompanied by impaired phagocytic capacity,[2,14,15] release of IL-6 and TNF-α, and an associated reduced response to vaccinations.[55] *In vitro* exposure to p-cresyl sulfate results in impaired phagocytosis and antigen presentation by monocyte-derived macrophages.[53] Tissue macrophages recovered from the peritoneal dialysis effluent of ESRD patients exhibit an immature phenotype and evidence of activation, features that may impair their ability to clear bacteria.[56,57] Together these monocyte−macrophage abnormalities contribute to the immune deficiency and increased incidence and severity of infections in the CKD population.

Polymorphonuclear Leukocyte Abnormalities in CKD

PMN are short-lived (5 days) professional phagocytes that avidly engulf antibody-coated and complement-coated microbes, damaged cells, and cellular debris. They have many intracellular granules that contain bacteriocidal proteins such as cationic proteins and defensins, proteolytic enzymes and cathepsin G (to degrade bacterial proteins), lysozyme (to lyse bacterial cell walls), NAD(P)H oxidase-II (to generate ROS), myeloperoxidase (to produce HOCl), and lactoferrin (to inhibit bacterial replication *via* iron deprivation). PMNs are the first line of defense against invading microbes and

important players in inflammation. In CKD patients the number of circulating PMNs progressively increases with declining renal function.[58] In ESRD patients PMNs demonstrate spontaneous activation. Circulating PMNs in HD patients exhibit upregulation of TLR-4, TLR-2, Cd11b, and CD18 expression, increased superoxide and hydrogen peroxide production, and marked degranulation, pointing to their spontaneous activation.[28,29] These abnormalities contribute to the prevailing systemic oxidative stress, inflammation, and tissue damage in this population. Increased numbers of circulating PMNs and high neutrophil-to-lymphocyte ratios have been associated with endothelial dysfunction, cardiovascular events,[59] CKD incidence,[60] and CKD progression.[61]

The spontaneous activation of PMNs is accompanied by their impaired migratory function,[62] decreased phagocytic and bactericidal capacity, and increased apoptosis.[14,15,63,64] The resultant CKD-associated impaired recruitment of neutrophils into inflamed tissue has been associated with increased fibroblast growth factor 23 (FGF-23) levels. *In vitro*, FGF-23 has been shown to directly inhibit PMN adhesion and transendothelial migration by binding to FGF2, blocking neutrophil integrin expression through activation of protein kinase A.[65] The increased apoptosis has been attributed to increased sensitivity of uremic PMNs to fas-fas-ligand–mediated apoptosis and to the effects of oxidative stress.[66–68] Collectively, these abnormalities contribute to the increased risk of infection in CKD. The PMN abnormalities are transiently intensified by HD,[28,29] most likely due to exposure to dialyzer membranes, cytoskeletal stresses from roller pumps, and influx of impurities from the dialysate compartment.[69] Kidney transplantation improves PMN function,[70] pointing to the role of uremia in the pathogenesis of these abnormalities.

Dendritic Cell Abnormalities in CKD

DCs, the major APCs, continuously survey the antigenic milieu of the body and act as sensors of microbial invasion and tissue damage. DCs prime and regulate immune responses in T cells, B cells, and NK cells and thereby play a critical part in tumor surveillance, defense against microbial pathogens, and tolerance to self antigens. Several sources of DC have been described, including Langerhans cells of the skin, monocytes that differentiate into DC, and circulating immature DCs.[50] Two types of circulating DCs have been identified. Plasmacytoid DCs (pDC) that possess intracellular TLRs (including TLR7 and TLR9), which sense viral or self-nucleic acids, and produce large amounts of type I interferons (such as IFNα) in response to viral infections, and myeloid DCs, which possess cell surface TLRs (including TLR3 and TLR4) and produce IL-12 and type I interferons in response to TLR3 and TLR4 agonists.

CKD stage 4 and 5 are associated with DC depletion and dysfunction.[16,71,72] Langerhans cell density is reduced in dialysis patients, compared with normal individuals.[73] Several studies have shown that DC derived from circulating monocytes of patients with CKD stage 4 and 5 are less effective in stimulating T cells[43,72,74], possibly due to uremia-induced reduction in expression of CD36 costimulatory molecule by DCs.[75] Circulating DCs are also significantly decreased in dialysis patients,[16,71] primarily due to the reduction of the pDC subset.[16] Circulating DC depletion in ESRD is transiently exacerbated by HD[16] and reversed by renal transplantation.[72] Given the critical role of DCs in regulation of innate and adaptive immunity, DC depletion contributes to impaired defense against infections and poor response to vaccination in patients with late-stage CKD. In an attempt to improve DC number and function, Verkade et al.[76] treated HD patients with granulocyte/macrophage colony stimulating factor. After treatment, DCs largely disappeared from the circulation, presumably due to their migration into lymphoid tissues, and response to hepatitis B vaccination improved.

Although DC numbers are reduced in HD patients, their basal and LPS-stimulated TNF production is increased.[16] These findings point to participation of DCs in the pathogenesis of systemic inflammation in CKD.

Natural Killer Cell Abnormalities in CKD

NK cells are cytotoxic lymphocytes that are critical to the innate immune system and can function as an interface to the adaptive immune response. NK cells rapidly respond to virally infected cells and tumor formation in the absence of antibodies.[77] NK cells are derived from the common lymphoid progenitor that generates B and T lymphocytes and differentiates and matures in the bone marrow, lymph node, spleen, tonsils, and thymus before entering the circulation. NK cells exist as classical and nonclassical subsets that commonly express CD16 and CD56 surface markers. Up to 80% of human NK cells also express CD8. A subset of NK cells, termed natural killer T cells, express TCR and BCR on their surface and differ phenotypically, by origin and respective effector functions. These NK cells also play a role in the adaptive immune response and can develop antigen-specific immunological memory.[78]

Studies of NK cells in CKD patients are limited and have yielded conflicting results.[79,80] In a study of 219 HD patients, Vacher-Coponat et al.[81] found reduced

numbers of NK cells associated with increased expression of activation markers (CD69 and NKp44 receptors) but normal NK function compared to healthy controls. In contrast, others have reported reduced expression of pivotal-activating receptor NKG2D on NK cells in HD patients.[82] Thus decreased number of NK cells in CKD patients may be associated with their impaired function and might contribute to reduced tumor surveillance and increased viral infections.

Role of Intestinal Epithelium and Other Nonimmune Cells

Studies in experimental animals with CKD have shown upregulation of ROS production machinery and chemokine expression in the cellular constituents of various tissues, highlighting their participation in the prevailing oxidative and inflammatory states.[32] The gastrointestinal epithelium serves as the barrier against entry of microbial toxins, antigens, and other harmful luminal contents into the intestinal wall and systemic circulation. The intestinal epithelial barrier consists of the epithelial cells and the paracellular junctional complex, which seals the gap between the adjacent epithelial cells. The epithelial tight junction is a major component of the junctional complex that plays a central role in preventing the influx of the noxious products into the circulation. By allowing the entry of microbial products and other noxious luminal contents into the body's internal milieu, disruption of the gastrointestinal epithelial barrier results in local and systemic inflammation. There is considerable evidence pointing to the dysfunction of the gastrointestinal epithelial barrier and its contribution to systemic inflammation in humans and animals with advanced CKD.[38] HD patients commonly exhibit endotoxemia in the absence of clinical infection[83] and histological evidence of inflammation throughout the gastrointestinal tract.[84] Heavy losses of the key protein constituents of colonic epithelial tight junction have been found in animals with CKD.[85] These findings explain the source of endotoxemia, which is commonly present and is a major cause of inflammation in the CKD population.[83] *In vivo* and *in vitro* studies identified urea (which enters the gastrointestinal tract of uremic humans and animals) and the byproducts of its hydrolysis by microbial urease (namely ammonia and ammonium hydroxide), as the main cause of disruption of intestinal barrier function and structure in uremia.[86–88] These findings explain the underlying mechanism of the previously demonstrated salutary effects of a low protein diet and longer/more frequent dialysis regimens, which help to lower the urea burden in the CKD/ESRD population.

COMPONENTS OF ADAPTIVE IMMUNITY AND THEIR ABNORMALITIES IN CKD

T Lymphocytes

T cells represent a major component of the adaptive immune system and play a central part in cell-mediated immunity. They are distinguished from other lymphocytes by the expression of the TCR. Exposure of naive T cells to antigen leads to clonal expansion and differentiation, and generation of memory and effector T cells. Effector T cells perform their effector function *via* secretion of cytokines and destruction of target cells. At the conclusion of a specific immune reaction, the population of the related effector T cells contracts. A small number of the memory T cells however remain indefinitely, enabling the host to mount a robust immune response on reexposure to the same pathogen. T cells are derived from bone marrow stem cells that populate the thymus as thymocytes and subsequently differentiate into functionally distinct subtypes.

Helper T Cells (CD4+ T Cells)

Helper T cells express CD4 protein on their surface. They play a key role in various immunologic processes, such as activation of cytotoxic T cells and macrophages, maturation of B cells into plasma cells and memory B cells, antibody production by B cells, recruitment of PMNs, eosinophils and basophils to the loci of infection/inflammation, amplification of microbiocidal activity of macrophages as well as development of tolerance or suppression of the inflammatory response, among others. When presented with the peptide fragments of the processed antigens by the APCs, CD4+ T cells rapidly proliferate and secrete cytokines to direct the immune response. Helper T cells can differentiate into several distinct subtypes, including Th1, Th2, Th3, Th17, or T follicular helper cells. Each of these subtypes secretes a different panel of cytokines that drive the immune response in specific manners. The CD4+ cell differentiation into the given subtypes is driven by the signaling patterns from the APCs.[7,50]

Cytotoxic T Lymphocytes (CD8+ T Cells)

These cells express CD8 protein on their surface. CD8+ T cells can destroy virally infected cells and tumor cells and participate in transplant rejection. CD8+ T cells recognize antigens associated with MHC class I, which is expressed by nearly all cells in the body. The regulatory T cells inactivate and transform CD8+ cells into an anergic state by secreting IL-10, adenosine, and other molecules, a process that is critical in preventing autoimmune diseases.[7,50]

Memory T Cells

Following acute infection a small fraction of the primed CD4+ or CD8+ cells persist indefinitely as central memory T cells and effector memory T cells, which typically express CD45RO. On reexposure to their cognate antigen, these cells undergo rapid proliferation to form large numbers of effector T cells. Memory T cells play a central part in adaptive immunity by providing the immune system with "memory" against past infections.[7,50]

Regulatory T Cells

Treg cells are derived from two distinct origins: (a) adapted regulatory T cells (also known as Tr1 cells or Th3 cells), which originate from alternative differentiation of naïve T cells, and (b) natural regulatory T cells (also known as CD4+ CD25+ FoxP3+ Treg cells), which mature in the thymus as a distinct lineage and comprise 5−10% of the circulating CD4+ T cells.

Treg cells, previously known as suppressor T cells, play a central role in maintaining immunological self-tolerance, limiting the inflammatory response to foreign antigens, ceasing T cell-mediated immunity on completion of the immune reaction, and suppressing autoreactive T cells that escape negative selection in the thymus. Activated Tregs suppress proliferation and blunt the effector functions of B cells, monocytes, and other T cells *via* cytokine-mediated or contact-dependent mechanisms. Through their actions Tregs protect the host by preventing the inflammatory response from becoming perpetual or disproportionately exuberant.[7,50]

CKD-Associated T Cell Abnormalities

Patients with advanced CKD and ESRD exhibit reduced numbers of total circulating T cells, accompanied by a profound difference in T cell composition. CKD patients have reduced CD4/CD8 ratio, increased Th1/Th2 ratio, and depletion of naïve and central memory CD4+ and CD8+ T cells.[19,20,89] The reduction in naïve and memory T cells is associated with reduced thymic output of naïve T cells[90] and increased expression of apoptotic markers and apoptosis of both naïve and central memory CD4+ and CD8+ T cells.[20] The magnitude of the naïve and central memory CD4+ and CD8+ T cell depletion is directly related to severity of azotemia, oxidative stress, secondary hyperparathyroidism, iron overload, and inflammation.[20] Given the critical role of naïve and central memory T-cells in orchestrating the immune response to the *de novo* exposure and reexposure to pathogens, their depletion must be, in part, responsible for increased incidence and poor outcome of various infections in the CKD population.

T cell dysfunction in CKD patients may also be associated with impaired response to vaccination. Using a highly sensitive multiparameter flow cytometry assay that permits the detection of antigen specific T-cells, Litjens et al.[91] demonstrated that the formation of hepatitis B surface antigen-specific CD4+ T cells was impaired in dialysis patients undergoing hepatitis B vaccination. The authors suggested that lack of adequate antigen-specific T cell differentiation was in part the cause for the observed poor response to vaccination.

T cell dysfunction may also play a role in CKD-associated chronic inflammation and increased cardiovascular risk. Patients with ESRD maintained on HD have an imbalance of Treg to Th17 cells. Compared with normal controls, they have reduced Treg cell frequency and lower Treg-related cytokine (IL-10, TGFβ1) levels, along with increased Th17 cell frequency and elevated Th17-related cytokine (IL-17, IL-6, IL-23) levels. These abnormalities were especially present in patients with a history of cardiovascular events.[92] Additionally, patients with CKD 5 have increased numbers of terminally differentiated CD4+ memory T cells that do not express CD28 (CD4+CD28-cells).[93] This T cell subpopulation, activated by human heat-shock protein (HSP) 60 and HSP70, is increased in patients with acute coronary syndrome and in CKD patients.[94] The initiation of HD appears to exacerbate these abnormalities.[95] These CD4+CD28-cells (previously categorized as Th1 helper cells) are highly proinflammatory, express large amounts of IFN-γ and TNF-α on activation, and are cytotoxic,[96] *via* the expression of activating killer cell-immunoglobulin-like receptor KIR2DS2, mainly in the absence of inhibitory KIR2DL3. Expression of KIR2DS2 is increased in HD patients compared to nondialysis-dependent CKD patients and is associated with reduced expression of the inhibitory KIR2DL3 expression.[97] These proinflammatory cells are thought to participate in the destabilization of atherosclerotic plaques. Their increased presence in CKD patients has been shown to be strongly associated with atherosclerotic changes[98] and a history of cardiovascular disease.[99]

Increased apoptosis has been reported in circulating lymphocytes of patients with early CKD and appeared to increase across stages 1−4.[100] Meier et al.[30] and Hendrikx et al.[31] have demonstrated increased apoptosis and marked reduction of the Treg cells (CD4+/CD25+) in dialysis-independent CKD 5 patients and ESRD patients maintained on peritoneal or HD. The observed depletion of the Treg cells was accompanied by their impaired ability to inhibit PHA-induced CD4+ cell proliferation, reflecting reduction in their anti-inflammatory capacity. The magnitude of Treg cell depletion and dysfunction was greatest in HD-treated patients followed by peritoneal dialysis-treated and dialysis-independent CKD5 patients. Incubation of

isolated Treg cells from normal subjects with uremic plasma lowered the number and reduced the suppressive capacity of these cells, pointing to the deleterious effect of the uremic milieu. This effect could be reproduced by addition of oxidized LDL, illustrating the interconnection between oxidative stress and lipid disorders with immunological abnormalities and the associated atherogenic diathesis in CKD.

Given the critical role of Treg cells in mitigating inflammation, Treg cell deficiency and dysfunction in the CKD/ESRD population may contribute to the prevailing systemic inflammation and cardiovascular and other complications. Use of recombinant erythropoietin (EPO) has been shown to have T-cell associated immunomodulating, anti-inflammatory effects. Through its effect on an EPO receptor and CD131 on APCs, EPO has been shown to increase TGFβ secretion, which results in conversion of naïve CD4+ T cells to functional Treg cells. Purroy et al. showed that in doses used to correct anemia in CKD patients, EPO inhibited conventional T cell proliferation, while facilitating Treg proliferation. Conventional T cell proliferation was inhibited *via* tyrosine phosphate SHP-1−dependent uncoupling of IL-2Rβ signaling, and Treg proliferation was achieved through increased IL-2Rγ and decreased IL-2Rβ signaling.[101]

B Lymphocytes

B lymphocytes are generated from hematopoietic stem cells in the bone marrow throughout life. They contribute to the immune system by producing antigen-specific antibodies. The pleotropic cytokine, IL-7, plays a major part in B-lymphopoiesis by promoting maturation of pre-B cells to B cells in the bone marrow.[102] After differentiation and selection in the bone marrow, newly emerging B lymphocytes (termed transitional B cells; CD19+ CD10+) migrate to the spleen. Further differentiation of transitional B cells into mature long-lived lymphocytes is driven by B cell activating factor of tumor necrosis family (BAFF).[103] B cells failing any maturation steps undergo clonal deletion by apoptosis, and those recognizing self-antigen during maturation become suppressed (anergy or negative selection). In the blood and lymphatic system B cells conduct immune surveillance *via* their BCR, which consists of a membrane-bound immunoglobulin molecule capable of binding a specific antigen. In adults, innate B1 cells (CD5+ B cells), which account for 25−27% of peripheral blood B lymphocytes, produce mainly IgM antibodies with high cross-reactivity but low affinity. These antibodies constitute a readily available pool of immunoglobulin for use against a variety of infections, before specific high-affinity antibodies are produced. In contrast, the conventional B cells (CD5− B cells, also known as B2 cells) produce more diverse and high-affinity antibodies and account for 75−80% of peripheral blood B lymphocytes. When the naive mature B lymphocytes recognize an antigen with their receptors and receive an additional signal from the T helper cells, they undergo proliferation and differentiation into long-lived memory B cells (CD27+) and short-lived plasma cells. Most activated B cells differentiate into plasma cells that secrete antibodies against the specific epitope of the inciting antigen. A small minority of these cells survive as memory cells that recognize the given antigen. However, with each reexposure, the number of surviving memory cells rises and specificity of immune response improves. Memory cells, which can survive decades, actively circulate from blood to lymph nodes and populate mucosal tissues. On subsequent encounter with the antigen, memory B cells rapidly produce immunoglobulin isotypes with high affinity for the given antigen. In adult humans, memory B cells constitute approximately 40% of all circulating B cells. The subpopulations of circulating B cells include innate B1 cells (CD19+,CD5+), conventional B2 cells (CD19+, CD5−), newly formed transitional B cells (CD19+, CD10+, CD27−), naïve B cells (CD19+, CD27−), and memory B cells (CD19+, CD27+).[7,18]

CKD-Associated B Cell Abnormalities

Several studies have demonstrated significant B lymphopenia in patients with CKD stage 5 with or without renal replacement therapy.[18,104] In addition, a diminished population of CD5+ innate B cells and CD27+ memory B cells has been demonstrated in children with CKD5.[104] Pahl et al.[18] demonstrated depletion of several other B cell subtypes in adult HD patients. The observed B cell lymphopenia was accompanied by elevated levels of IL-7 and BAFF, which are the key B cell differentiation and survival factors. The number of transitional B cells was not significantly reduced in the dialysis patients. These observations suggest that decreased output of B cells from bone marrow may not be the main cause of the B cell lymphopenia in CKD. This view is supported by the finding that plasma levels of IL-7, a cytokine that facilitates conversion of pre-B cells to B cells, was increased in the ESRD patients.

Two alternative mechanisms can account for B lymphopenia in CKD. First, the uremic milieu may increase susceptibility of B cells to apoptosis. This supposition is supported by the study of Fernández-Fresnedo et al. who reported increased apoptosis of B cells in predialysis CKD stage 5 and HD patients.[105] The second possibility is that the uremic environment may interfere with the maturation of transitional B cells to mature B cells

by promoting resistance to BAAF-mediated differentiation and survival signals. This supposition was supported by marked downregulation of BAAF receptor in HD patients reported by Pahl et al.[18] Thus B cell deficiency and dysfunction in advanced CKD can be simultaneously mediated by increased B cell apoptosis and impaired transitional B cell differentiation and maturation. In contrast to the observed reduction of BAFF receptor expression in transitional B cells, BAFF receptor expression was unchanged in circulating mature B cells (CD19+ CD10− cells). Because BAFF receptor expression and activity contributes to the survival of mature B lymphocytes,[106] the observed elevation of the circulating BAFF levels and the normality of BAFF receptor expression in mature B cells preclude the deficiency of either as the primary cause of the observed reduction of mature circulating B cells in advanced stages of CKD.

The studies of the effect of CKD/ESRD on B cell populations in humans have been restricted to the examination of cells found in blood samples. This is inadequate for a full understanding of the impact of the disease, due to lack of relevant studies of bone marrow and lymphoid tissues, critical sites in the maturation and functional development of these cells. Further studies are needed to explore the effects of uremia on B cell precursors in the bone marrow and downstream signal transduction pathways involved in B cell growth, differentiation, and survival. Regardless of the cause, uremia-induced naïve and memory B cell lymphopenia are, in part, responsible for the defective humoral response to infections, vaccination, and recall antigens and increased incidence of infection in CKD patients.

CLINICAL CONSIDERATIONS

Role of Vitamin D and CKD-Mineral Bone Disorders

CKD is associated with a progressive impairment of vitamin D metabolism, declining circulating $1,25(0H)D_3$ and resultant alterations in S[Ca], S[P], FGF-23, and parathyroid hormone (PTH) levels. In addition 25(OH)D levels are reduced in many CKD patients. These changes that result in secondary hyperparathyroidism and mineral-bone disorders have also been implicated in the pathogenesis of altered immune responses and chronic inflammation. In fact, altered vitamin D parameters and markers of mineral-bone disorders have been associated with increased infectious and cardiovascular mortality rates in CKD patients.[107]

Vitamin D possesses "classical" actions that affect mineral bone metabolism and "nonclassical" actions that include regulation of the innate and adaptive immune systems.[108] Activation of the TLR pathway in the human monocyte−macrophage by PAMPs shed by microbial agents such as mycobacterium tuberculosis results in increased expression of the vitamin D receptor (VDR), CYP27B1-hydroxylase, and local synthesis of $1,25(OH)_2D_3$, which stimulates production of cathelicidin and culminates in the killing of the ingested microbe.[108] Active vitamin D, $1,25(OH)_2D_3$, suppresses B lymphocyte proliferation and immunoglobulin production and inhibits the differentiation of B lymphocytes to plasma cells and memory B cells.[109] Active vitamin D can suppress proliferation of T lymphocytes and result in inhibition of Th1 cytokine production[110] while enhancing Th2 cytokine production, either directly or through its effects on APCs.[111,112] Vitamin D promotes the generation of Treg lymphocytes, likely mediated by suppression of myeloid DC maturation and enhancement of IL-10 production.[113]

Studies in CKD patients have implicated alterations of vitamin D levels and the hormones associated with mineral-bone metabolism in the dysfunction of both innate and adaptive immune cells. Increased circulating PTH levels in dialysis patients result in elevated cytosolic calcium concentrations, which reduce PMN-phagocytosis, B cell proliferation, and antibody production.[17] Parathyroidectomy or the use of calcium channel blockers improves PMN and B cell function,[17] suggesting these therapeutic interventions may result in reduced infections in CKD patients.

Elevated levels of FGF-23 have been shown to be independently associated with increases of proinflammatory cytokine levels in patients with CKD 2−4, although the underlying mechanism of action is unclear.[114] There are emerging data that FGF-23 can directly interact with PMNs and macrophages through the binding of FGFR/α-Klotho receptors.[115] Elevated FGF-23 levels result in reduced PMN recruitment and infection severity in CKD animal models with pneumonia.[65] However, PMNs lack the FGF-23 coreceptor α-Klotho. Although some have hypothesized that the effect can be modulated through the noncanonical FGFR2 pathway, this receptor has not been shown to be a target for FGF-23 in several functional studies.[115] There are however compelling data that FGF-23 directly effects macrophages. Macrophages express FGFR1, and exposure to inflammatory stimuli results in upregulation of α-Klotho expression. *In vitro* stimulation of macrophages with FGF-23 results in induction of TNF-mRNA and increased protein expression that can be blocked with FGFR inhibitors.[116,117] The effects of FGF-23 may be mediated by its effects of vitamin D metabolism. FGF-23, a regulator of CYP27B1 in the kidney, inhibits local CYP27B1 expression and synthesis of $1,25(OH)_2D_3$ in monocytes obtained from peritoneal

dialysis effluent as well as normal circulating monocytes.[118] The findings of low vitamin D and high FGF-23 serum levels have been recently reported to be associated with infectious and cardiac deaths in a large cohort of ESRD patients.[119] Correction of 25(OH) Vit D deficiency in HD patients resulted in increased monocyte VDR expression and expansion of proinflammatory, CD16+ monocytes associated with increased TLR2 and cathelicidin expression. These findings however were associated with a reduction of circulating levels of inflammatory cytokines.

These data point to the complex and diverse effects of vitamin D, PTH, and FGF-23 levels on immune cells and suggest that their CKD-associated alterations play a significant role in the pathogenesis of immune deficiency and chronic inflammation. More studies are needed to determine the role of vitamin D deficiency, hyperparathyroidism, and FGF-23 levels on immune dysfunction, to dissect the potential confounding paracrine and endocrine effects, and to ultimately guide future therapeutic strategies.

Role of Iron Deficiency and Iron Overload in CKD-Associated Immunological Disorders

Losses of blood in the HD circuit, routine blood samples drawn for laboratory testing, and impaired intestinal absorption of iron in dialysis patients frequently result in the development of iron deficiency in this population. Conversely administration of intravenous iron preparations commonly used to treat anemia often results in iron overload and the rise in poorly liganded catalytically active iron in the plasma and tissues in HD patients. The immune system is adversely affected by both iron depletion and iron overload. Iron deficiency results in thymus atrophy and T cell lymphopenia.[120] Iron overload causes CD4+ T cell depletion in transfusion-dependent thalassemic patients and expansion of CD8+CD28− T lymphocytes in patients with hemochromatosis.[24,25] Non−transferrin-bound iron increases iron uptake by lymphocytes and impairs their proliferation.[121] This phenomenon may, in part, account for immune dysfunction and impaired cellular and humoral immunity in patients with iron overload.[24,25] This is exemplified by the diminished antibody production in response to hepatitis B vaccination in HD patients treated with intravenous (IV) iron preparations.[122] Gupta et al.[123] found that exposure of peripheral blood mononuclear cells to relevant concentrations of sodium ferric gluconate, iron sucrose, or iron dextran for 24−72 hours induced a significant time-dependent intracellular oxidative stress and shortened cell survival, particularly in helper CD4+ T lymphocytes. They concluded that IV iron products exert deleterious effects on human CD4+ and CD16+ lymphocytes by increasing intracellular generation of ROS and causing apoptosis. This supposition is supported by experiments that showed that exposure of Jurkat cells (an immortalized T cell line) to hydrogen peroxide results in the release of iron from lysosomes leading to DNA damage, mitochondrial membrane potential instability, and apoptosis, events that could be prevented by the iron chelator, deferoxamine.[124] High doses of IV iron preparations impair phagocytic activity and microbial killing capability of polymorphonuclear leukocytes.[125,126] Pharmacologically relevant concentrations of iron sucrose impair phagocytic function and promote apoptosis of polymorphonuclear leukocytes.[127] Thus both iron deficiency and iron overload can contribute to immune deficiency and increase susceptibility to infection. These observations point to the importance of the judicious use of IV iron preparations in dialysis patients. Administration of IV iron products has been shown to result in increased ROS generation and cytokine production, and loss of mitochondrial membrane potential in the blood mononuclear cells of HD patients.[128] Sindrilaru et al.[129] showed *in vivo* iron-loading results in formation of proinflammatory M1 macrophages that sustain local inflammation and prevent healing. Accumulation of excess iron in macrophages in the artery wall, diseased kidney, and other tissues can, therefore, contribute to the pathogenesis of oxidative stress, inflammation, atherosclerosis, and CKD progression.

To address concerns regarding the effects of iron use in ESRD patients, a recent, prospective, open label study was conducted across multiple dialysis centers in the United Kingdom. HD patients with ferritin levels <400 mcg/L and transferrin saturation levels (TSAT) of <30% were randomized to receive high dose IV iron (400 mg/month) proactively or low-dose reactively administered IV iron. Treatment was withheld for serum ferritin of 700 mcg/L or TSAT of 40%. At the end of the study period, a median of 2.1 years, the high-dose group received a median of 264 mg/month (interquartile range of 200−336 mg), whereas the low-dose group received a median monthly dose of 145 mg (interquartile range of 100−190 mg). The blinded primary endpoint of a composite of nonfatal myocardial infarction, stroke, heart failure, or death was similar in both groups. Those treated with high dose iron required lower erythropoietin doses and fewer blood transfusions. Additionally, there was no evidence of increased infectious complications in the high-dose group. Thus, while available data provide convincing evidence for the role of iron overload in the pathogenesis of inflammation and impaired adaptive immunity, recent

clinical experience suggests that IV iron can be safely used at the doses tested in this study with the dosing restrictions described for the duration studied.[130]

CONCLUSIONS

CKD-associated inflammation is due to activation of the innate immune system orchestrated by monocytes, macrophages, granulocytes, and cellular constituents of nearly all organs and tissues in the body. CKD-associated inflammation is coupled with immune deficiency, which is caused by depletion of the antigen-presenting dendritic cells, naïve and central memory T cells and B cells, and impaired phagocytic ability of monocytes and PMNs.

References

1. Carrero JJ, Stenvinkel P. Inflammation in end-stage renal disease–what have we learned in 10 years? *Semin Dial* 2010;**23**:498–509. PubMed: 21039875.
2. Girndt M, Sester U, Sester M, Kaul H, Kohler H. Impaired cellular immunity in patients with endstage renal failure. *Nephrol Dial Transplant* 1999;**14**:2807–10. PubMed: 10570074.
3. Sarnak MJ, Jaber BL. Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. *Kidney Int* 2000;**58**:1758–64. PubMed: 11012910.
4. Eleftheriadis T, Antoniadi G, Liakopoulos V, Kartsios C, Stefanidis I. Disturbances of acquired immunity in hemodialysis patients. *Semin Dial* 2007;**20**:440–51.
5. Allon M, Depner TA, Radeva M, Bailey J, Beddhu S, Butterly D, Coyne DW, Gassman JJ, Kaufman AM, Kaysen GA, Lewis JA, Schwab SJ. Impact of dialysis dose and membrane on infection-related hospitalization and death: results of the HEMO Study. *JASN* 2003;**14**:1863–70.
6. Sarnak MJ, Jaber BL. Pulmonary infectious mortality among patients with end-stage renal disease. *Chest* 2001;**120**:1883–7.
7. Vaziri ND, Pahl MV, Crum A, Norris K. Effect of uremia on structure and function of immune system. *J Ren Nutr* 2012;**22**:149–56.
8. Heath WR, Carbone FR. Dendritic cell subsets in primary and secondary T cell responses at body surfaces. *Nat Immunol* 2009;**10**:1237–44.
9. Veldhoen M. The role of T helper subsets in autoimmunity and allergy. *Curr Opin Immunol* 2009;**21**:606–11.
10. Jameson SC, Masopust D. Diversity in T cell memory: an embarrassment of riches. *Immunity* 2009;**31**:859–71.
11. Waldschmidt T, Noelle R. Immunology: long live the mature B cell, a baffling mystery resolved. *Science* 2001;**293**:2012–3.
12. Herzenberg L, Haughton G, Rajewsky K. CD5 B cells in development and disease. *Ann NY Acad Sci* 1992;**651**:591–601.
13. Uckun F. Regulation of human B-cell ontogeny. *Blood* 1990;**76**:1908–23.
14. Alexiewicz JM, Smogorzewski M, Fadda GZ, Massry SG. Impaired phagocytosis in dialysis patients: studies on mechanisms. *Am J Nephrol* 1991;**11**:102–11. PubMed: 1951470.
15. Massry S, Smogorzewski M. Dysfunction of polymorphonuclear leukocytes in uremia: role of parathyroid hormone. *Kidney Int* 2001;**78**:S195–6.
16. Agrawal S, Gollapudi P, Elahimehr R, Pahl MV, Vaziri ND. Effects of end-stage renal disease and haemodialysis on dendritic cell subsets and basal and LPS-stimulated cytokine production. *Nephrol Dial Transplant* 2010;**25**:737–46. PubMed: 19903659.
17. Smogorzewski M, Massry SG. Defects in B-cell function and metabolism in uremia: role of parathyroid hormone. *Kidney Int* 2001;**78**:S186–9.
18. Pahl MV, Gollapudi S, Sepassi L, Gollapudi P, Elahimehr R, Vaziri ND. Effect of end-stage renal disease on B-lymphocyte subpopulations, IL-7, BAFF and BAFF receptor expression. *Nephrol Dial Transplant* 2010;**25**:205–12. PubMed: 19684120.
19. Moser B, Roth G, Brunner M, Lilaj T, Deicher R, Wolner E, Kovarik J, Boltz-Nitulescu G, Vychytil A, Ankersmit HJ. Aberrant - T cell activation and heightened apoptotic turnover in end-stage renal failure patients: a comparative evaluation between non-dialysis, haemodialysis, and peritoneal dialysis. *Biochem Biophys Res Commun* 2003;**308**:581–5. PubMed:12914790.
20. Yoon J, Gollapudi S, Pahl M, Vaziri N. Naïve and Central Memory T-cell lymphopenia in endstage renal disease. *Kidney Int* 2006;**70**:371–6. PubMed: 16738532.
21. Rostoker G, Griuncelli M, Loridon C, Couprie R, Benmaadi A, Bounhiol C, Roy M, Machado G, Janklewicz P, Drahi G, Dahan H, Cohen Y. Hemodialysis associated hemosiderosis in the era of erythropoiesis-stimulating agents. *Am J Med* 2012;**125**:991–9.
22. Vaziri ND. Understanding iron: promoting its safe use in patients with chronic kidney failure treated by hemodialysis. *Am J Kidney Dis* 2013;**61**:992–1000.
23. Vaziri ND. Epidemic of iron overload in dialysis population caused by intravenous iron products: a plea for moderation. *Am J Med* 2012;**125**:951–2.
24. Farmakis D, Giakoumis A, Polymeropoulos E, Aessopos A. Pathogenetic aspects of immune deficiency associated with beta-thalassemia. *Med Sci Monit* 2003;**9**:RA19–22.
25. Porto G, De Sousa M. Iron overload and immunity. *World J Gastroenterol* 2007;**13**(35):4707–15.
26. Sunder-Plassmann G, Patruta SI, Hörl WH. Pathobiology of the role of iron in infection. *Am J Kidney Dis* 1999;**34**:S25–29.
27. Chang J, Ma JZ, Zeng Q, Cechova S, Gantz A, Nievergelt C, O'Connor D, Lipkowitz M, Le TH. Loss of GSTM1, a NRF2 target, is associated with accelerated progression of hypertensive kidney disease in the African American Study of Kidney Disease (AASK). *Am J Physiol Renal Physiol* 2013;**304**(4):F348–55. PubMed: 21613384.
28. Yoon JW, Pahl MV, Vaziri ND. Spontaneous leukocyte activation and oxygen-free radical generation in end-stage renal disease. *Kidney Int* 2007;**71**:167–72. PubMed: 17136029.
29. Gollapudi P, Yoon JW, Gollapudi S, Pahl MV, Vaziri ND. Leukocyte toll-like receptor expression in end-stage kidney disease. *Am J Nephrol* 2010;**31**:247–54. PubMed: 20090311.
30. Meier P, Golshayan D, Blanc E, Pascual M, Burnier M. Oxidized LDL modulates apoptosis of regulatory T cells in patients with ESRD. *Am J Soc Nephrol* 2009;**20**:1368–84.
31. Hendrikx TK, van Gurp EA, Mol WM, Schoordijk W, Sewgobind VD, Ijzermans JN, Weimar W, Baan CC. End-stage renal failure and regulatory activities of CD4+CD25bright+FoxP3+ T-cells. *Nephrol Dial Transplant* 2009;**24**:1969–78. PubMed: 19193737.
32. Vaziri ND. Oxidative stress in uremia: nature, mechanisms, and potential consequences. *Semin Nephrol* 2004;**24**:469–73. PubMed: 15490413.
33. Vaziri ND, Navab M, Fogelman AM. HDL metabolism and activity in chronic kidney disease. *Nat Rev Nephrol* 2010;**6**:287–96. PubMed: 20308998.
34. Vaziri ND, Norris K. Lipid disorders and their relevance to outcomes in chronic kidney disease. *Blood Purif* 2011;**31**:189–96. PubMed: 21228589.

35. Kim HJ, Vaziri ND. Contribution of impaired Nrf2-Keap1 pathway to oxidative stress and inflammation in chronic renal failure. *Am J Physiol Renal Physiol* 2010;**298**:F662−671. PubMed: 20007347.
36. Ruiz S, Pergola PE, Zager RA, Vaziri ND. Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease. *Kidney Int* 2013;**83**:1029−41.
37. Aminzadeh MA, Nicholas SB, Norris KC, Vaziri ND. Role of impaired Nrf2 activation in the pathogenesis of oxidative stress and inflammation in chronic tubulo-interstitial nephropathy. *Nephrol Dial Transplant* 2013. PMID:23512109.
38. Vaziri ND. CKD impairs barrier function and alters microbial flora of the intestine - a major link to inflammation and uremic toxicity. *Curr Opin Nephrol Hypertens* 2012;**21**:587−92.
39. Heine GH, Ortiz A, Massy ZA, Lindholm B, Wiecek A, Martinez-Castelao A, Covic A, Goldsmith D, Suleymanlar G, London GM, Parati G, Sicari R, Zocalli C. Fliser D on behalf of EURECA-m working group of ERA-EDTA. Monocyte subpopulations and cardiovascular risk in chronic kidney disease. *Nat Rev Nephrol* 2012;**8**:362−9.
40. Lim WH, Kireta S, Leedham E, Russ GR, Coates PT. Uremia impairs monocyte and monocyte-derived dendritic cell function in hemodialysis patients. *Kidney Int* 2007;**72**:1138−48.
41. Lajdova I, Oksa A, Horvathova M, Spustova V. Expression of purinergic P2X(7) receptors in subpopulations of peripheral blood mononuclear cells in early-stage of chronic kidney disease. *J Physiol Pharmacol* 2017;**68**(5):779−85. PubMed PMID: 29375053.
42. Grabulosa CC, Manfredi SR, Canziani ME, Quinto BMR, Barbosa RB, Rebello JF, Batista MC, Cendoroglo M, Dalboni MA. Chronic kidney disease induces inflammation by increasing Toll-like receptor-4, cytokine and cathelicidin expression in neutrophils and monocytes. *Exp Cell Res* 2018;**365**(2): 157−62. PubMed PMID: 29481790.
43. Rogacev KS, Seiler S, Zawada AM, Reichart B, Herath E, Roth D, Ulrich C, Fliser D, Heine GH. CD14++CD16+ monocytes and cardiovascular outcome in patients with chronic kidney disease. *Eur Heart J* 2011;**32**(1):84−92.
44. Ducloux D, Legendre M, Bamoulid J, Rebibou JM, Saas P, Courivaud C, Crepin T. ESRD-associated immune phenotype depends on dialysis modality and iron status: clinical implications. *Immun Ageing* 2018;**15**:16. PubMed PMID: 30026783.
45. Pahl MV, Vaziri ND, Yuan J, Adler SG. Upregulation of monocyte/macrophage HGFIN (Gpnmb/Osteoactivin) expression in end-stage renal disease. *Clin J Am Soc Nephrol* 2010;**5**:56−61. PubMed: 19833906.
46. Moradi H, Ganji S, Kamanna V, Pahl MV, Vaziri ND. Increased monocyte adhesion- promoting capacity of plasma in end-stage renal disease - response to antioxidant therapy. *Clin Nephrol* 2010;**74**:273−81. PubMed: 20875379.
47. Ando M, Gafvels M, Bergstrom J, Lindholm B, Lundkvist I. Uremic serum enhances scavenger receptor expression and activity in the human monocytic cell line U937. *Kidney Int* 1997;**51**:785−92.
48. Chmielewski M, Bryl E, Marzec L, Aleksandrowicz E, Witkowski JM, Rutkowski B. Expression of scavenger receptor CD36 in chronic renal failure patients. *Artif Organs* 2005;**29**:608−14.
49. Bowe B, Xie Y, Xian H, Li T, Al-Aly Z. Association between monocyte count and risk of incident CKD and progression to ESRD. *Clin J Am Soc Nephrol* 2017;**12**(4):603−13. PubMed PMID: 28348030.
50. Betjes MGH. Immune cell dysfunction and inflammation in end-stage renal disease. *Nat Rev Nephrol* 2013;**9**:255−65.
51. Trojanowicz B, Ulrich C, Kohler F, Bode V, Seibert E, Fiedler R, Girndt M. Monocytic angiotensin-converting enzyme 2 relates to atherosclerosis in patients with chronic kidney disease. *Nephrol Dial Transplant* 2017;**32**(2):287−98. PubMed PMID: 28186543.
52. Yang J, Fang P, Yu D, Zhang L, Zhang D, Jiang X, Yang WY, Bottiglieri T, Kunapuli SP, Yu J, Choi ET, Ji Y, Yang X, Wang H. Chronic kidney disease induces inflammatory CD40+ monocyte differentiation via homocysteine elevation and DNA hypomethylation. *Circ Res* 2016;**119**(11):1226−41. PubMed PMID: 27992360.
53. Azevedo ML, Bonan NB, Dias G, Brehm F, Steiner TM, Souza WM, Stinghen AE, Barreto FC, Elifio-Esposito S, Pecoits-Filho R, Moreno-Amaral AN. p-Cresyl sulfate affects the oxidative burst, phagocytosis process, and antigen presentation of monocyte-derived macrophages. *Toxicol Lett* 2016;**263**:1−5. PubMed PMID: 27760375.
54. Barisione C, Garibaldi S, Furfaro AL, Nitti M, Palmieri D, Passalacqua M, Garuti A, Verzola D, Parodi A, Ameri P, Altieri P, Fabbi P, Ferrar PF, Brunelli C, Arsenescu V, Balbi M, Palombo D, Ghigliotti G. Moderate increase of indoxyl sulfate promotes monocyte transition into profibrotic macrophages. *PLoS One* 2016;**11**(2):e0149276. PubMed PMID: 26925780.
55. Girndt M, Köhler H, Schiedhelm-Weick E, Schlaak JF, Meyer zum Büschenfelde KH, Fleischer B. Production of interleukin-6, tumor necrosis factor α and interleukin-10 *in vitro* correlates with the clinical immune defect in chronic hemodialysis patients. *Kidney Int* 1995;**47**:559−65.
56. Betjes MG, Tuk CW, Struijk DG, Krediet RT, Arisz L, Hoefsmit EC, Beelen RH. Immuno-effector characteristics of peritoneal cells during CAPD treatment: a longitudinal study. *Kidney Int* 1993; **43**:641−8.
57. Betjes MG, Tuk CW, Visser CE, Zemel D, Krediet RT, Arisz L, Beelen RH. Analysis of the peritoneal cellular immune system during CAPD shortly before a clinical peritonitis. *Nephrol Dial Transplant* 1994;**9**:684−92.
58. Sela S, Shurtz-Swirski R, Cohen-Mazor M, Mazor R, Chezar J, Shapiro G, Hassan K, Shkolnik G, Geron R, Kristal B. Primed peripheral polymorphonuclear leukocyte: a culprit underlying chronic low-grade inflammation and systemic oxidative stress in chronic kidney disease. *J Am Soc Nephrol* 2005;**16**: 2431−8.
59. Solak Y, Yilmaz MI, Sonmez A, Saglam M, Cakir E, Unal HU, Gok M, Caglar K, Oguz Y, Yenicesu M, Karaman M, Ay SA, Gaipov A, Turk S, Vural A, Carrero JJ. Neutrophil to lymphocyte ratio independently predicts cardiovascular events in patients with chronic kidney disease. *Clin Exp Nephrol* 2013;**17**(4):532−40. PubMed PMID: 23180042.
60. Tian N, Penman AD, Manning Jr RD, Flessner MF, Mawson AR. Association between circulating specific leukocyte types and incident chronic kidney disease: the Atherosclerosis Risk in Communities (ARIC) study. *J Am Soc Hypertens*. 2012 ;**6**(2):100−8. PubMed PMID: 22054781.
61. Kocyigit I, Eroglu E, Unal A, Sipahioglu MH, Tokgoz B, Oymak O, Utas C. Role of neutrophil/lymphocyte ratio in prediction of disease progression in patients with stage-4 chronic kidney disease. *J Nephrol* 2013 ;**26**(2):358−65. PubMed PMID: 22573523.
62. Pindjakova J, Griffin MD. Defective neutrophil rolling and transmigrationin acute uremia. *Kidney Int* 2011;**80**:447−50.
63. Mahajan S, Kalra OP, Asit KT, Ahuja G, Kalra V. Phagocytic polymorphonuclear function in patients with progressive uremia and the effect of acute hemodialysis. *Ren Fail* 2005;**27**:357−60.
64. Anding K, Gross P, Rost JM, Allgaier D, Jacobs E. The influence of uraemia and haemodialysis on neutrophil phagocytosis and antimicrobial killing. *Nephrol Dial Transplant* 2003;**18**: 2067−73.
65. Rossaint J, Oehmichen J, Van Aken H, Reuter S, Pavenstädt HJ, Meersch M, Unruh M, Zarbock A. FGF23 signaling impairs neutrophil recruitment and host defense during CKD. *J Clin Investig* 2016;**126**(3):962−74. PubMed PMID: 26878171.

66. Jaber B, Perianayagam MC, Balakrishnan VS, King AJ, Pereira BJ. Mechanisms of neutrophil apoptosis in uremia and relevance of the Fas (APO-1, CD95)/Fas ligand system. *J Leukoc Biol* 2001;**69**: 1006–12.
67. Glorieux G, Vanholder R, Lameire N. Uraemic retention and apoptosis: what is the balance for the inflammatory status in uraemia? *Eur J Clin Investig* 2003;**33**:631–4.
68. Majewska E, Baj Z, Sulowska Z, Rysz J, Luciak M. Effects of uraemia and haemodialysis on neutrophil apoptosis and expression of apoptosis-related proteins. *Nephrol Dial Transplant* 2003;**18**: 2582–8.
69. Vaziri ND, Wang J, Cesario T, Yousefi S, Valenzuela R, Carandang G. Induction, transcription, synthesis and adsorption of interleuken-1 by dialyzer membranes. *J Am Soc Nephrol* 1994;**4**:1884–9.
70. Klein JB, McLeish KR, Ward RA. Transplantation, not dialysis, corrects azotemia-dependent priming of the neutrophil oxidative burst. *Am J Kidney Dis* 1999;**33**:483–91.
71. Hesselink DA, Betjes MG, Verkade MA, Athanassopoulos P, Baan CC, Weimar W. The effects of chronic kidney disease and renal replacement therapy on circulating dendritic cells. *Nephrol Dial Transplant* 2005;**20**:1868–73. PubMed: 15886215.
72. Verkade MA, van Druningen CJ, Vaessen LM, Hesselink DA, Weimar W, Betjes MG. Functional impairment of monocyte-derived dendritic cells in patients with severe chronic kidney disease. *Nephrol Dial Transplant* 2007;**22**:128–38. PubMed: 17005 525.
73. Mettang TP, Weber J, Machleidt C, Hübel E, Kiefer T, Kuhlmann U. Epidermal Langerhans cells in uremic patients on hemodialysis or continuous ambulatory peritoneal dialysis. *Nephron* 1993;**65**:278–83.
74. Verkade MA, van Druningen CJ, Op de Hoek CT, Weimar W, Betjes MG. Decreased antigen-specific T-cell proliferation by moDC among hepatitis B vaccine non-responders on haemodialysis. *Clin Exp Med* 2007;**7**:65–71.
75. Meuer SC, Hauer M, Kurz P, Meyer zum Buschenfelde KH, Kohler H. Selective blockade of the antigen-receptor-mediated pathway of T cell activation in patients with impaired primary immune responses. *J Clin Investig* 1987;**80**:743–9.
76. Verkade MA, van de Wetering J, Klepper M, Vaessen LM, Weimar W, Betjes MG. Peripheral blood dendritic cells and GM-CSF as an adjuvant for hepatitis B vaccination in hemodialysis patients. *Kidney Int* 2004;**66**:614–21.
77. Vivier E, Raulet DH, Moretta A, Caligiuri MA, Zitvogel L, Lanier LL, Yokoyama WM, Ugolini S. Innate or adaptive immunity? The example of natural killer cells. *Science* 2011;**331**:44–9.
78. Arina A, Murillo O, Dubrot J, Azpilikueta A, Alfaro C, PÃrez-Gracia JL, Bendandi M, Palencia B, HervÃ¡s-Stubbs S, Melero I. Cellular liaisons of natural killer lymphocytes in immunology and immunotherapy of cancer. *Expert Opin Biol Ther* 2007;**5**:599–615.
79. Griveas I, Visvardis G, Fleva A, Papadopoulou D, Mitsopoulos E, Kyriklidou P, Manou E, Ginikopoulou E, Meimaridou D, Paulitou A, Sakellariou G. Comparative analysis of immunophenotypic abnormalities in cellular immunity of uremic patients undergoing either hemodialysis or continuous ambulatory peritoneal dialysis. *Ren Fail* 2005;**27**:279–82.
80. Cala S, Mazuran R, Kordic D. Negative effect of uraemia and cuprophane haemodialysis on natural killer cells. *Nephrol Dial Transplant* 1990;**5**:437–40.
81. Vacher-Coponat H, Brunet C, Lyonnet L, Bonnet E, Loundou A, Sampol J, Moal V, Dussol B, Brunet P, Berland Y, Dignat-George F, Paul P. Natural killer cell alterations correlate with loss of renal function and dialysis duration in uraemic patients. *Nephrol Dial Transplant* 2008;**23**:1406–14.
82. Peraldi MN, Berrou J, Dulphy N, Seidowsky A, Haas P, Boissel N, Metivier F, Randoux C, Kossari N, Guérin A, Geffroy S, Delavaud G, Marin-Esteban V, Glotz D, Charron D, Toubert A. Oxidative stress mediates a reduced expression of the activating receptor NKG2D in NK cells from end-stage renal disease patients. *J Immunol* 2009;**182**:1696–705.
83. Feroze U, Kalantar-Zadeh K, Sterling KA, Molnar MZ, Noori N, Benner D, Shah V, Dwivedi R, Becker K, Kovesdy CP, Raj DS. Examining associations of circulating endotoxin with nutritional status, inflammation, and mortality in hemodialysis patients. *J Ren Nutr* 2012;**22**:317–26.
84. Vaziri ND, Dure-Smith B, Miller R, Mirahmadi MK. Pathology of gastrointestinal tract in chronic hemodialysis patients: an autopsy study of 78 cases. *Am J Gastroenterol* 1985;**80**:608–11.
85. Vaziri ND, Yuan J, Rahimi A, Ni Z, Said H, Subramanian VS. Disintegration of colonic epithelial tight junction in uremia: a likely cause of CKD-associated inflammation. *Nephrol Dial Transplant* 2012;**27**:2686–93.
86. Vaziri ND, Yuan J, Norris K. Role of urea in intestinal barrier dysfunction and disruption of epithelial tight junction in chronic kidney disease. *Am J Nephrol* 2013;**37**:1–6.
87. Vaziri ND, Goshtasby N, Yuan J, Jellbauer S, Moradi H, Raffatellu M, Kalantar-Zadeh K. Uremic human plasma degrades intestinal epithelial barrier structure and function. *Am J Nephrol* 2012;**36**:438–43.
88. Vaziri ND, Yuan J, Khazaeli M, Masuda Y, Ichii H, Liu S. Oral activated charcoal adsorbent (AST-120) ameliorates CKD-induced intestinal epithelial barrier disruption and systemic inflammation. *Am J Nephrol* 2013;**37**:518–25.
89. Litjens NH, van Druningen CJ, Betjes MG. Progressive loss of renal function is associated with activation and depletion of naive T lymphocytes. *Clin Immunol* 2006;**118**:83–91.
90. Betjes MG, Langerak AW, van der Spek A, de Wit EA, Litjens NH. Premature aging of circulating T cells in patients with end-stage renal disease. *Kidney Int* 2011;**80**:208–17.
91. Litjens NH, Huisman M, van den Dorpel M, Betjes MG. Impaired immune responses and antigen-specific memory CD4+ T cells in hemodialysis patients. *J Am Soc Nephrol* 2008;**19**:1483–90.
92. Zhang J, Hua G, Zhang X, Tong R, DU X, Li Z. Regulatory T cells/T-helper cell 17 functional imbalance in uraemic patients on maintenance haemodialysis: a pivotal link between microinflammation and adverse cardiovascular events. *Nephrology* 2010;**15**(1):33–41. PubMed PMID: 20377769.
93. Betjes MG, Huisman M, Weimar W, Litjens NH. Expansion of cytolytic CD4+CD28- T cells in end-stage renal disease. *Kidney Int* 2008;**74**:760–7.
94. Yadav AK, Kumar V, Jha V. Heat shock proteins 60 and 70 specific proinflammatory and cytotoxic response of CD4+CD28null cells in chronic kidney disease. *Mediat Inflamm* 2013;**2013**:384807. PubMed PMID: 24347824.
95. Lisowska KA, Debska-Ślizień A, Jasiulewicz A, Heleniak Z, Bryl E, Witkowski JM. Hemodialysis affects phenotype and proliferation of CD4-positive T lymphocytes. *J Clin Immunol* 2012;**32**(1): 189–200. PubMed PMID: 21993694.
96. Yadav AK, Jha V. CD4+CD28null cells are expanded and exhibit a cytolytic profile in end-stage renal disease patients on peritoneal dialysis. *Nephrol Dial Transplant* 2011;**26**:1689–94.
97. Zal B, Chitalia N, Ng YS, Trieu V, Javed S, Warrington R, Kaski JC, Banerjee D, Baboonian C. Killer cell immunoglobulin receptor profile on CD4(+) CD28(-) T cells and their pathogenic role in non-dialysis-dependent and dialysis-dependent chronic kidney disease patients. *Immunology* 2015;**145**(1):105–13. PubMed PMID: 25484131.

98. Yadav AK, Lal A, Jha V. Cytotoxic CD4+CD28 null T lymphocytes, systemic inflammation and atherosclerotic risk in patients with chronic kidney disease. *Nephron Clin Pract* 2012;**120**(4): c185–93. PubMed PMID: 22907478.
99. Betjes MG, de Wit EE, Weimar W, Litjens NH. Circulating proinflammatory CD4+CD28null T cells are independently associated with cardiovascular disease in ESRD patients. *Nephrol Dial Transplant* 2010;**25**:3640–6.
100. Dounousi E, Koliousi E, Papagianni A, Ioannou K, Zikou X, Katopodis K, Kelesidis A, Tsakiris D, Siamopoulos KC. Mononuclear leukocyte apoptosis and inflammatory markers in patients with chronic kidney disease. *Am J Nephrol* 2012;**36**(6):531–6. PubMed PMID:23258075.
101. Purroy C, Fairchild RL, Tanaka T, Baldwin 3rd WM, Manrique J, Madsen JC, Colvin RB, Alessandrini A, Blazar BR, Fribourg M, Donadei C, Maggiore U, Heeger PS, Cravedi P. Erythropoietin receptor-mediated molecular crosstalk promotes T cell immunoregulation and transplant survival. *J Am Soc Nephrol* 2017;**28**(8): 2377–92. PubMed PMID: 28302753.
102. Milne CD, Paige CJ. IL-7: a key regulator of B lymphopoiesis. *Semin Immunol* 2006;**18**:20–30. PubMed: 16303314.
103. Kalled L. Impact of the BAFF/BR3 axis on B cell survival, germinal center maintenance and antibody production. *Semin Immunol* 2006;**18**:290–6. PubMed: 16931038.
104. Bouts A, Davin JC, Krediet RT, Monnens LA, Nauta J, Schröder CH, van Lier RA, Out TA. Children with chronic renal failure have reduced numbers of memory B cells. *Clin Exp Immunol* 2004;**137**:589–94. PubMed: 15320911.
105. Fernández-Fresnedo G, Ramos MA, González-Pardo MC, de Francisco AL, Lopez-Hoyos M, Arias M. B lymphopenia in uremia is related to an accelerated in vitro apoptosis and dysregulation of Bcl-2. *Nephrol Dial Transplant* 2000;**15**:502–10. PubMed: 10727545.
106. Mackay F, Schneider P, Rennert R, Browning J. BAFF and APRIL: a tutorial on B cell survival. *Annu Rev Immunol* 2003;**21**:231–64. PubMed: 12427767.
107. Sterling KA, Eftekhari P, Girndt M, Kimmel P, Raj D. The immunoregulatory function of vitamin D: implications in chronic kidney disease. *Nat Rev Nephrol* 2012;**8**:403–12.
108. Adams JS, Hewison M. Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. *Nat Clin Pract Endocrinol Metabol* 2008;**4**:80–90.
109. Chen S, Sims GP, Chen XX, Gu YY, Chen S, Lipsky PE. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. *J Immunol* 2007;**179**:1634–47. PubMed: 17641030.
110. Lemire JM, Adams JS, Kermani-Arab V, Bakke AC, Sakai R, Jordan SC. 1,25-Dihydroxyvitamin D3 suppresses human T helper/inducer lymphocyte activity *in vitro*. *J Immunol* 1985;**134**: 3032–5. PubMed: 3156926.
111. Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HF, O'Garra A. 1α,25-Dihydroxyvitamin D3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. *J Immunol* 2001;**167**:4974–80. PubMed: 11673504.
112. Piemonti L, Monti P, Sironi M, Fraticelli P, Leone BE, Dal Cin E, Allavena P, Di Carlo V. Vitamin D3 affects differentiation, maturation, and function of human monocyte derived dendritic cells. *J Immunol* 2000;**164**:4443–51. PubMed: 10779743.
113. Penna G, Amuchastegui S, Giarratana N, Daniel KC, Vulcano M, Sozzani S, Adorini L. 1,25-Dihydroxyvitamin D3 selectively modulates tolerogenic properties in myeloid but not plasmacytoid dendritic cells. *J Immunol* 2007;**178**:145–53. PubMed: 17182549.
114. Munoz Mendoza J, Isakova T, Ricardo AC, Xie H, Navaneethan SD, Anderson AH, Bazzano LA, Xie D, Kretzler M, Nessel L, Hamm LL, Negrea L, Leonard MB, Raj D, Wolf M. Chronic renal insufficiency cohort. Fibroblast growth factor 23 and inflammation in CKD. *Clin J Am Soc Nephrol* 2012;**7**(7):1155–62.
115. Fitzpatrick EA, Han X, Xiao Z, Quarles LD. Role of fibroblast growth factor-23 in innate immune responses. *Front Endocrinol* 2018;**9**:320. PubMed PMID: 29946298.
116. Han X, Li L, Yang J, King G, Xiao Z, Quarles LD. Counter-regulatory paracrine actions of FGF-23 and 1,25(OH)2 D in macrophages. *FEBS Lett* 2016;**590**(1):53–67.
117. Masuda Y, Ohta H, Morita Y, Nakayama Y, Miyake A, Itoh N, et al. Expression of Fgf23 in activated dendritic cells and macrophages in response to immunological stimuli in mice. *Biol Pharm Bull* 2015;**38**(5):687–93.
118. Bacchetta J, Sea JL, Chun RF, Lisse TS, Wesseling-Perry K, Gales B, Adams JS, SaluskyIB, Hewison M. Fibroblast growth factor 23 inhibits extrrenal synthesis of 1,25-dihydroxyvitamin D in human monocytes. *J Bone Miner Res* 2013;**28**(1):46–55. PubMed: 22886720.
119. Chonchol M, Greene T, Zhang Y, Hoofnagle AN, Cheung AK. Low vitamin D and high fibroblast growth factor 23 serum levels associate with infectious and cardiac deaths in the HEMO study. *J Am Soc Nephrol* 2016;**27**(1):227–37.
120. Bowlus CL. The role of iron in T cell development and autoimmunity. *Autoimmun Rev* 2003;**2**:73–8.
121. Djeha A, Brock JH. Uptake and intracellular handling of iron from transferrin and iron chelates by mitogen stimulated mouse lymphocytes. *Biochem Biophys Acta* 1992;**1133**:147–52.
122. Liu JH, Liu YL, Lin HH, Yang YF, Kuo HL, Lin PW, Huang CC. Intravenous iron attenuates postvaccination anti-HBsAg titers after quadruple hepatitis B vaccination in dialysis patients with erythropoietin therapy. *Int J Clin Pract* 2009;**63**:387–93.
123. Gupta A, Zhuo J, Zha J, Reddy S, Olp J, Pai A. Effect of different intravenous iron preparations on lymphocyte intracellular reactive oxygen species generation and subpopulation survival. *BMC Nephrol* 2010;**17**:11–6.
124. Tenopoulou M, Doulias PT, Barbouti A, Brunk U, Galaris D. Role of compartmentalized redox-active iron in hydrogen peroxide-induced DNA damage and apopotosis. *Biochem J* 2005;**387**:703–10.
125. Deicher R, Ziai F, Cohen G, Müllner M, Hörl WH. High dose parenteral iron sucrose depresses neutrophil intracellular killing capacity. *Kidney Int* 2003;**64**:728–36.
126. Guo D, Jaber BL, Lee S, Perianayagam MC, King AJ, Pereira BJ, Balakrishnan VS. Impact of iron dextran on polymorphonuclear cell function among hemodialysis patients. *Clin Nephrol* 2002;**58**: 134–42.
127. Ichii H, Masuda Y, Hassanzadeh T, Saffarian M, Gollapudi S, Vaziri ND. Iron sucrose impairs phagocytic function and promotes apoptosis in polymorphonuclear leukocytes. *Am J Nephrol* 2012; 19;**36**:50–7.
128. Pai AB, Conner T, McQuade CR, Olp J, Hicks P. Non-transferrin bound iron, cytokine activation and intracellular reactive oxygen species generation in hemodialysis patients receiving intravenous iron dextran or iron sucrose. *Biometals* 2011;**24**: 603–13.
129. Sindrilaru A, Peters T, Wieschalka S, Baican C, Baican A, Peter H, Hainzl A, Schatz S, Qi Y, Schlecht A, Weiss JM, Wlaschek M, Sunderkötter C, Scharffetter-Kochanek K. An unrestrained proinflammatory M1 macrophage population induced by iron impairs wound healing in humans and mice. *J Clin Investig* 2011;**121**: 985–97.
130. Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA, McMurray JJV, Murray H, Tomson CRV, Wheeler DC, Winearls CG, Ford I. PIVOTAL investigators and committees. Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med* 2019;**380**(5):447–58. PubMed PMID: 30365356.

QUESTIONS AND ANSWERS

Question 1

T cells represent a major component of the adaptive immune system and play a central role in cell-mediated immunity. Which T-cell abnormalities have been associated with CKD?

A. Patients with advanced CKD and ESRD have increased number of total circulating T cells
B. HD patients have depletion of naïve and central memory CD4+ and CD8+ T cells
C. CKD patients have increased apoptosis and marked reduction of Treg cells
D. None of the above
E. Both B and C

Answer: E

Patients with advanced CKD and ESRD exhibit reduced, rather than increased numbers of total circulating T cells, with a reduced CD4/CD8 ratio, increased Th1/Th2 ratio, and depletion of naïve and central memory CD4+ and CD8+ T cells. Additionally, increased apoptosis and marked reduction of the Treg cells (CD4+/CD25+) in dialysis-independent stage 5 CKD patients and ESRD patients maintained on dialysis have been reported. Thus both B and C are true, making E the correct response. Given the critical role of naïve and central memory T cells in orchestrating the immune response to the *de novo* exposure and reexposure to pathogens, and of Treg cells in mitigating inflammation, T-cell deficiency and dysfunction in CKD population may contribute to the prevailing immune dysfunction, increased risk of infection, and systemic inflammation.

Question 2

Vitamin D affects both the innate and the adaptive immune systems. Which one of the following statements is true?

A. Local conversion of 25(OH) vitamin D to active 1,25(OH) vitamin D by monocyte−macrophages stimulates production of cathelicidin and results in killing of ingested mycobacterium
B. Supplementation with ergocalciferol in 25(OH) deficient individuals can improve immune dysfunction in CKD patients
C. 1-25(OH) vitamin D can stimulate B proliferation and result in increased plasma cell transformation and increased immunoglobulin production
D. Elevations in PTH associated with late stages of CKD have been shown to improve neutrophil phagocytosis through alterations in intracellular calcium concentrations

Answer: A

Local conversion of 25(OH) vitamin D to active 1,25(OH) vitamin D by monocyte−macrophages stimulates production of cathelicidin and results in killing of ingested mycobacterium.

Vitamin D abnormalities and CKD-associated mineral bone disorders may alter the host's response to infection. Although supplementation with ergocalciferol results in improved 25(OH) vitamin D levels, no studies in CKD patients have shown improved immune function. Active vitamin D affects a variety of cell functions in the adaptive immune system, but active vitamin D suppresses rather than stimulates B proliferation and further results in reduced plasma cell transformation and immunoglobulin production in experimental settings. Elevations in PTH associated with late stages of CKD also affect the immune response to infection, but have not been shown to improve impaired neutrophil phagocytosis. The mechanism is thought however to be mediated through increases in intracellular calcium concentrations. Finally, activation of the TLR pathway in the human monocyte−macrophages by mycobacterium tuberculosis stimulates local synthesis of $1,25(OH)_2D_3$, which results in production of cathelicidin and killing of the ingested microbes, thus making A the only correct response.

Question 3

Intravenous iron preparations are commonly used in conjunction with erythropoietic agents to manage anemia in late stages of CKD. Which of these statements is true regarding the effect of parenteral iron preparations on the immune system?

A. Iron overload has not been implicated in immune disturbances
B. Intravenous iron has been shown to result in increased intracellular oxidative stress and shortened T-cell lymphocyte survival
C. Studies in CKD patients maintained on HD and treated with intravenous iron preparations have failed to show any effect of neutrophil function
D. None of the above

Answer: B

Intravenous iron has been shown to result in increased intracellular oxidative stress and shortened T-cell lymphocyte survival.

The immune system is adversely affected by iron overload. Intravenous iron preparations have been associated with increased inflammatory response and impaired cellular immunity and reduced antibody response to vaccinations. Studies of circulating neutrophils from stage 5 CKD patients maintained on HD

and treated with intravenous iron preparations have shown impaired phagocytic activity and microbial killing capacity. Finally, iron overload causes increased intracellular oxidative stress and reduced lymphocyte proliferation and CD4+ T cell depletion, making B the only correct answer.

Question 4

Advanced CKD is associated with increased incidence and heightened severity of microbial infections. Which of the following factors contribute to this abnormality?

A. The phagocytic capacity of PMNs and monocytes is impaired in patients with advanced CKD
B. Arteriovenous fistulas, grafts, and indwelling catheters or peritoneal catheters provide easy ports of entry for microorganisms in ESRD patients
C. Immunosuppressive medications used to prevent graft rejection in kidney transplant recipients or prescribed to treat the underlying autoimmune disorders in CKD patients impair host response to microbial infections
D. Impairment of the adaptive cellular and humoral immune systems in patients with advanced CKD results in poor response to vaccination and reexposure to pathogens
E. All the above

Answer: E

CKD-induced impairment of the phagocytic capacity as well as the adaptive cellular and humoral immune responses work in concert to comprise the host response to microbial infections. The defense against infectious pathogens is compromised by vascular access or peritoneal catheters in ESRD patients or use of immunosuppressive medications in transplant recipients or in those with autoimmune disorders. Thus all the statements are true, making E the correct response.

Question 5

Systemic inflammation plays a major role in the pathogenesis of CVD, cachexia, anemia, and numerous other morbidities in CKD patients. Which of the following factors contribute to the CKD-associated systemic inflammation?

A. Accumulation of uremic toxins and metabolites such as indoxyl sulfate
B. Impairment of the intestinal epithelial barrier structure and function, which enables the entry of microbial endotoxins and other luminal contents into the body's internal milieu
C. Accumulation of highly proinflammatory oxidized LDL particles and deficiency and impaired anti-inflammatory properties of HDL in CKD patients
D. Depletion and dysfunction of Treg lymphocytes
E. All of the above

Answer: E

CKD results in accumulation of proinflammatory uremic toxins and metabolites, formation of oxidized LDL, and activation of the innate immune system, all of which contribute to the pathogenesis of systemic inflammation. The gut epithelium provides a barrier to substances that may have deleterious effects on immune function, but this defense may be compromised in CKD patients. The high burden of the proinflammatory factors in CKD is compounded by impaired natural anti-inflammatory mechanisms, including abnormalities in lipid metabolism, as well as Treg cell depletion and dysfunction. Thus all the statements are true making E the correct response.

CHAPTER

33

Chronic Kidney Disease and Gastrointestinal Disorders

Susie Q. Lew[a], *Jai Radhakrishnan*[b]

[a]Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States; [b]Division of Nephrology, Department of Medicine, Columbia University Irving Medical Center, New York, NY, United States

Abstract

The kidneys and the gastrointestinal (GI) tract share a bidirectional relationship. Patients with chronic kidney disease (CKD) commonly experience GI symptoms including dysgeusia, anorexia, dyspepsia, hiccups, nausea, and vomiting. GI hemorrhage occurs more frequently in CKD patients. Lower GI tract symptoms occurring in CKD patients include constipation and diarrhea. CKD also affects gastric motility, the pancreas, and the gall bladder. Disorders of the GI tract may result in renal injury. Inflammatory bowel disease may affect kidney function through development of acid/base disorders, hypovolemia, and kidney stones. Patients undergoing Roux-en-Y gastric bypass surgery may develop kidney stones and kidney injury. Amyloidosis may involve the GI tract and the kidney independently. This chapter reviews the nexus between the kidneys and the GI tract and explores the etiology, pathophysiology, and management of the relevant disorders.

INTRODUCTION

Patients with chronic kidney disease (CKD) frequently experience upper gastrointestinal (GI) symptoms including dysgeusia, anorexia, hiccups, stomatitis, nausea, vomiting, and gastroparesis. Constipation and diarrhea represent the main lower GI tract symptoms associated with CKD. GI hemorrhage may originate from lesions anywhere along the GI tract. Hemorrhage may be exacerbated by the coagulopathy of uremia, but usually has an underlying etiology.

Although many of these symptoms are nonspecific, they do occur in the setting of uremia in patients with acute kidney injury (AKI) and advanced CKD. These symptoms provide indications to initiate renal replacement therapy in these settings.[1–4]

Conversely, disorders of the GI tract such as inflammatory bowel disease (IBD) and interventions such as gastric bypass surgery may lead to renal injury. Alterations in acid–base and volume status, electrolyte imbalance, and kidney stone formation may lead to or contribute to subsequent CKD in such patients. Thus, a bidirectional relationship exists between the kidneys and the GI tract (Figure 33.1).

GASTROINTESTINAL MANIFESTATIONS OF KIDNEY DISEASE

The lack of standardized definitions and the presence of comorbid conditions in the CKD population make estimating the prevalence of GI symptoms in CKD patients difficult. For the most part, patients do not report GI symptoms due to their sporadic nature and the absence of a temporal relationship to kidney disease. However, patients may recall a noticeable increase in frequency or appearance of symptoms if questioned. Most GI symptoms and complications of CKD are found in the late stages of CKD. Although nonspecific, significant GI symptoms in the setting of a low estimated glomerular filtration rate (eGFR) signal the need for initiation of renal replacement therapy.

Dysgeusia

Uremic patients may complain of uriniferous odor of the breath, known as uremic fetor, and an unpleasant metallic or a foul taste in the mouth, known as

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00033-4

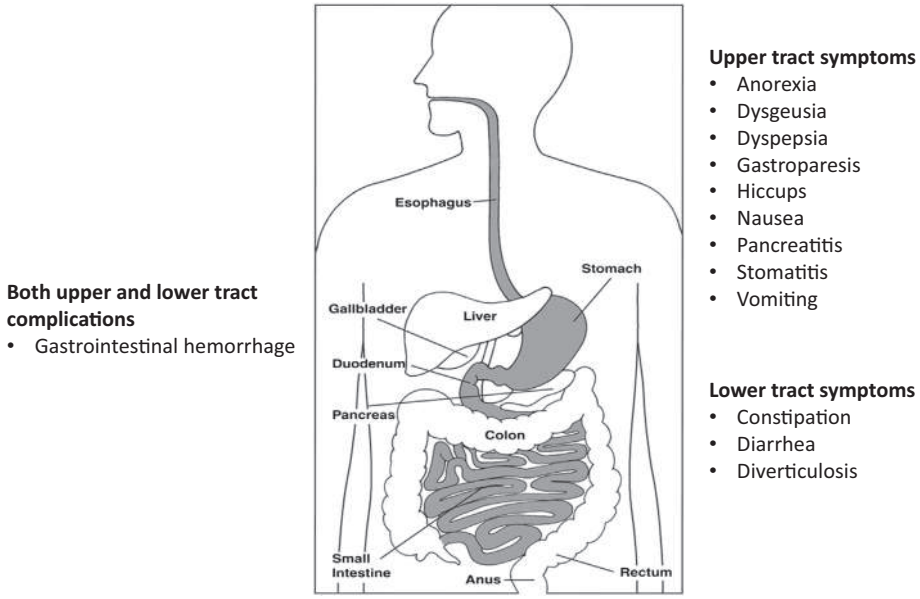


FIGURE 33.1 Gastrointestinal manifestations of chronic kidney disease.

dysgeusia.[5,6] Breakdown of large amounts of salivary urea to ammonia by bacterial urease in the mouth results in uremic fetor and dysgeusia.[5,6]

Initiation of dialysis corrects uremia, which in turn improves uremic fetor and uremia-induced dysgeusia. Uremic fetor may improve with eating a low-protein diet.

Dysgeusia also improves with dialysis. Other confounding factors, however, may mask symptomatic improvement. The role of zinc deficiency in CKD patients remains controversial.[7–9] Poor oral hygiene may also contribute to dysgeusia.[10]

Anorexia

Anorexia (a lack or loss of appetite for food) occurs in late CKD stages and frequently continues into CKD stage 5 treated with dialysis. Most of the studies of anorexia, however, have been performed in dialysis patients. Malnutrition, cachexia, and reduced caloric and protein intake have been reported in patients with anorexia-receiving dialysis.[11–13] Lower quality of life indices, higher rates of hospitalization, and higher mortality risk have also been associated with anorexia.[13,14]

The exact pathogenesis of anorexia in uremic patients remains unknown and is likely to be multifactorial. Many mediators contribute to the control of appetite.[15,16] Orexigenic substances such as ghrelin, neuropeptide Y, and agouti-related peptide stimulate the appetite. Anorexigenic substances such as leptin, cholecystokinin, insulin, and melanocyte-stimulating hormone induce anorexia. Other factors such as serotonin, melanocortin, trypophan, corticotrophin-related hormone, TNF-alpha, and interleukin-1β play roles in modifying appetite and feeding behavior as well.[15–17] In patients with substantial decrements in glomerular filtration rate (GFR), high levels of proinflammatory cytokines, leptin, free tryptophan, serotonin (hyperserotoninergic-like syndrome) along with deficiency of neural nitric oxide, and disorders in various receptors such as melanocortin receptor-4 can be found within the cerebrospinal fluid, which individually may cause anorexia.[18]

Ghrelin plays a key role in anorexia.[19,20] Ghrelin, a gut peptide, stimulates the production of growth hormone from the pituitary gland.[21] The stomach synthesizes ghrelin that is then released into the general circulation.[20–22] CKD patients have high plasma ghrelin levels compared to healthy controls, due to its reduced renal excretion.[20,22] The biological effects of ghrelin are mediated through the growth hormone secretagogue receptor (GHS-R). Animal studies show uremic anorexia and GI motility dysfunction correlate with downregulation of ghrelin and GHS-R in the hypothalamus of rats with chronic renal failure.[23] The salutary effects of ghrelin on food intake and meal appreciation suggest that ghrelin could be an effective treatment for anorexic CKD patients. Three distinct forms of ghrelin exist: acyl ghrelin, des-acyl ghrelin, and n-octanoyl modified.[19] Conflicting results regarding circulating ghrelin levels

in CKD patients may result from confounding factors that affect its measurement. Some examples of confounding factors include age, gender, ethnicity, obesity, renal functional status, and ghrelin type.[19,20]

GI dysmotility, commonly found in patients with CKD, also contributes to anorexia.[24,25] Patients with CKD may present with delayed gastric emptying,[25–28] decreased small intestinal motility,[29] and irritable bowel syndrome.[30]

Anorexia and malnutrition have been associated with poor outcomes in individuals with CKD. In children and adolescents with CKD, weight loss occurs when eGFR decreases to $<35\ mL/min/1.73\ m^2$, and this weight loss was associated with higher risk for progression to end-stage renal disease (ESRD).[31] In adults, protein-energy wasting (PEW), a condition associated with a decline in body protein mass and energy reserves, has a prevalence of >20–25% in early CKD, which increases with CKD progression.[32] Potential causes of PEW include inadequate nutrient intake (i.e. anorexia, dietary restriction, socioeconomic constraints), urinary protein losses, hypercatabolism caused by comorbid illnesses or uremia, and metabolic acidosis.[32]

Removal of uremic toxins by dialysis improves anorexia.[16] For those patients already treated with dialysis who experience anorexia, daily dialysis may be needed for a period of time to improve anorexic symptoms.[16,33] The HEMO study, however, did not show a difference in dialysis-related anorexia in the high-dose thrice weekly compared to high-flux membrane treatment groups.[34]

Dietary adjustments such as the ingestion of branched-chain amino acid supplements improve appetite as well as protein and caloric intake.[33,35,36] Administration of branched-chain amino acids exerts significant antianorectic and anticachectic effects in uremic patients.[36]

A pharmacological approach may improve appetite or suppress symptoms. Megestrol acetate, a synthetic orally active derivative of the naturally occurring hormone progesterone, increases appetite *via* stimulation of neuropeptide Y in the hypothalamus. Megestrol acts by modulating calcium channels in the ventromedial hypothalamus, a well-known satiety center, and inhibition of proinflammatory cytokines such as IL-1, IL-6, and TNF-α.[37,38] Megestrol acetate improves protein and energy intake as well as appetite. However, adverse effects may limit the use of megestrol acetate in patients with severe decrements in GFR.[12,38] Common adverse effects include headaches, dizziness, confusion, diarrhea, hyperglycemia, thromboembolic phenomena, breakthrough uterine bleeding, peripheral edema, hypertension, adrenal suppression, and adrenal insufficiency.[12]

Hiccups

Hiccups consist of repetitive, involuntary, intermittent spasmodic contractions of the diaphragm. The inspiratory rush of air causes the epiglottis to close, causing the "hic" sound. Intractable hiccups occur with diaphragmatic irritation, hyponatremia, and uremia. Intractable hiccups may lead to malnutrition, weight loss, fatigue, dehydration, and insomnia.

Hiccups are generally self-limiting. Pharmacological interventions to stop intractable hiccups are shown in Table 33.1. Care should be taken when using high or

TABLE 33.1 Medications for Chronic Kidney Disease Patients with Upper GI Symptoms

Medication Class	Medication
ANTIEMETICS	
Dopamine antagonists (CNS)	Droperidol
	Haloperidol
	Chlorpromazine
	Promethazine
	Prochloperazine
Antihistamines (CNS H1 histamine receptor antagonists)	Diphenhydramine
	Dimenhydrinate
	Meclizine
	Promethazine
	Hydroxyzine
5-HT3 receptor antagonists (CNS and GI)	Granisetron
	Ondansetron
HICCUPS	
Antipsychotics	Chlorpromazine
	Haloperidol
Anticonvulsants	Phenytoin
	Valproic acid
	Carbamazepine
	Gabapentin
Muscle relaxants	Baclofen
	Cyclobenzaprine
Central nervous system stimulants	Methylphenidate
Dopamine antagonists	Metoclopramide
Tricyclic antidepressants	Amitriptyline
Proton pump inhibitors	
Others	Nifedipine

prolonged doses of those medications that are excreted by the kidneys (such as baclofen, gabapentin, metoclopramide) and cardioactive drugs such as quinidine are best avoided.

Stomatitis and Salivary Gland Inflammation

Oral bacterial urease converts urea to ammonia. High levels of salivary ammonia ulcerate the buccal mucosa causing uremic stomatitis, characterized by a red, thickened buccal mucosa with gray and gluey exudates.[5,6] Associated findings with uremic stomatitis include dry burning mouth, poor dental hygiene, glossitis, and parotitis. Uremia may also cause mucosal ulcerations, bleeding, or intramural hematoma.[4]

Stomatitis generally improves when CKD patients begin dialysis. Measures to keep the oral cavity infection-free should be recommended to patients.

Nausea and Vomiting

Nausea and vomiting commonly occur in CKD and dialysis patients regardless of CKD stage or dialysis status.[4,39] The exact mechanisms underlying the pathogenesis of nausea and vomiting remain elusive and appear likely to be multifactorial. Nausea and vomiting may be caused by encephalopathic or neurologic disorders associated with uremia. These nonspecific symptoms may result from responses to endogenous changes in bodily function or from exogenous stimuli.[39] Nevertheless, clinicians frequently base their decision to initiate dialysis on patient symptoms of nausea and vomiting, along with appropriate chemical indicators of uremia.

Uremia-associated nausea and vomiting usually improve with dialysis. However, the dialysis treatment itself may induce these symptoms. Acid–base disorders due to rapid infusion of acetate from acetate-based dialysate and compounded by delayed conversion to bicarbonate could cause nausea and vomiting.[40] Rapid changes and extreme fluctuation of blood pressure during dialysis, reaction to the dialyzer, or medications administered during the treatment may also cause nausea and vomiting.

Antiemetic agents may provide temporary symptomatic relief for uremia-related nausea and vomiting. Antiemetics by class of agents that may be used in CKD patients are listed in Table 33.1.

Limited data exist regarding the efficacy of antiemetics in CKD patients. Previously, the D_2-receptor antagonist haloperidol was the drug of choice to treat uremia-induced nausea. Because its metabolite may accumulate in renal failure, the recommended haloperidol dose should be 50% of normal. Metoclopramide may also be used to treat nausea, but there may be an increased risk of extrapyramidal reaction from drug accumulation, and the dosage will need to be substantially reduced as renal function declines. Cyclizine should be avoided as it may be associated with hypotension and tachyarrhythmia in CKD patients with cardiac disease.[41] Ondansetron, which selectively antagonizes serotonin 5-HT3 receptors, demonstrates more efficacy than metoclopramide, and the dose does not need to be adjusted with renal failure.[42]

Gastroesophageal Reflux Disease and Dyspepsia

Adult CKD patients compared to the general population do not demonstrate a higher incidence of gastroesophageal reflux disease.[43] The prevalence of *Helicobacter pylori* infection and peptic ulcer disease seem not to be different in CKD patients compared to the general population.[27] Positive *Helicobacter* serology was not related to the presence of dyspepsia or gastroparesis in uremic patients.[44] The evaluation of gastroesophageal reflux disease in CKD patients is similar to that of the general population.[45]

The approach to treating gastroesophageal reflux disease and dyspepsia includes nonpharmacologic approaches and pharmacotherapeutic maneuvers, similar to non-CKD patients.[45] Lifestyle modifications require patients to eat smaller, frequent meals and remain upright after meals for at least 3 hours before reclining. Foods such as alcohol, chocolate, citrus juice, and tomato-based products should be avoided. The addition of an H_2 antagonist or proton pump inhibitor (PPI) may also provide symptomatic relief. Adjustment of H_2 antagonist dose depends on the level of kidney function and degree of renal clearance. PPI effectively treat gastroesophageal reflux disease. However, side effects limit its long-term use.[46] Additional information on the association of PPI use and the risk of CKD will be discussed at the end of this chapter.

Aluminum-based and magnesium-based antacids can result in complications associated with excessive body levels of these cations. It may be prudent to avoid these medications altogether and use calcium-based antacids. The anion found in antacids will mask metabolic acidosis. Nephrologists frequently capitalize on antacid use to treat both gastroenterologic and renal disorders simultaneously. CKD patients cannot excrete a large bicarbonate load quickly. Therefore, administration of large amounts of bicarbonate equivalents could cause severe metabolic alkalosis in CKD patients. Thus, electrolyte and acid–base status need frequent monitoring in CKD patients using antacids.

Gastrointestinal Hemorrhage

Clinical findings of hematemesis, melena, hematochezia, a positive stool occult blood test, or unexplained anemia suggest the diagnosis of GI hemorrhage.

Individuals with mild to moderate CKD are at higher risk of GI hemorrhage. The risk of GI hemorrhage in an individual with CKD stage 3 was 1.5 times and CKD stages 4 and 5 were 7 times higher compared to CKD stage 1.[47] In addition, compared to urine albumin:creatinine ratio <10 mg/g, the risk of GI hemorrhage was twice as high in microalbuminuria and macroalbuminuria.[47]

Direct visualization by esophagogastroduodenoscopy provides an opportunity for diagnosis and management of lesions in the esophagus, stomach, or proximal duodenum. Occult and obscure GI hemorrhage may require repeat upper endoscopy or procedures allowing access to the small intestine.[48] Push enteroscopy allows further evaluation of approximately 10–50 cm of jejunal mucosa beyond the ligament of Treitz. Double balloon enteroscopy, a modified push enteroscopy, allows intervention capability including bleeding control with electrocoagulation, dilation, biopsy, and polypectomy.[48] Wireless video capsule endoscopy facilitates the identification of small bowel bleeding sources that elude detection by other endoscopic techniques.[49]

Occasionally, an imaging procedure may be required to identify a lesion not accessible by conventional endoscopy. Small bowel series and enteroclysis pose risks of barium and radiation exposure. Barium retention limits the ability to perform repetitive examinations in a timely fashion and may cause constipation or obstipation. Enteroclysis often fails to identify flat mucosal lesions such as angiodysplasias.

A technetium 99-m labeled red blood cell bleeding scan may be used to identify cryptic or brisk sources of blood loss. A bleeding scan may detect the source of hemorrhage if the bleeding rate is greater than 0.1–0.4 mL/min.

An angiographic study may follow a positive bleeding scan or be performed with a normal bleeding scan to localize the source of brisk hemorrhage.[50] Angiography may detect bleeding lesions or associated structural abnormalities that are not actively bleeding, such as angiodysplasias, tumors, and inflammatory lesions. Radiographic contrast–associated nephropathy limits angiography use in the setting of CKD. Life-threatening GI bleeding, however, may warrant the risks associated with contrast exposure in patients with CKD. In such situations, the risk from contrast-associated nephropathy must be carefully balanced against the benefits of the procedure.

The pathogenesis of GI hemorrhage in CKD patients remains uncertain. In advanced uremia, a progressive, diffuse, and erosive gastritis occurs with thinning of the mucosa, diffuse hyperemia, and bleeding.[6] Earlier accounts of uremic gastroenterocolitis described "mild edema and hemorrhage in the mucosa and submucosa to confluent superficial ulcerations with frankly necrotic areas."[51] Several factors contribute to GI hemorrhage in uremia.

The most common cause of upper GI bleeding (UGIB) in CKD patients is peptic ulcer disease, with its origin from gastric greater than duodenal sources.[52] Vascular ectasia occurs more frequently in CKD patients than in those with normal renal function. The prevalence of vascular ectasia seems to be related to the duration and severity of renal disease.[52] Uremic bleeding diathesis results from coagulation factor abnormalities, alteration of the fibrinolytic system, vascular abnormalities, and platelet dysfunction.[53–55]

In patients with obscure GI bleeding (OGIB), the incidence of small bowel vascular lesions was significantly higher in CKD patients than in age- and sex-matched non-CKD patients when capsule endoscopy was used for evaluation.[56] CKD stage 4 or greater was identified as an independent predictor of having vascular lesions in patients with OGIB.[57]

Clinicians debate the role of hypergastrinemia in causing upper GI pathology. An elevated gastrin level may be seen with CKD, but this is not consistent.[58] Anephric patients have elevated serum gastrin levels,[59] whereas 50% of patients with acute renal failure and 55% with CKD have elevated serum gastrin levels.[59,60] CKD patients also have high pro-gastrin-releasing peptide levels.[61] A low basal acid output, a high basal intragastric pH, and an increased peak acid output occur in response to gastric acid secretion studies in patients with both acute and chronic renal failure.[59] Elevated serum gastrin levels result from inadequate renal inactivation of gastrin.[62] However, hypergastrinemia was associated with hypochlorhydria rather than increased acid secretion in ESRD patients.[60]

Ulcerogenic medications such as salicylates, corticosteroids, nonsteroidal anti-inflammatory drugs, and iron may cause gastritis or duodenitis. *H. pylori* infection may also contribute to UGIB. The prevalence of *H. pylori* infection appears to be higher in CKD patients than in the general population.[63,64] However, no clear relationship has been established between *H. pylori* infection, dyspeptic symptoms, and GI lesions in CKD patients.[63]

Patients with CKD and UGIB have a 30% higher hospitalization rate compared to patients without renal disease.[65] The CKD patient population clearly has a

higher risk of morbidity and mortality associated with GI hemorrhage.

Fortunately, timely diagnosis of CKD and early initiation of dialysis with adequate clearance have decreased the incidence and prevalence of gastritis. Moreover, early medical management with initiation of PPI and H_2 receptor antagonists in symptomatic patients effectively corrects gastritis and duodenitis. PPIs become potent antisecretory agents by inhibiting the gastric H,K-APTase in parietal cells. By raising the gastric pH above 6, PPIs result in improvement of coagulation and platelet aggregation.[66,67]

Severe bleeding resulting in hemodynamic instability requires hemodynamic resuscitation, blood product transfusion, and correction of any metabolic abnormalities and coagulopathy.

Specific interventions to address platelet dysfunction include administration of deamino-8-D-arginine vasopressin (DDAVP), cryoprecipitate, estrogen, and dialysis.[68] DDAVP shortens bleeding time in uremic patients.[69] A dose of DDAVP 0.3 μg/kg intravenously becomes effective within 30 minutes and lasts for at least 4 hours.[70] DDAVP releases von Willebrand factor from endothelial cells. Once von Willebrand factor has been released, additional doses of DDAVP will not cause additional von Willebrand factor release. If DDAVP does not shorten a prolonged bleeding time with the initial dose, additional administration will not correct an abnormal bleeding time. Clinicians should monitor for the development of side effects of DDAVP, such as hyponatremia or hypertension.

An intravenous infusion of cryoprecipitate provides functional coagulation factors such as factor VIII, von Willebrand factor, and fibrinogen.[71] Volume overload in CKD patients may limit the use of cryoprecipitate.

Administration of estrogen corrects uremia-induced platelet dysfunction.[72] Estrogen becomes effective in 6 hours and the effect lasts for approximately 2–3 weeks.[72] Unexpected vaginal bleeding may occur in postmenopausal female patients. Male patients may develop unwanted female features with prolonged use of estrogen. Informing patients of possible side-effects associated with treatment with estrogen is essential.

Red blood cell transfusion to achieve a hematocrit level above 26% shortens bleeding time.[73] This increase in the number of circulating red blood cells possibly displaces platelets closer to the vascular endothelium, thereby improving clot formation. However, red blood cell transfusion places patients at risk for viral infections and exposure to antigens, which may negatively impact their candidacy for a kidney transplant.

Initiation of dialysis removes the uremic toxins associated with coagulopathy.[68,74] Dialysis, while frequently effective for the short term, does not completely correct platelet dysfunction. Patients with CKD who do not have a vascular access for dialysis will require a central venous catheter to initiate dialysis. Dialysis may be temporary if there are no other indications to continue dialysis once bleeding has been controlled.

Surgical intervention for GI hemorrhage rarely becomes necessary due to recent advances in endoscopic and radiographic procedures. Hemostasis under endoscopic intervention occurs with electrocauterization, epinephrine (adrenaline)/saline injection, hemoclip,[75] and argon plasma coagulation.[76–78] Angiographic embolization injects particles (i.e. gelatin sponge, polyvinyl alcohol, metallic coils, N-butyl cyanoacrylate) directly in the blood vessel to stop bleeding.[79]

The most frequent causes for lower GI bleeding in CKD patients are angioectasias, diverticulosis, hemorrhoids, and ischemic colitis. Angioectasias can be found throughout the GI tract. The management can be either localized endoscopic therapy and systemic hormonal treatment, or surgery for refractory cases.[80,81]

The outcome of GI bleeding in CKD and ESRD patients has improved with the introduction of advanced interventional endoscopy, *H. pylori* infection diagnosis and management, and widespread use of PPIs.

Diverticulosis

Diverticulosis occurs in patients with CKD without polycystic kidney disease at a rate similar to that of the general population.[82] Constipation due to dietary restriction of fluid, fruits, and vegetables as well as the use of phosphate binders predispose CKD patients to diverticular disease.

A higher prevalence of diverticular disease was previously reported to exist among patients with autosomal dominant polycystic kidney disease (ADPKD) with ESRD compared with other ESRD patients without ADPKD.[82] However, a prospective study compared ADPKD patients not on dialysis, with family members without ADPKD, and healthy controls and found no significant difference in diverticular disease among the three groups. Further, there were no differences among the groups in the percentage with only right-colon diverticula, the mean number of diverticula, or the size of the largest diverticula.[83]

Management of diverticulosis and diverticulitis in CKD patients is similar to that in the general population. Instituting preventive measures and decreasing risk factors may decrease diverticulosis and the number of episodes of diverticulitis. Patients may correct constipation by eating high-fiber foods or using the appropriate laxatives. An episode of diverticulitis requires treatment with antibiotic therapy, bowel rest, and a low-fiber diet.

Constipation

Causes of constipation in CKD patients are similar to those in the general population[84] (Table 33.2). CKD patients may also encounter an additional cause for constipation, such as use of oral phosphate binders.

Dietary factors play a key role in the pathogenesis of constipation. Fluid restriction to avoid hyponatremia and volume overload, as well as the elimination of many high-fiber, potassium-rich fruits and vegetable may contribute to constipation in CKD patients.

Side effects from medications may cause or worsen constipation. Prescribing medications that contain calcium or aluminum, such as antacid medications, worsen constipation. CKD patients frequently use calcium-based medications, such as calcium carbonate, to treat metabolic acidosis and hyperphosphatemia. Other medications frequently used in CKD patients, which can cause or worsen constipation, include diuretics to treat hypertension and volume overload, iron to treat iron deficiency anemia, opiates or analgesics for pain management, and antidepressants.

Metabolic disorders that induce constipation include diabetes mellitus, acidosis, neuropathy, and hypokalemia. Endocrine disorders managed by nephrologists that may cause constipation include hypercalcemia, hyperparathyroidism, milk–alkali syndrome, and pheochromocytoma. Other diagnoses to consider include gastroparesis, irritable bowel syndrome, eating disorders, depression, neurological conditions, and hypothyroidism.

The approach to managing chronic constipation is shown in Figure 33.2. The first step in treating constipation requires addressing the underlying cause. The second step requires modification of diet, which may not always be possible in CKD patients. Finally, laxatives may help loosen the stool and stimulate bowel movement[84] (Table 33.3).

CKD patients have disorders associated with renal handling of magnesium and phosphorus, often associated with the development of hypermagnesemia and hyperphosphatemia. Magnesium-based laxatives such as magnesium citrate, magnesium hydroxide, magnesium oxide, and magnesium sulfate should be used with caution or avoided in CKD patients. Similarly, phosphate-based laxatives, such as sodium phosphate, should be avoided in CKD patients.[85] The following categories of laxatives may be used in CKD patients without further compromising renal function.

TABLE 33.2 Chronic Kidney Disease Constipation: Common Causes

Category	Example
Intake	Insufficient fluid intake
	Inadequate fiber in the diet
	Excessive dairy products
	Disruption of regular diet or routine
Organic	Hypothyroidism
	Neurological conditions
	Irritable bowel syndrome
	Colon cancer
	Inactivity
Medications	Overuse of laxatives
	Antacid medications containing calcium or aluminum
	Phosphate binders containing calcium
	Calcium-based base equivalent to correct metabolic acidosis
	Narcotics
	Antidepressants
	Oral iron
Psychosomatic	Depression
	Eating disorder
	Stress
	Rectal pain

Adapted from Table 18.4. Lembo AJ, Ullman SP. Constipation. In: Feldman M, Friedman LS, Brandt LJ, editors. Feldman: Sleisenger and Fordtran's gastrointestinal and liver disease. *9th ed. Philadelphia, PA: Saunders; 2010:258–84; with permission from Elsevier.*

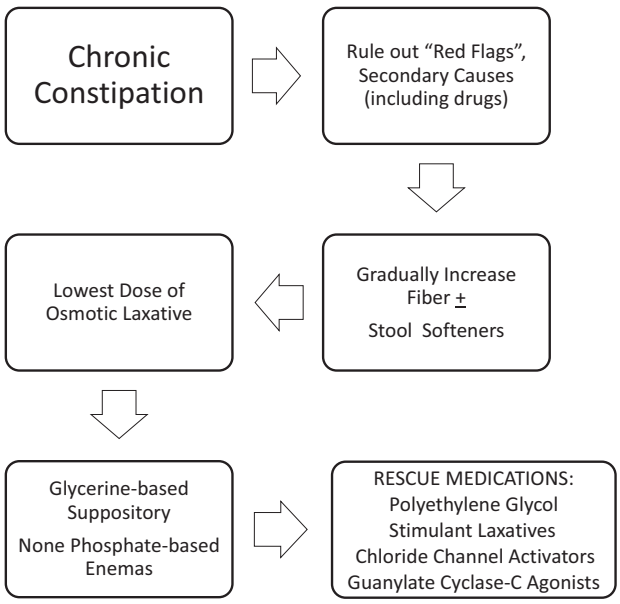


FIGURE 33.2 Algorithm recommended for the treatment of constipation.

TABLE 33.3 Chronic Kidney Disease Constipation: Appropriate Laxative Use

Type of Laxative	Generic Name
Bulk	
	Psyllium
	Calcium polycarbophil
	Bran
	Methylcellulose
	Guar gum
Osmotic Laxatives	
Poorly Absorbed Sugars	
Disaccharides	Lactulose
Sugar alcohol	Sorbitol
	Mannitol
Polyethylene glycol	Polyethylene glycol
Stimulant Laxatives	
Anthraquinones	Cascara sagrada
	Senna
Ricinoleic acid	Castor oil
Diphenylmethane derivatives	Bisacodyl
	Sodium picosulfate
Stool Softeners	Docusate sodium
Emollients	Mineral oil
Enemas, Suppositories	Mineral oil retention enema
	Tap water enema
	Soapsuds enema
	Glycerin suppository
	Bisacodyl suppository
Chloride Channel Activators	Lubiprostone
Guanylate cyclase-C agonists	Linaclotide
	Plecanatide

Adapted from Table 18.9. Lembo AJ, Ullman SP. Constipation. In: Feldman M, Friedman LS, Brandt LJ, editors. Feldman: Sleisenger and Fordtran's gastrointestinal and liver disease. *9th ed. Philadelphia, PA: Saunders; 2010:258–84; with permission from Elsevier.*

Bulk-forming laxatives generally contain fibers that add bulk and water to stool so that it can pass more easily through the digestive tract. Fiber can be found in foods such as apples, broccoli, prunes, bran, or medications such as psyllium, methylcellulose, and polycarbophil. The patient needs to drink adequate quantities of fluid, which may present an obstacle to using this class of laxative. Stool softeners, also known as emollients, such as docusate soften the stool for easier passage. Lubricants, such as mineral oil, allow for easier passage of stool.

The saline class of laxatives includes agents such as magnesium citrate, magnesium hydroxide, magnesium sulfate, and sodium phosphate. CKD patients should generally avoid this class of medication due to their kidneys' inability to efficiently excrete magnesium and phosphate. Stimulant laxatives enhance the movement of intestinal muscles and thus induce a bowel movement. Examples of stimulant laxatives include bisacodyl, senna, casanthranol, cascara, castor oil, and phenolphthalein. Osmotic laxatives increase the amount of fluid secreted within the intestines, resulting in softer stools. Examples of osmotic laxatives include lactulose, and polyethylene glycol. Enemas may be required in severe cases of constipation. Enemas containing just water, mineral oil, or soap may be used. Purgatives containing stimulants and osmotic agents may be used for colonoscopy bowel preparation. Phosphate-based purgatives have been associated with acute and chronic kidney injury and should be avoided.[86–88] Lubiprostone, a chloride channel activator, treats chronic idiopathic constipation and opioid-induced constipation. Linaclotide and plecanatide, guanylate cyclase-C agonists used in the treatment of chronic constipation or chronic irritable bowel syndrome, work by increasing the secretion of chloride and water in the intestines, resulting in softer stools and stimulating bowel movements.[89,90]

Diarrhea

Diarrhea describes stools that appear loose and watery. Diarrhea in CKD patients may occur because of an alteration in fecal bile acids and the presence of unusual keto-bile acids and low levels of deoxycholic acid.[91]

In general, diarrhea tends to be self-limiting. A patient with persistent diarrhea (greater than 4 weeks) requires further evaluation. The evaluation procedure for patients with CKD mimics that for patients with normal renal function. Patients with CKD have increased risks of incident and recurrent *Clostridium difficile*-associated diarrhea.[92]

Long-term ongoing diarrhea may result in derangements in volume, electrolyte, and acid–base status. A host of electrolytes such as potassium, magnesium, sodium, chloride, and bicarbonate, among others, can be lost with diarrhea. Excessive sodium depletion results in hypotension with or without orthostasis. Volume replacement with water will result in hyponatremia in CKD patients and will not correct hypotension. Stool bicarbonate loss may worsen metabolic acidosis due to renal disease.

Treatment consists of measures directed at the underlying disorder. Supportive care and symptomatic relief can be initiated while evaluating the etiology of diarrhea.

Electrolyte deficiencies usually require either oral or intravenous supplementation to restore normal total body levels. An ideal replacement solution for a patient with persistent diarrhea would contain sodium, potassium, magnesium, bicarbonate, and glucose. The replacement rate depends on the degree of volume and electrolyte depletion and on the extent of ongoing losses.

Antidiarrheal medications containing a heavy metal, such as bismuth, should be used with caution and avoided in late stages of CKD. Loperamide and diphenoxylate may be used, providing symptomatic relief.

General Complications After Surgery

Patients with CKD stages 3 and 4 have a higher incidence of postoperative infections than matched controls (60% vs. 40%) after colorectal surgery.[93] The exact mechanism underlying this finding remains unclear.

Gastroparesis

Gastroparesis consists of clinical symptoms and documentation of delayed gastric emptying.[94] Symptoms of gastroparesis include nausea, vomiting, early satiety, postprandial fullness, bloating, and upper abdominal pain. Complications of gastroparesis include esophagitis, Mallory–Weiss tear from chronic vomiting, malnutrition, volume depletion with AKI, electrolyte disturbances, and bezoar formation. Patients with diabetes mellitus and scleroderma often suffer from gastroparesis. The pathophysiology of gastroparesis in CKD remains undefined. Gastroparesis encompasses abnormalities of the autonomic nervous system, smooth muscle cells, and enteric neurons. The diagnosis of gastroparesis requires an upper endoscopy and gastric-emptying scintigraphy. Alternative diagnostic procedures include wireless capsule motility, antroduodenal manometry, and breath testing.[94]

Several studies have tried to delineate gastric-emptying time in both predialysis CKD and maintenance dialysis patients. There were conflicting results with regard to gastric-emptying duration in CKD patients.[95,96] Our understanding of how renal function affects gastric emptying needs further exploration.

Medical management of gastroparesis in CKD patients includes the use of dietary modification, prokinetic and antiemetic therapies.[97] A diet consisting of liquids and semisolids empties from the stomach more easily than solids. Fats and fibers tend to retard gastric emptying. Fat and fiber intake, therefore, should be minimized in CKD patients with gastroparesis. The recommended diet for patients with gastroparesis consists of multiple small low-fat, low-fiber meals daily. The patient should eat sufficient semisolids and drink liquids to obtain adequate calories, if solids cannot be tolerated. A patient may receive conflicting advice regarding fiber content if he/she also suffers from constipation. Instead of adding fiber to the diet, treatment of constipation with an osmotic laxative improves dyspeptic symptoms associated with gastroparesis as well as gastric-emptying delay. Additionally, CKD patients taking liquid diets have issues regarding volume and electrolyte disturbances. Approved treatment options for gastroparesis include metoclopramide and gastric electrical stimulation.[98,99]

There are several treatments for severe intractable gastroparesis, mostly in diabetic patients.[98] Such treatments may be applied to CKD patients, especially if they also have diabetes. The use of intrapyloric botulinum toxin injection *via* endoscopy shows promise.[98–100] The surgical approach to treat intractable gastroparesis involves resecting 70% of the stomach, including the antrum and pylorus, with closure of the duodenum and restoration of GI continuity with a 60 cm Roux-en-Y jejunal loop.[101] This procedure may correct intractable vomiting in patients with diabetic gastroparesis. Gastric peroral endoscopic myotomy (G-POEM), a minimally invasive surgical procedure, treats refractory gastroparesis by dissecting the muscular layer in the pylorus.[102] G-POEM results in improvement in the overall symptoms of gastroparesis, in gastric emptying, and in quality-of-life inventories.[103] The future use of ghrelin, ghrelin gene–derived peptides, and artificial analogues may hold promise for the treatment of gastroparesis as well as other GI disorders.[104]

Disorders of the Pancreas

Patients with CKD (and those receiving dialysis) may have elevated serum amylase, lipase, and trypsinogen levels in the absence of clinical pancreatitis. Multiple factors contribute to elevated enzyme levels, including decreased peripheral clearance, pancreatic overproduction, and increased release from the pancreas in addition to a decrease in renal clearance.[105–107]

Acute pancreatitis in CKD patients occurs frequently without known causes compared to non-CKD patients, suggesting a role of either renal failure or other factors.[108,109] IgG-4–related disease, a newly described form of autoimmune pancreatitis, may be associated with interstitial nephritis and membranous nephropathy.[110] CKD patients suffering from acute pancreatitis have high morbidity and mortality rates, regardless of

cause, compared to the general population.[109] The treatment of acute pancreatitis includes removing any offending agent, supportive care, and provision of symptomatic relief. Restriction of oral intake helps rest the pancreas. The main focus in treating acute pancreatitis involves appropriate volume resuscitation to maintain hemodynamic stability, keeping in mind that fluid may sequester in unconventional compartments. Analgesic administration aids in pain management. Patients may need nutritional support while on oral intake restriction. Once abdominal pain has resolved, oral feeding with foods low in fat and protein may be carefully started.

Disorders of the Gall Bladder

A cross-sectional study of hospitalized patients from Taiwan reported a higher incidence of gallstones in CKD patients compared to the general population after controlling for other risk factors. The etiology of this association remains unknown.[111]

GASTROINTESTINAL TRACT DISORDERS ASSOCIATED WITH RENAL INJURY AND CKD

Inflammatory Bowel Disease

In a case control study, 15.9% of patients with IBD (Crohn's disease and ulcerative colitis) had eGFR less than 60 mL/min/1.73 m^2.[112] Severe diarrhea and consequent fluid losses may cause decreased GFR. Rarely, the short bowel syndrome from multiple resections may be associated with hypochloremic metabolic alkalosis and decrements in GFR requiring aggressive volume repletion and blockade of gastric hypersecretion to correct renal functional, acid–base and volume disorders.[113] Crohn's disease may also be associated with enteric hyperoxaluria, as well as nephrocalcinosis and nephrolithiasis, with subsequent effects on renal function.[114]

Renal insufficiency from AA amyloidosis occurs as a rare complication of longstanding, uncontrolled IBD (especially Crohn's disease), but its incidence may be decreasing with better control of disease.[115]

Other rare causes of renal failure associated with IBD include glomerulonephritis and interstitial nephritis (including drug-induced interstitial nephritis especially with treatment using aminosalicylates).

Renal events associated with IBD have decreased due to a better understanding of the disease and its treatment. IBD pharmacotherapy currently includes aminosalicylates, antibiotics, corticosteroids, immunomodulators, and anti-TNF agents. Volume resuscitation to maintain hemodynamic stability during acute flares may limit the occurrence of AKI. A patient not responding to IBD medical management will require surveillance for renal complications.

Gastric Bypass and Renal Injury

Patients undergoing Roux-en-Y gastric bypass surgery develop kidney stones and renal injury. These patients usually exhibit hyperoxaluria or hypocitraturia.[116–118] Renal biopsies performed on patients who underwent Roux-en-Y gastric bypass with elevated serum creatinine concentration (S[Cr]) showed both acute and chronic changes.[119] Renal pathology revealed diffuse tubular degenerative changes, abundant tubular calcium oxalate deposits, and varying degrees of tubulointerstitial scarring.[119] Renal pathology also showed glomerulosclerosis, perhaps related to underlying conditions such as diabetes mellitus, obesity, and hypertension.[119] Postoperative decrease in GFR frequently resulted in rapid progression to a dialysis-dependent status.[119] Institution of pharmacotherapy aims to reduce hyperoxaluria and hypocitraturia. Potassium citrate or calcium citrate administration inhibits bone resorption by providing bioavailable calcium, reducing urinary saturation of uric acid, and increasing the inhibitory activity against calcium oxalate agglomeration by providing alkali, which increases urinary pH and citrate.[120]

Medications Causing Renal Injury

GI-associated medications may cause acute and chronic renal injury. CKD patients or those at high risk of developing kidney disease should use these medications with caution.

Case reports and case series describe renal injury (nephrocalcinosis and irreversible renal failure) after using oral sodium phosphate preparations.[86,88,121–123] Risk factors for kidney injury with oral sodium phosphate include hypertension, volume depletion, reduced GFR, or use of medications such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or diuretics.[123] Kidney biopsies in patients with acute phosphate nephropathy show an interstitial pattern of calcium and phosphate deposition.[86] This class of medication should be avoided in patients with CKD or patients with these risk factors.

Medications used for treating IBD such as aminosalicylates (including mesalamine) have been associated with the development of interstitial nephritis.[124] Early identification and withdrawal of these drugs can lead to a partial or complete reversal of renal dysfunction.

PPI use has been associated with a higher risk of incident CKD.[46] The PPI class has also been associated with an increased risk of dementia,[125,126] *C. difficile* diarrhea and recurrence,[127,128] hypomagnesemia,[129] pneumonia,[130] vascular calcification,[131] neutropenia,[132] and bone fracture.[133] Many of these disorders have negative effects on kidney function.

Gut Microbiome

The gut microbiome plays important roles in both the maintenance of health and the pathogenesis of disease. Gut microbiome dysbiosis, resulting from alterations of composition and function of the gut microbiome and disruption of gut barrier function, exists in patients with CKD. Gut microbiome dysbiosis generates excessive amounts of uremic toxins. Most of them are derived from the unbalanced fermentation of nitrogen compounds in relation to nondigestible carbohydrates, such as p-cresyl sulfate and indoxyl sulfate in particular. The impaired intestinal barrier permits translocation of these toxins into the systemic circulation. These uremic toxins have been implicated in the progression of CKD, development of cardiovascular disease, and risk of death in CKD patients.[134,135] Evidence suggests that the gut microbiome is altered in patients with CKD.[136] Several factors contributing to gut microbiome dysbiosis in CKD include decreased consumption of dietary fiber, constipation, impaired protein assimilation, antibiotic use, and iron therapy.[134]

DISEASES AFFECTING THE KIDNEY AND THE GASTROINTESTINAL TRACT

Amyloidosis

Amyloidosis results from extracellular deposition of insoluble fibrillary protein in various organs. Amyloidosis may affect the entire GI tract, causing symptoms of macroglossia, vomiting, hemorrhage, and diarrhea. The spleen may become enlarged with risk of rupture. The diagnosis requires a tissue sample. When a kidney biopsy cannot be performed to diagnose CKD due to amyloidosis, tissue from the duodenum obtained during an upper endoscopy had a high sensitivity for diagnosing amyloidosis and highly correlated with the presence of renal amyloidosis.[137] In subjects with kidney biopsy proven AA amyloidosis, the frequency of GI amyloid deposition was duodenum 97%, antrum and rectal 76%, esophagus 59%, and gingival mucosa 32%.[137] GI involvement rarely occurs with AL amyloid, presenting in 8% of biopsies. Only 1% of patients had clinical manifestations.[138] The extent of GI involvement in patients with dialysis-related (β-2 microglobulin) amyloidosis remains unknown.

The treatment of AL amyloidosis has advanced rapidly with disease stabilization often occurring in patients treated early with antiplasma cell therapy.[139] Similarly, the use of targeted therapy against inflammatory cytokines in autoimmune disease has been associated with a decreased incidence of AA amyloidosis.[140] GI involvement may respond to symptomatic treatment (i.e. octreotide and antimotility agents for diarrhea).[141]

SUMMARY

GI symptoms and disease are common in CKD patients and may significantly impact quality of life and nutritional status. GI disorders may range from mild symptoms such as dysgeusia to life threatening ailments such as hemorrhage.

Many of the GI manifestations may have correctable underlying etiologies and should not be automatically ascribed to the uremic state. Close collaboration with the gastroenterologist is critical in elucidating and treating the cause of GI symptoms and hemorrhage. There are effective treatments currently available for symptomatic relief of common symptoms such as hiccups, constipation, nausea, and vomiting in CKD patients.

Ongoing research provides new insights into the relationship between the GI system and the kidney, with increasing awareness of their codependence in disease mechanism.

References

1. Lew S, Borum M, Ing T. Gastrointestinal complications of acute kidney injury. In: Jorres A, Ronco C, Kellum J, editors. *Management of acute kidney problems*. Heidelberg, Germany: Springer Publishers; 2010. p. 209–20.
2. Lew S, Bosch J, Daugirdas J, Blake P, Ing T. Digestive tract. In: Daugirdas J, Blake P, Ing T, editors. *Handbook of dialysis*. Philadelphia, PA: Lippincott Williams & Wilkins; 2006. p. 647–55.
3. Shirazian S, Radhakrishnan J. Gastrointestinal disorders and renal failure: exploring the connection. *Nat Rev Nephrol* 2010;**6**: 480–92.
4. Zelnick E, Goyal R. Gastrointestinal manifestations of chronic renal failure. *Semin Nephrol* 1981;**1**:124–36.
5. Gruskin SE, Tolman DE, Wagoner RD. Oral manifestations of uremia. *Minn Med* 1970;**53**:495–9.
6. Schreiner G, Maher J. *Uremia: biochemistry, pathogenesis and treatment*. Springfield, IL: Charles C Thomas; 1961.

7. Muirhead N, Kertesz A, Flanagan PR, Hodsman AB, Hollomby DJ, Valberg LS. Zinc metabolism in patients on maintenance hemodialysis. *Am J Nephrol* 1986;**6**:422–6.
8. Takaoka T, Sarukura N, Ueda C, et al. Effects of zinc supplementation on serum zinc concentration and ratio of apo/holo-activities of angiotensin converting enzyme in patients with taste impairment. *Auris Sasus Larynx* 2010;**37**:190–4.
9. Osaki T, Ohshima M, Tomita Y, Matsugi N, Nomura Y. Clinical and physiological investigations in patients with taste abnormality. *J Oral Pathol Med* 1996;**25**:38–43.
10. Bartoshuk LM, Gent J, Catalanotto FA, Goodspeed RB. Clinical evaluation of taste. *Am J Otolaryngol* 1983;**4**:257–60.
11. Bossola M, Muscaritoli M, Tazza L, et al. Variables associated with reduced dietary intake in hemodialysis patients. *J Ren Nutr* 2005; **15**:244–52.
12. Bossola M, Muscaritoli M, Tazza L, et al. Malnutrition in hemodialysis patients: what therapy? *Am J Kidney Dis* 2005;**46**: 371–86.
13. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. *Am J Clin Nutr* 2004; **80**:299–307.
14. Lorenzo V, de Bonis E, Rufino M, et al. Caloric rather than protein deficiency predominates in stable chronic haemodialysis patients. *Nephrol Dial Transplant* 1995;**10**:1885–9.
15. Bergstrom J. Mechanisms of uremic suppression of appetite. *J Ren Nutr* 1999;**9**:129–32.
16. Bossola M, Tazza L, Giungi S, Luciani G. Anorexia in hemodialysis patients: an update. *Kidney Int* 2006;**70**:417–22.
17. Aguilera A, Selgas R, Diez JJ, Bajo MA, Codoceo R, Alvarez V. Anorexia in end-stage renal disease: pathophysiology and treatment. *Expert Opin Pharmacother* 2001;**2**:1825–38.
18. Aguilera A, Sanchez-Tomero JA, Selgas R. Brain activation in uremic anorexia. *J Ren Nutr* 2007;**17**:57–61.
19. Cheung WW, Mak RH. Ghrelin in chronic kidney disease. *Int J Pept* 2010;**2010**.
20. Kojima M, Kangawa K. Ghrelin: structure and function. *Physiol Rev* 2005;**85**:495–522.
21. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* 1999;**402**:656–60.
22. Yoshimoto A, Mori K, Sugawara A, et al. Plasma ghrelin and desacyl ghrelin concentrations in renal failure. *J Am Soc Nephrol* 2002;**13**:2748–52.
23. Fu RG, Ge H, Yao GL, et al. Uremic anorexia and gastrointestinal motility dysfunction correlate with the changes of ghrelin system in hypothalamus. *Nephrology* 2013;**18**:111–6.
24. Van Vlem B, Schoonjans R, Vanholder R, Vandamme W, De Vos M, Lameire N. Dyspepsia and gastric emptying in chronic renal failure patients. *Clin Nephrol* 2001;**56**:302–7.
25. Hirako M, Kamiya T, Misu N, et al. Impaired gastric motility and its relationship to gastrointestinal symptoms in patients with chronic renal failure. *J Gastroenterol* 2005;**40**:1116–22.
26. Strid H, Simren M, Stotzer PO, Abrahamsson H, Bjornsson ES. Delay in gastric emptying in patients with chronic renal failure. *Scand J Gastroenterol* 2004;**39**:516–20.
27. Lin X, Mellow MH, Southmayd 3rd L, Pan J, Chen JD. Impaired gastric myoelectrical activity in patients with chronic renal failure. *Dig Dis Sci* 1997;**42**:898–906.
28. Ravelli AM. Gastrointestinal function in chronic renal failure. *Pediatr Nephrol* 1995;**9**:756–62.
29. Strid H, Simren M, Stotzer PO, Ringstrom G, Abrahamsson H, Bjornsson ES. Patients with chronic renal failure have abnormal small intestinal motility and a high prevalence of small intestinal bacterial overgrowth. *Digestion* 2003;**67**:129–37.
30. Kahvecioglu S, Akdag I, Kiyici M, et al. High prevalence of irritable bowel syndrome and upper gastrointestinal symptoms in patients with chronic renal failure. *J Nephrol* 2005;**18**:61–6.
31. Ku E, Kopple JD, McCulloch CE, et al. Associations between weight loss, kidney function decline, and risk of ESRD in the chronic kidney disease in children (CKiD) cohort study. *Am J Kidney Dis* 2018;**71**:648–56.
32. Kovesdy CP, Kopple JD, Kalantar-Zadeh K. Management of protein-energy wasting in non-dialysis-dependent chronic kidney disease: reconciling low protein intake with nutritional therapy. *Am J Clin Nutr* 2013;**97**:1163–77.
33. Bossola M, Giungi S, Luciani G, Tazza L. Interventions to counteract anorexia in dialysis patients. *J Ren Nutr* 2011;**21**:16–9.
34. Dwyer JT, Larive B, Leung J, et al. Nutritional status affects quality of life in Hemodialysis (HEMO) Study patients at baseline. *J Ren Nutr* 2002;**12**:213–23.
35. Hiroshige K, Sonta T, Suda T, Kanegae K, Ohtani A. Oral supplementation of branched-chain amino acid improves nutritional status in elderly patients on chronic haemodialysis. *Nephrol Dial Transplant* 2001;**16**:1856–62.
36. Laviano A, Muscaritoli M, Cascino A, et al. Branched-chain amino acids: the best compromise to achieve anabolism? *Curr Opin Clin Nutr* 2005;**8**:408–14.
37. Boccanfuso JA, Hutton M, McAllister B. The effects of megestrol acetate on nutritional parameters in a dialysis population. *J Ren Nutr* 2000;**10**:36–43.
38. Rammohan M, Kalantar-Zadeh K, Liang A, Ghossein C. Megestrol acetate in a moderate dose for the treatment of malnutrition-inflammation complex in maintenance dialysis patients. *J Ren Nutr* 2005;**15**:345–55.
39. Kang JY. The gastrointestinal tract in uremia. *Digest Dis Sci* 1993; **38**:257–68.
40. Man NK, Fournier G, Thireau P, Gaillard JL, Funck-Brentano JL. Effect of bicarbonate-containing dialysate on chronic hemodialysis patients: a comparative study. *Artif Organs* 1982;**6**:421–8.
41. Douglas C, Murtagh FE, Chambers EJ, Howse M, Ellershaw J. Symptom management for the adult patient dying with advanced chronic kidney disease: a review of the literature and development of evidence-based guidelines by a United Kingdom Expert Consensus Group. *Palliat Med* 2009;**23**:103–10.
42. Ljutic D, Perkovic D, Rumboldt Z, Bagatin J, Hozo I, Pivac N. Comparison of ondansetron with metoclopramide in the symptomatic relief of uremia-induced nausea and vomiting. *Kidney Blood Press Res* 2002;**25**:61–4.
43. Fallone CA, Mayrand S. Gastroesophageal reflux and hyperacidity in chronic renal failure. *Perit Dial Int* 2001;**21**(Suppl. 3): S295–9.
44. Schoonjans R, Van VB, Vandamme W, et al. Dyspepsia and gastroparesis in chronic renal failure: the role of *Helicobacter pylori*. *Clin Nephrol* 2002;**57**:201–7.
45. Richter JE, Friedenberg FK. Gastroesophageal reflux disease. In: Feldman M, Friedman LS, Brandt LJ, editors. *Feldman: Sleisenger and Fordtran's gastrointestinal and liver disease*. 9th ed. Phildadelphia, PA: Saunders; 2010. p. 705–26.
46. Lazarus B, Chen Y, Wilson FP, et al. Proton pump inhibitor use and the risk of chronic kidney disease. *J Am Med Assoc* 2016;**176**: 238–46.

47. Ishigami J, Grams ME, Naik RP, Coresh J, Matsushita K. Chronic kidney disease and risk for gastrointestinal bleeding in the community: the atherosclerosis risk in communities (ARIC) study. *Clin J Am Soc Nephrol* 2016;**11**:1735–43.
48. Concha R, Amaro R, Barkin JS. Obscure gastrointestinal bleeding: diagnostic and therapeutic approach. *J Clin Gastroenterol* 2007;**41**: 242–51.
49. Iddan G, Meron G, Glukhovsky A, Swain P. Wireless capsule endoscopy. *Nature* 2000;**405**:417.
50. Rollins ES, Picus D, Hicks ME, Darcy MD, Bower BL, Kleinhoffer MA. Angiography is useful in detecting the source of chronic gastrointestinal bleeding of obscure origin. *Am J Roentgenol* 1991;**156**:385–8.
51. Jaffe RH, Laing DR. Changes of the digestive tract in uremia. *Arch Intern Med* 1934;**53**:851–64.
52. Chalasani N, Cotsonis G, Wilcox CM. Upper gastrointestinal bleeding in patients with chronic renal failure: role of vascular ectasia. *Am J Gastroenterol* 1996;**91**:2329–32.
53. Di Minno G, Martinez J, McKean ML, De La Rosa J, Burke JF, Murphy S. Platelet dysfunction in uremia. Multifaceted defect partially corrected by dialysis. *Am J Med* 1985;**79**:552–9.
54. Gralnick HR, McKeown LP, Williams SB, Shafer BC, Pierce L. Plasma and platelet von Willebrand factor defects in uremia. *Am J Med* 1988;**85**:806–10.
55. Chen KS, Huang CC, Leu ML, Deng P, Lo SK. Hemostatic and fibrinolytic response to desmopressin in uremic patients. *Blood Purif* 1997;**15**:84–91.
56. Kawamura H, Sakai E, Endo H, et al. Characteristics of the small bowel lesions detected by capsule endoscopy in patients with chronic kidney disease. *Gastroenterol Res Pract* 2013;**2013**:814214.
57. Sakai E, Endo H, Taniguchi L, et al. Factors predicting the presence of small bowel lesions in patients with obscure gastrointestinal bleeding. *Dig Endosc* 2013;**25**:412–20.
58. Owyang C, Miller LJ, DiMagno EP, Brennan Jr LA, Go VL. Gastrointestinal hormone profile in renal insufficiency. *Mayo Clin Proc* 1979;**54**:769–73.
59. Wesdorp RI, Falcao HA, Banks PB, Martino J, Fischer JE. Gastrin and gastric acid secretion in renal failure. *Am J Surg* 1981;**141**: 334–8.
60. Muto S, Murayama N, Asano Y, Hosoda S, Miyata M. Hypergastrinemia and achlorhydria in chronic renal failure. *Nephron* 1985; **40**:143–8.
61. Kamata K, Uchida M, Takeuchi Y, et al. Increased serum concentrations of pro-gastrin-releasing peptide in patients with renal dysfunction. *Nephrol Dial Transplant* 1996;**11**:1267–70.
62. Yamagata S, Ishimori A, Sakurada H, Miura Y, Tsuda K. Role of the kidney in gastrin metabolism. *Tohoku J Exp Med* 1976; **118**(Suppl. l):45–51.
63. Nardone G, Rocco A, Fiorillo M, et al. Gastroduodenal lesions and *Helicobacter pylori* infection in dyspeptic patients with and without chronic renal failure. *Helicobacter* 2005;**10**:53–8.
64. Khedmat H, Ahmadzad-Asl M, Amini M, et al. Gastro-duodenal lesions and *Helicobacter pylori* infection in uremic patients and renal transplant recipients. *Transplant Proc* 2007;**39**:1003–7.
65. Sood P, Kumar G, Nanchal R, et al. Chronic kidney disease and end-stage renal disease predict higher risk of mortality in patients with primary upper gastrointestinal bleeding. *Am J Nephrol* 2012; **35**:216–24.
66. Bjorkman DJ. Gastrointestinal hemorrhage and occult gastrointestinal bleeding. In: Goldman L, Ausiello D, editors. *Cecil textbook of medicine*. Philadelphia, PA: WB Saunders; 2004. p. 795–800.
67. Hoogerwerf W, Pasricha P. Pharmacotherapy of gastric acidity, peptic ulcers, and gastroesophageal reflux disease. In: Brunton L, Lazo J, Parker K, editors. *Goodman & Gilman's the pharmacological basis of therapeutics*. New York: McGraw-Hill; 2006. p. 967–81.
68. Couch P, Stumpf JL. Management of uremic bleeding. *Clin Pharm* 1990;**9**:673–81.
69. Zeigler ZR, Megaludis A, Fraley DS. Desmopressin (d-DAVP) effects on platelet rheology and von Willebrand factor activities in uremia. *Am J Hematol* 1992;**39**:90–5.
70. Mannucci PM, Remuzzi G, Pusineri F, et al. Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med* 1983;**308**:8–12.
71. Janson PA, Jubelirer SJ, Weinstein MJ, Deykin D. Treatment of the bleeding tendency in uremia with cryoprecipitate. *N Engl J Med* 1980;**303**:1318–22.
72. Livio M, Mannucci PM, Vigano G, et al. Conjugated estrogens for the management of bleeding associated with renal failure. *N Engl J Med* 1986;**315**:731–5.
73. Fernandez F, Goudable C, Sie P, et al. Low haematocrit and prolonged bleeding time in uraemic patients: effect of red cell transfusions. *Br J Haematol* 1985;**59**:139–48.
74. Rabiner SF, Drake RF. Platelet function as an indicator of adequate dialysis. *Kidney Int Suppl* 1975:144–6.
75. Lin HJ, Hsieh YH, Tseng GY, Perng CL, Chang FY, Lee SD. A prospective, randomized trial of endoscopic hemoclip versus heater probe thermocoagulation for peptic ulcer bleeding. *Am J Gastroenterol* 2002;**97**:2250–4.
76. Grund KE, Storek D, Farin G. Endoscopic argon plasma coagulation (APC) first clinical experiences in flexible endoscopy. *Endosc Surg Allied Technol* 1994;**2**:42–6.
77. Hui AJ, Sung JJ. Endoscopic treatment of upper gastrointestinal bleeding. *Curr Treat Options Gastroenterol* 2005;**8**:153–62.
78. Sung JJ, Tsoi KK, Lai LH, Wu JC, Lau JY. Endoscopic clipping versus injection and thermo-coagulation in the treatment of non-variceal upper gastrointestinal bleeding: a meta-analysis. *Gut* 2007;**56**:1364–73.
79. Orron DE, Bloom AI, Neeman Z. The role of transcatheter arterial embolization in the management of nonvariceal upper gastrointestinal bleeding. *Gastrointest Endosc Clin N Am* 2018;**28**: 331–49.
80. Kalman RS, Pedrosa MC. Evidence-based review of gastrointestinal bleeding in the chronic kidney disease patient. *Semin Dial* 2015;**28**:68–74.
81. Saeed F, Agrawal N, Greenberg E, Holley JL. Lower gastrointestinal bleeding in chronic hemodialysis patients. *Internet J Nephrol* 2011;**2011**:272535.
82. Scheff RT, Zuckerman G, Harter H, Delmez J, Koehler R. Diverticular disease in patients with chronic renal failure due to polycystic kidney disease. *Ann Intern Med* 1980;**92**:202–4.
83. Sharp CK, Zeligman BE, Johnson AM, Duley I, Gabow PA. Evaluation of colonic diverticular disease in autosomal dominant polycystic kidney disease without end-stage renal disease. *Am J Kidney Dis* 1999;**34**:863–8.
84. Lembo AJ, Ullman SP. Constipation. In: Feldman M, Friedman LS, Brandt LJ, editors. *Feldman: Sleisenger and Fordtran's gastrointestinal and liver disease*. 9th ed. Philadelphia, PA: Saunders; 2010. p. 258–84.
85. Orias M, Mahnensmith RL, Perazella MA. Extreme hyperphosphatemia and acute renal failure after a phosphorus-containing bowel regimen. *Am J Nephrol* 1999;**19**:60–3.

86. Markowitz GS, Whelan J, D'Agati VD. Renal failure following bowel cleansing with a sodium phosphate purgative. *Nephrol Dial Transplant* 2005;**20**:850–1.
87. Markowitz GS, Stokes MB, Radhakrishnan J, D'Agati VD. Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure. *J Am Soc Nephrol* 2005;**16**:3389–96.
88. Markowitz GS, Nasr SH, Klein P, et al. Renal failure due to acute nephrocalcinosis following oral sodium phosphate bowel cleansing. *Hum Pathol* 2004;**35**:675–84.
89. Lembo AJ, Kurtz CB, Macdougall JE, et al. Efficacy of linaclotide for patients with chronic constipation. *Gastroenterology* 2010;**138**: 886–95. e1.
90. Shailubhai K, Comiskey S, Foss JA, et al. Plecanatide, an oral guanylate cyclase C agonist acting locally in the gastrointestinal tract, is safe and well-tolerated in single doses. *Dig Dis Sci* 2013;**58**: 2580–6.
91. Gordon SJ, Miller LJ, Haeffner LJ, Kinsey MD, Kowlessar OD. Abnormal intestinal bile acid distribution in azotaemic man: a possible role in the pathogenesis of uraemic diarrhoea. *Gut* 1976;**17**:58–67.
92. Phatharacharukul P, Thongprayoon C, Cheungpasitporn W, Edmonds PJ, Mahaparn P, Bruminhent J. The risks of incident and recurrent Clostridium difficile-associated diarrhea in chronic kidney disease and end-stage kidney disease patients: a systematic review and meta-analysis. *Dig Dis Sci* 2015;**60**: 2913–22.
93. Canedo J, Ricciardi K, DaSilva G, Rosen L, Weiss EG, Wexner SD. Are postoperative complications more common following colon and rectal surgery in patients with chronic kidney disease? *Colorectal Dis* 2013;**15**:85–90.
94. Tang DM, Friedenberg FK. Gastroparesis: approach, diagnostic evaluation, and management. *Dis Mon* 2011;**57**:74–101.
95. Freeman JG, Cobden I, Heaton A, Keir M. Gastric emptying in chronic renal failure. *Br Med J* 1985;**291**:1048.
96. McNamee PT, Moore GW, McGeown MG, Doherty CC, Collins BJ. Gastric emptying in chronic renal failure. *Br Med J* 1985;**291**: 310–1.
97. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L, American College of G. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013;**108**:18–37. quiz 8.
98. Khoo J, Rayner CK, Jones KL, Horowitz M. Pathophysiology and management of gastroparesis. *Expert Rev Gastroenterol Hepatol* 2009;**3**:167–81.
99. Gumaste V, Baum J. Treatment of gastroparesis: an update. *Digestion* 2008;**78**:173–9.
100. Thomas MP, Wilson CH, Nayar M, et al. Endoscopic botulinum toxin injection for the treatment of diabetic gastropathy in pancreas and islet-cell transplant patients. *Exp Clin Transpl* 2012; **10**:168–71.
101. Ejskjaer NT, Bradley JL, Buxton-Thomas MS, et al. Novel surgical treatment and gastric pathology in diabetic gastroparesis. *Diabet Med* 1999;**16**:488–95.
102. Khashab MA, Stein E, Clarke JO, et al. Gastric peroral endoscopic myotomy for refractory gastroparesis: first human endoscopic pyloromyotomy (with video). *Gastrointest Endosc* 2013;**78**:764–8.
103. Dacha S, Mekaroonkamol P, Li L, et al. Outcomes and quality-of-life assessment after gastric per-oral endoscopic pyloromyotomy (with video). *Gastrointest Endosc* 2017;**86**:282–9.
104. Strasser F. Clinical application of ghrelin. *Curr Pharmaceut Des* 2012;**18**:4800–12.
105. Kimmel PL, Tenner S, Habwe VQ, Henry J, Lakshminarayan S, Steinberg W. Trypsinogen and other pancreatic enzymes in patients with renal disease: a comparison of high-efficiency hemodialysis and continuous ambulatory peritoneal dialysis. *Pancreas* 1995;**10**:325–30.
106. Royse VL, Jensen DM, Corwin HL. Pancreatic enzymes in chronic renal failure. *Arch Intern Med* 1987;**147**:537–9.
107. Pedersen EB, Brock A, Kornerup HJ. Serum amylase activity and renal amylase activity clearance in patients with severely impaired renal function and in patients treated with renal allotransplantation. *Scand J Clin Lab Investig* 1976;**36**:137–40.
108. Golay V, Roychowdhary A. Acute pancreatitis in chronic kidney disease–a common but often misunderstood combination. *Ren Fail* 2012;**34**:1338–40.
109. Pitchumoni CS, Arguello P, Agarwal N, Yoo J. Acute pancreatitis in chronic renal failure. *Am J Gastroenterol* 1996;**91**:2477–82.
110. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012;**366**:539–51.
111. Lai SW, Liao KF, Lai HC, Chou CY, Cheng KC, Lai YM. The prevalence of gallbladder stones is higher among patients with chronic kidney disease in Taiwan. *Medicine* 2009;**88**:46–51.
112. Lewis B, Mukewar S, Lopez R, Brzezinski A, Hall P, Shen B. Frequency and risk factors of renal insufficiency in inflammatory bowel disease inpatients. *Inflamm Bowel Dis* 2013;**9**:1846–51.
113. Jacobi J, Schnellhardt S, Opgenoorth M, et al. Severe metabolic alkalosis and recurrent acute on chronic kidney injury in a patient with Crohn's disease. *BMC Nephrol* 2010;**11**:6.
114. Hueppelshaeuser R, von Unruh GE, Habbig S, et al. Enteric hyperoxaluria, recurrent urolithiasis, and systemic oxalosis in patients with Crohn's disease. *Pediatr Nephrol* 2012;**27**:1103–9.
115. Sattianayagam PT, Gillmore JD, Pinney JH, et al. Inflammatory bowel disease and systemic AA amyloidosis. *Digest Dis Sci* 2013;**58**:1689–97.
116. Maalouf NM, Tondapu P, Guth ES, Livingston EH, Sakhaee K. Hypocitraturia and hyperoxaluria after Roux-en-Y gastric bypass surgery. *J Urol* 2010;**183**:1026–30.
117. Lieske JC, Kumar R, Collazo-Clavell ML. Nephrolithiasis after bariatric surgery for obesity. *Semin Nephrol* 2008;**28**:163–73.
118. Nelson WK, Houghton SG, Milliner DS, Lieske JC, Sarr MG. Enteric hyperoxaluria, nephrolithiasis, and oxalate nephropathy: potentially serious and unappreciated complications of Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2005;**1**:481–5.
119. Nasr SH, D'Agati VD, Said SM, et al. Oxalate nephropathy complicating Roux-en-Y Gastric Bypass: an underrecognized cause of irreversible renal failure. *Clin J Am Soc Nephrol* 2008;**3**:1676–83.
120. Sakhaee K, Griffith C, Pak CY. Biochemical control of bone loss and stone-forming propensity by potassium-calcium citrate after bariatric surgery. *Surg Obes Relat Dis* 2012;**8**:67–72.
121. Cakar M, Kanbay M, Sarlak H, et al. Findings of biopsy-proven chronicity and end-stage renal failure associated with oral sodium phosphate solution. *Ren Fail* 2012;**34**:499–501.
122. Brunelli SM. Association between oral sodium phosphate bowel preparations and kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009;**53**:448–56.
123. Lien YH. Is bowel preparation before colonoscopy a risky business for the kidney? *Nat Clin Pract Nephrol* 2008;**4**:606–14.
124. Margetts PJ, Churchill DN, Alexopoulou I. Interstitial nephritis in patients with inflammatory bowel disease treated with mesalamine. *J Clin Gastroenterol* 2001;**32**:176–8.
125. Gomm W, von Holt K, Thome F, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. *JAMA Neurol* 2016;**73**:410–6.

126. Wise J. Proton pump inhibitors may be linked to dementia risk. *BMJ* 2016;**352**:i972.
127. Yearsley KA, Gilby LJ, Ramadas AV, Kubiak EM, Fone DL, Allison MC. Proton pump inhibitor therapy is a risk factor for Clostridium difficile-associated diarrhoea. *Aliment Pharmacol Ther* 2006;**24**:613–9.
128. Linsky A, Gupta K, Lawler EV, Fonda JR, Hermos JA. Proton pump inhibitors and risk for recurrent *Clostridium difficile* infection. *Arch Intern Med* 2010;**170**:772–8.
129. Biyik M, Solak Y, Ucar R, et al. Hypomagnesemia among outpatient long-term proton pump inhibitor users. *Am J Therapeut* 2017;**24**:e52–5.
130. Chen CH, Lin HC, Lin HL, et al. Proton pump inhibitor usage and the associated risk of pneumonia in patients with chronic kidney disease. *J Microbiol Immunol* 2015;**48**:390–6.
131. Fusaro M, Noale M, Tripepi G, et al. Long-term proton pump inhibitor use is associated with vascular calcification in chronic kidney disease: a cross-sectional study using propensity score analysis. *Drug Saf* 2013;**36**:635–42.
132. Gouraud A, Vochelle V, Descotes J, Vial T. Proton pump inhibitor-induced neutropenia: possible cross-reactivity between omeprazole and pantoprazole. *Clin Drug Investig* 2010;**30**:559–63.
133. Laria A, Zoli A, Gremese E, Ferraccioli GF. Proton pump inhibitors in rheumatic diseases: clinical practice, drug interactions, bone fractures and risk of infections. *Reumatismo* 2011;**63**:5–10.
134. Armani RG, Ramezani A, Yasir A, Sharama S, Canziani MEF, Raj DS. Gut microbiome in chronic kidney disease. *Curr Hypertens Rep* 2017;**19**:29.
135. Nallu A, Sharma S, Ramezani A, Muralidharan J, Raj D. Gut microbiome in chronic kidney disease: challenges and opportunities. *Transl Res* 2017;**179**:24–37.
136. Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. *J Am Soc Nephrol* 2014;**25**:657–70.
137. Yilmaz M, Unsal A, Sokmen M, et al. Duodenal biopsy for diagnosis of renal involvement in amyloidosis. *Clin Nephrol* 2012;**77**:114–8.
138. Menke DM, Kyle RA, Fleming CR, Wolfe 3rd JT, Kurtin PJ, Oldenburg WA. Symptomatic gastric amyloidosis in patients with primary systemic amyloidosis. *Mayo Clin Proc* 1993;**68**:763–7.
139. Wechalekar AD, Gillmore JD, Bird J, et al. Guidelines on the management of AL amyloidosis. *Br J Haematol* 2015;**168**:186–206.
140. Keersmaekers T, Claes K, Kuypers DR, de Vlam K, Verschueren P, Westhovens R. Long-term efficacy of infliximab treatment for AA-amyloidosis secondary to chronic inflammatory arthritis. *Ann Rheum Dis* 2009;**68**:759–61.
141. Lovat LB, Pepys MB, Hawkins PN. Amyloid and the gut. *Dig Dis* 1997;**15**:155–71.
142. Vakil N. Peptic ulcer disease. In: Feldman M, Friedman LS, Brandt LJ, editors. *Feldman: Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. 9th ed. Philadelphia, PA: Saunders; 2010. p861–868.

QUESTIONS AND ANSWERS

Question 1

A 61-year-old woman with CKD stage 4 presented with abdominal pain and bloody emesis. She has hypertension and type 2 diabetes mellitus. She did not have any overt uremic symptoms.

On examination, her blood pressure was 150/90 mmHg, pulse 88 beats per minute, and respiratory rate 20 breaths per minute. The patient presented with normal lung sounds on auscultation and percussion. On cardiac examination she had normal S1, S2 sounds without murmurs, or rub. The abdominal examination did not reveal any tenderness, masses, or organomegaly. She had 1+ pedal edema. She did not have asterixis.

Laboratory values revealed the following:

S[Na]139 mEq/L
S[K] 4.9 mEq/L
S[HCO3] 21 mEq/L
S[Cl] 105 mEq/L
BUN 98 mg/dL
S[Cr] 4.1 mg/dL
Glucose 188 mg/dL
S[Ca] 8.5 mg/dL
Hgb 8.3 g/dL
Hct 24%
Platelet count 200,000/μL

She underwent an upper endoscopic procedure.

Which of the following etiologies most likely contributed to upper GI bleeding in this patient?

A. Gastric cancer
B. Mallory Weiss tear
C. Peptic ulcer
D. Esophageal varices
E. Hiatal hernia

Answer: C

Peptic ulcer (C) most likely contributed to upper GI bleeding in this patient.

Peptic ulcer disease (gastric greater than duodenal) represents the most common cause of upper gastrointestinal bleeding (UGIB) in patients with CKD. Vascular ectasia occurs more frequently in patients with CKD than in those with normal renal function, and its prevalence seems to be related to the duration and severity of renal disease. Patients with CKD do not have an increased risk of gastric cancer. Mallory–Weiss tear may be seen with forceful vomiting. Esophageal varices accompany liver disease such as cirrhosis. Hiatal hernia does not appear to be more frequent in CKD patients. Increased intraabdominal pressure may unmask any abdominal hernia in a patient performing PD.

Question 2

A 62-year-old woman with CKD stage 4 has GI bleeding from duodenitis. She has a long history of left knee pain associated with a sport injury sustained as a young adult. She takes over-the-counter pain medications for symptomatic relief. Over the last few years she alternates between nonsteroidal anti-inflammatory medications and corticosteroids to treat her knee. On a routine medical examination five years ago, she had an elevated S[Cr] and bland urine. She underwent a kidney biopsy, which showed interstitial nephritis consistent with analgesic nephropathy. Last week, she complained of a constant dull mid epigastric discomfort, which worsened with eating food, and she saw tarry stools. A gastroenterologist diagnosed GI bleeding from duodenitis.

Which of the following does **not** contribute to upper GI hemorrhage in this patient?

A. Ibuprofen ingestion
B. Platelet dysfunction
C. Anemia
D. Corticosteroid use
E. Vitamin D supplementation

Answer: E

Vitamin D supplementation does not contribute to upper GI hemorrhage. Ulcerogenic medications such as salicylates, corticosteroids, nonsteroidal anti-inflammatory drugs, and iron may cause gastritis or duodenitis.[142] Thus, medications such as ibuprofen and corticosteroids can cause GI hemorrhage. CKD patients have platelet dysfunction as demonstrated by a prolonged bleeding time.[53–55] In addition, fewer red blood cells are trapped by the fibrin clot in the presence of anemia.

Question 3

A 63-year-old man has CKD stage 4 from hypertension. He requires four medications for adequate blood pressure control. A gastroenterologist diagnosed him with upper GI bleed and started him on a proton pump inhibitor last month. Persistent anemia and tarry stools led to his readmission to the hospital.

On physical examination, his blood pressure was 100/60 mm Hg with orthostatic changes, pulse 100 beats per min, respiratory rate 20 breaths per minute, and temperature 98.6°F. He had normal lung sounds to auscultation and percussion. He had normal S1 and S1 heart sounds without murmurs or rub. The abdominal exam did not reveal any tenderness, masses, or organomegaly. He had no pedal edema. Fecal occult blood test was positive.

Laboratory results:

PT: 13.0 seconds
INR: 1.0
PTT: 25 seconds
Bleeding time: greater than 15 minutes
Hgb: 7.0 g/dL
Hct: 21%
Platelet count: $300 \times 10^3/\mu L$
S[Cr]: 3.2 mg/dL
eGFR: 24 mL/min/1.73 m^2
BUN: 120 mg/dL

Which of the following should NOT be included in his treatment plan at this time?

A. Administer estrogen
B. Transfuse with packed red blood cells
C. Administer fresh frozen plasma
D. Administer DDAVP 0.3 μg/kg IV
E. Initiate hemodialysis

Answer: E

Initiation of hemodialysis (Answer E) does not belong in his treatment plan at this time. Although estrogen takes several days to become effective, it corrects prolonged bleeding time in uremic patients.[72] Estrogen may be used as a second tier agent to correct platelet dysfunction. This patient has severe anemia with hemodynamic compromise as evidenced by relatively low blood pressure and tachycardia. Volume resuscitation could be accomplished with crystalloid, colloid, or blood. Packed red blood cell transfusion would correct his volume deficiency as well as his anemia. In addition, an adequate number of red blood cells help plug the fibrin mesh in preparation to form a clot.[73] Fresh frozen plasma may be given if he has active bleeding and abnormal coagulation parameters.[71] Fresh frozen plasma also aids in correcting a prolonged bleeding time. Uremic platelets have a functional defect affecting the interaction of von Willebrand factor with glycoprotein IIb-IIIa. DDAVP releases von Willebrand factor from endothelial cells.[69,70] Once von Willebrand factor has been released, additional doses of DDAVP will not cause additional von Willebrand factor release. If DDAVP does not correct bleeding time with the initial dose, additional dosing will not correct an abnormal bleeding time.

His level of eGFR does not suggest the need for initiation of dialysis. An elevated BUN associated with upper GI bleeding is a result of nitrogen absorption from the gut. Intestinal bacteria with urease convert urea to nitrogen, which in turn is absorbed.

Question 4

A 64-year-old man has CKD stage 5 not on dialysis from polycystic kidney disease. He takes four antihypertensive medications to control his blood pressure. He presented to the emergency department with right-sided abdominal pain. The pain had no relationship to eating, bowel movements, or activity. He denied seeing black tarry stools or bright red blood in the stool.

On physical examination, his blood pressure was 140/90 mm Hg, pulse 70 beats per min, respiratory rate 12 breaths per minute, and temperature 100.6°F. He had normal lung findings on auscultation and percussion. He had normal heart sounds without murmurs or rub. The abdomen did not show any distention or protrusions. He expressed pain and rebound tenderness to abdominal palpation at the level of the umbilicus. The rectal examination did not reveal any hemorrhoids, masses, or tenderness. He had a negative Murphy's sign. His lower extremities did not have edema. Fecal occult blood test was positive.

On further questioning, he disclosed that he suffers from constipation. He tried to eat more vegetables but failed to maintain a daily intake of three servings. He takes docusate regularly and bisacodyl at least 4–5 times per month.

Laboratory results:

WBC: $11.6 \times 10^3/\mu L$
Hgb: 11.0 g/dL
Hct: 33%
Platelet count: $250 \times 10^3/\mu L$
S[Cr]: 6.2 mg/dL
eGFR: 10 mL/min/1.73 m^2
BUN: 70 mg/dL
Total Bilirubin: 0.2 mg/dL
AST: 15 IU/L
ALT: 15 IU/L

The patient awaits a CT scan of the abdomen.

What would be the most likely diagnosis among the differential diagnosis for right-sided abdominal pain in this patient?

A. Appendicitis
B. Cholecystitis
C. Diverticulitis
D. Abdominal wall hernia with bowel incarceration
E. Abdominal angina

Answer: C

Diverticulitis (Answer C) most likely caused his right sided abdominal pain.[82,83] Constipation due to dietary

restriction of fluid, fruits, and vegetables as well as the use of phosphate binders predispose dialysis patients to diverticular disease. The history and physical examination were not consistent with appendicitis, cholecystitis, or abdominal wall hernia. An imaging study, such as the abdominal CT scan, is a useful tool to differentiate these diagnoses. He did not have any episodes of low blood pressure or discomfort with meals to suggest abdominal angina.

Question 5

A 65-year-old woman with CKD stage 5 has a history of diabetes mellitus, hypertension, gout, coronary artery disease, congestive heart failure, and sleep apnea. She takes medications for her medical conditions with fair control and uses a continuous positive airway pressure device treatment of sleep apnea. She presented to the renal clinic for a follow-up visit and preparation for dialysis. She described nausea, morning heaving about once a week, loss of appetite, and a metallic taste.

On physical examination, she has a blood pressure of 150/90 mm Hg, pulse 63 beats per minute, respiratory rate 20 breaths per minute, and temperature 98.6°F. She has neck vein distention. She has bibasilar rales on lung examination. She has a grade 2/6 systolic ejection murmur but no rub on cardiac examination. The abdominal examination reveals normal bowel sounds on auscultation. The abdomen feels soft on palpation, and she has no guarding. She has 1+ pedal edema. She does not have asterixis.

Symptoms of nausea, vomiting, loss of appetite, and bad taste in the mouth may lead to all of the following **except**:

A. Poor quality of life
B. Weight loss
C. Low serum albumin (S[Alb]) level
D. Increased physical pain
E. Decreased urine output

Answer: D

Increased physical pain (Answer D) rarely accompanies GI uremic symptoms. Symptoms of nausea and vomiting may be unpleasant but rarely give rise to pain. Symptoms of nausea, vomiting, loss of appetite, and bad taste cause poor quality of life. Working individuals find it difficult to report to work and interact with coworkers. Patients may find it difficult to engage in activities outside of their home due to ongoing symptoms. Patients lose weight when they eat less. Poor protein intake results in a fall in S[Alb] level. The S[Alb] reflects nutritional status as well as inflammation in patients with CKD. Uremic patients frequently have cachexia and malnutrition from poor nutritional intake. Poor nutritional intake results from either dietary restriction or uremic symptoms. Nausea, vomiting, and poor intake may result in volume, acid/base, and electrolyte disorders.[4]

Question 6

A 66-year-old man with CKD stage 5 not on dialysis with a history of diabetes mellitus, hypertension, gout, coronary artery disease, congestive heart failure, and peripheral vascular disease presents with a complaint of constipation. He noticed occasional constipation for about three months. However, he now feels that if he does not take a laxative daily, he would not have a bowel movement.

He takes medications to control his diabetes mellitus, hypertension, gout, heart failure, and peripheral vascular disease. His medications include Lantus, Novolog, amlodipine, carvedilol, lisinopril, furosemide, calcium carbonate, vitamin D, metoclopramide, docusate, and bisacodyl.

On physical examination, he has a blood pressure of 150/90 mm Hg, pulse 72 beats per minute, respiratory rate 20 per minute, and temperature 98.6°F. He has neck vein distention and bibasilar rales. He has regular heart sounds without murmur or rub. The abdominal examination reveals normal bowel sounds. The abdomen feels soft on palpation, and he has no guarding. He has 2+ pedal edema. He does not have asterixis.

Laboratory results reveal the following: S[Na] 135 mEq/L, S[K] 5.4 mEq/L, S[Cl] 100 mEq/L, S[HCO3] 19 mEq/L, BUN 88 mg/dL, S[Cr] 7.1 mg/dL, S[Ca] 9.9 mg/dL, and glucose 133 mg/dL.

Possible mechanisms for constipation include all of the following **except**:

A. Ingestion of phosphate binder
B. Fluid restriction
C. Fruit restriction due to hyperkalemia
D. Gastroparesis
E. Decreased physical activity

Answer: E

Decreased physical activity does not cause constipation. Physical activity does not appear to play a role in bowel habits. Patients who remain bed-bound continue to have normal bowel movements. On the other hand, physically active people who eat a low fiber diet can suffer from constipation. Ingestion of phosphate binders, especially calcium-based medications, may cause constipation. Fluid restriction makes the stool hard and difficult to pass. Fruits have fiber and thus add bulk to stool. Most fruits contain high potassium content and

thus intake must be restricted in patients who present with hyperkalemia. Fruit ingestion plays an important role in preventing constipation. However, patients with gastroparesis eat a low-fiber diet to aid in gastric emptying. Gastroparesis may be associated with constipation. Treatment of constipation with an osmotic laxative improves dyspeptic symptoms and gastric-emptying delay. A high-fiber diet delays gastric emptying and therefore may worsen gastroparetic symptoms.[84]

CHAPTER

34

Endocrine Complications of Chronic Kidney Disease

Laura LaFave[a], *Danielle Haselby*[b], *Allyson Hart*[b]

[a]Division of Endocrinology, Hennepin Healthcare, University of Minnesota Medical School, Minneapolis, MN, United States; [b]Division of Nephrology, Hennepin Healthcare, University of Minnesota Medical School, Minneapolis, MN, United States

Abstract

Endocrine disorders are common in chronic kidney disease (CKD), and the interaction between the endocrine and renal systems is complex. Hormones are both synthesized and excreted by the kidneys, and endocrinopathies also play a role in uremic dysfunction. We review the hypothalamic–pituitary–target organ axis and discuss how this axis is affected by CKD, with emphasis on target endocrine glands including the gonads, adrenal glands, liver, thyroid gland, and adipose tissue.

INTRODUCTION

The hypothalamic–pituitary–target organ axis, which governs the endocrine system, is exquisitely sensitive to changes in the body's homeostasis (Figure 34.1). The kidneys are complex organs that both synthesize and degrade hormones. Because of the interaction between these organ systems, endocrinopathies are common in chronic kidney disease (CKD) and play a role in the development of the uremic syndrome, such as protein calorie malnutrition, sexual dysfunction, and menstrual abnormalities. The mechanisms underlying endocrine disturbances in CKD are complex, including altered feedback mechanisms, changes in hormone production, and alterations in transport as well as metabolism and clearance (Table 34.1). The effects of endocrinopathies in CKD may manifest either due to changes in hormone concentrations themselves, or changes in the target organ response (Table 34.2). Some hormones, such as erythropoietin and 1,25 OH vitamin D, are produced by the kidneys, and inadequate levels of those hormones are seen in patients as kidney function declines. In addition, sexual dysfunction is a highly prevalent and multifactorial comorbidity in patients with CKD. We discuss both the clinical and laboratory endocrine abnormalities that may present in patients with CKD, with emphasis on target endocrine glands affected in CKD, including the gonads, adrenal glands, liver, thyroid gland, and adipose tissue.

MALE GONADAL AXIS IN CKD

The gonads are particularly prone to disturbances in the hypothalamic–pituitary (HP) axis in general, and there is no exception to this in the setting of CKD. In men, follicle stimulating hormone (FSH) and luteinizing hormone (LH), both gonadotropins produced by the pituitary gland, are elevated. FSH in men is responsible for spermatogenesis, stimulating testicular growth, and production of testosterone-binding globulin in the Sertoli cells. Although FSH is elevated in men with CKD,[1] they have decreased spermatogenesis and lessened fertility or infertility, possibly caused by primary testes dysfunction or resistance at the level of the testes to the effects of FSH. LH is also elevated in men with CKD, due to loss of pulsatile release of gonadotropin releasing hormone (GnRH) from the hypothalamus.

Hyperprolactinemia, common in men with CKD, likely contributes to loss of regulation of the gonadotropins. There is also decreased renal clearance of both LH and GnRH. In men, LH stimulates production of testosterone in the Leydig cells of the testes. However, despite elevations of gonadotropins, between 26% and 66% of men with CKD have low levels of testosterone (hypogonadism).[1] This state of hypergonadotrophic hypogonadism may reflect a resistance to gonadotrophic effects at

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00034-6

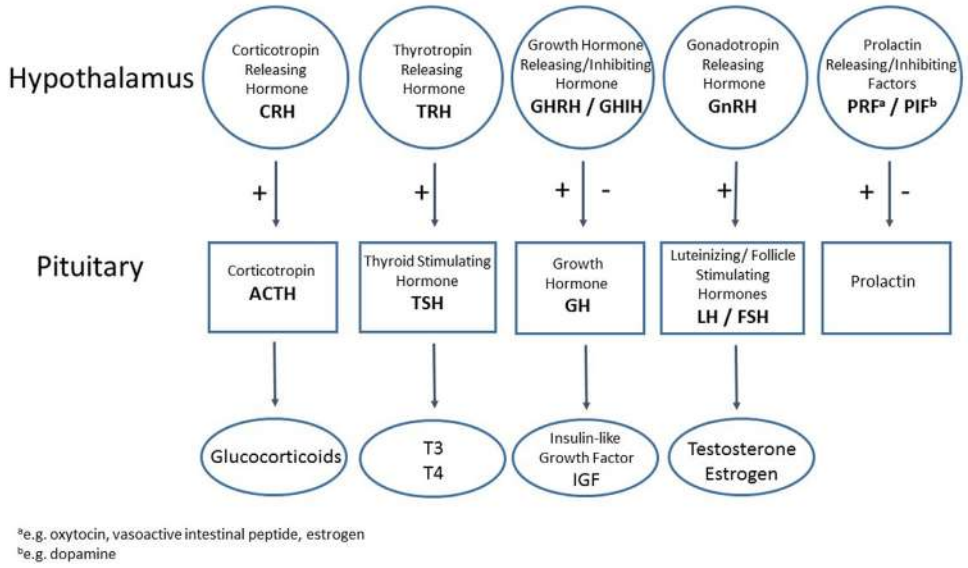


FIGURE 34.1 Overview of the hypothalamic–pituitary axis. *ACTH*, corticotropin; *CRH*, corticotropin releasing hormone; *GHIH*, growth hormone inhibiting hormone (somatostatin); *GHRH*, growth hormone releasing hormone; *GnRH*, gonadotropin releasing hormone; *PRF*, prolactin releasing factor; *PRI* prolactin inhibiting factor; *T3*, triiodothyoronine; *T4*, thyroxine; *TRH*, thyrotropin releasing hormone; *TSH*, thyroid stimulating hormone.

TABLE 34.1 Causes of Hormone Alterations in Chronic Kidney Disease

Modification of feedback mechanisms
Abnormal hormone production
Abnormal hormone transport
Altered metabolism
Altered elimination
Altered hormone binding proteins

TABLE 34.2 Impact of Chronic Kidney Disease on the Hypopituitary—Pituitary—Target Organ Axis

Axis	Effect in Chronic Kidney Disease
Gonadotropin axis	↑ GnRH (however, pulsatile release inhibited) ↑ FSH, ↑ LH ↓ Testosterone and Estrogen
Thyroid axis	Resistance to TRH ↔ or ↑ TSH ↓T3, ↔ T4
Adrenal axis	↔ CRH, ACTH. ↑ glucocorticoid levels
Growth hormone axis	↔ GHRH or GHIH Resistance to GH, levels ↔ or ↑ IGF-1 ↔ or ↓
Prolactin axis	↔ PRF, PIF ↑ Prolactin

ACTH, corticotropin; *CRH*, corticotropin releasing hormone; *GHIH*, growth hormone inhibiting hormone (somatostatin); *GHRH*, growth hormone releasing hormone; *GnRH*, gonadotropin releasing hormone; *PRF*, prolactin releasing factor; *PRI*, prolactin inhibiting factor; *T3*, triiodothyoronine; *T4*, thyroxine; *TRH*, thyrotropin releasing hormone; *TSH*, thyroid stimulating hormone.

the level of the testes, possibly exacerbated by hyperprolactinemia. Because testosterone circulates bound to sex hormone binding globulin (SHBG), measurement of testosterone levels in men with CKD can be complicated by the altered protein metabolism that may be present due to the underlying kidney disease. Evaluation should include measurement of fasting morning samples on two occasions, with both total and free testosterone levels. Free levels can be calculated using the measured total testosterone level and SHBG.[2]

Hypogonadism in men with CKD presents clinically with low libido, erectile dysfunction, anemia, fatigue, depression, and decreased muscle mass.[3] In addition to symptoms, low testosterone levels have been linked to increased arterial stiffness and endothelial dysfunction that may increase the risk of cardiovascular (CV) events and disease.[4] Hypogonadism is also associated with decreased bone mineral density and osteoporosis, with increased risk of fractures in men with CKD.[5] Testosterone therapy in men with CKD may improve muscle mass and bone mineral density, but there is scant evidence showing that it ameliorates anemia or prevents fractures. Treatment with testosterone replacement using topical or intramuscular androgens is reasonable to consider in men with CKD with testosterone levels under 200 ng/dL, those who are symptomatic, or in those at high risk for fracture.[6] Adverse effects of testosterone therapy include benign prostatic hypertrophy, increased rate of prostate cancer, erythrocytosis, and venous thromboembolism. Perhaps most concerning in the CKD population is the possible increased risk of

CV disease, although studies continue to be conflicted and inconclusive. There are no randomized controlled trials of testosterone treatment in hypogonadal men with CKD.

FEMALE GONADAL AXIS IN CKD

Disorders of menstruation and fertility are very common but underrecognized in women with CKD. In a study of 100 women with CKD or end-stage renal disease (ESRD) who were referred to gynecology by nephrologists, 39% were referred for menstrual disturbances and 12% for menopause. However, 85% of those women were found to have menstrual disorders and over a third were in menopause, indicating that these endocrine disturbances were underestimated.[7] Nearly half of these women were aged less than 40 years, with 14% of the women under 40 found to have primary ovarian failure.

Most of the available literature evaluating sex hormones in women with kidney disease focuses on ESRD. Data on gynecologic issues and fertility across the spectrum of CKD are lacking. As CKD progresses, the normal cyclic release of GnRH is compromised. This in turn causes the loss of pulsatile secretion of the gonadotropins (LH and FSH) from the pituitary gland.

Hyperprolactinemia is also common in women with CKD. High levels of prolactin result from both reduced renal clearance, as well as upregulation of hormone production due to CKD-related inhibition of dopaminergic activity in the pituitary gland.[8] Increased prolactin levels interfere with normal cyclic GnRH secretion. The resulting loss of pulsatile LH and FSH release leads to the decline and ultimate absence of estradiol release. Women with CKD have high rates of irregular or absent menses, anovulation, and infertility. Hyperprolactinemia is clearly not the sole cause of ovarian dysfunction in CKD, however, as evidenced by the fact that treatment with bromocriptine (a dopamine agonist) lowers prolactin levels but does not restore gonadotropin response.[9]

One of the most significant effects of estrogen deficiency in women with CKD is bone disease. Women with amenorrhea have lower bone mineral density compared with menstruating female patients with CKD. Some small interventional studies show benefit of treatment with transdermal estrogen[10] or selective estrogen receptor modulators.[11] However, the safety and efficacy of long-term treatment with estrogen or SERMs in women with CKD has not yet been established.

Hypoestrogenemia is also a risk factor for hyperlipidemia and CV disease in women with CKD. In the general population, premenopausal age women enjoy relative protection from CV disease compared with age-matched men. Women less than 45 years old with ESRD treated with hemodialysis have similar rates of CV mortality compared to their male counterparts,[12] suggesting that hypoestrogenemia adversely affects CV risk in this population. Hyperprolactinemia is also associated with CV events and mortality in patients with CKD,[13] suggesting a possible therapeutic target for CV and renal protection.[14]

THYROID COMPLICATIONS OF CKD

Thyroid hormones are integral to the development of kidney size and function.[15] Thyroid hormones (mostly T4 and some T3) are produced in the thyroid gland. Thyrotropin Releasing Hormone (TRH) from the hypothalamus stimulates the production of thyrotropin, or TSH, in the pituitary. TSH in turn stimulates the production and release of mostly T4, as well as some T3, in the target gland. In the circulation T4 is converted into T3 by deiodinase enzymes. T3 is the more active form of thyroid hormone. TSH, T4, and T3 are feedback on the hypothalamus and pituitary in a complex and elegant loop. Patients with congenital hypothyroidism have an increased prevalence of kidney and urogenital malformations, indicating the important role these ubiquitous hormones play in renal development.[16] Thyroid hormones act on nuclear receptors in target cells and effect gene transcription, but they can also cause nongenomic effects by binding to different components of the cell membrane and plasma. In doing so they regulate protein synthesis and cell growth. Through these mechanisms, thyroid disease also alters renal physiology, with both direct renal and indirect CV effects on glomerular filtration rate (GFR) (Figure 34.2), as well as on renal tubular ion transport, resulting in alterations in sodium, water, and acid excretion.[17] Hypothyroidism is a well-recognized cause of hyponatremia due to a combination of decreased renal blood flow, impaired urinary dilution, and increased fractional excretion of sodium.[18,19] Hyperthyroidism is associated with polyuria secondary to increased water and solute excretion.[20]

Thyroid hormone levels themselves may also be altered in CKD. The most commonly observed thyroid function test change in CKD patients is low T3 levels. One study of 2284 CKD patients with normal TSH levels demonstrated an increasingly high prevalence of low T3 levels with declining GFR.[21] The conversion of T4 to T3 is lowered by malnutrition, inflammation, nonthyroidal illness, and some medications. Low T3 levels may be an indication of illness in patients with CKD.[22]

Because T4 is extensively bound to proteins, serum T4 levels in CKD patients may be low. Free T4 (unbound hormone) may be measured directly in serum, but typical analog assays of free T4 depend on protein

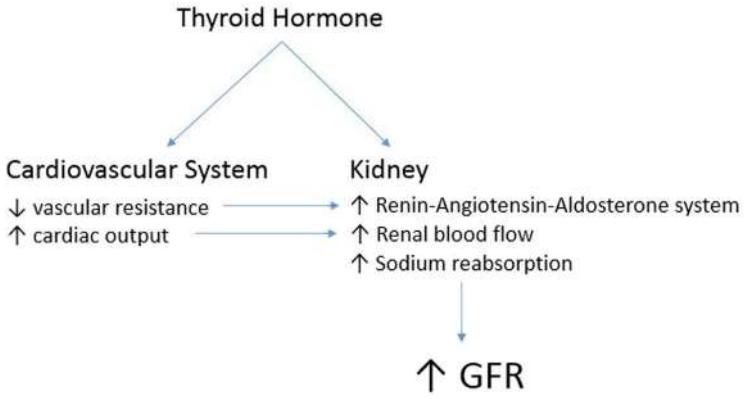


FIGURE 34.2 Effect of thyroid hormone on glomerular filtration rate (GFR).

binding, and also may not be reliable when circulating proteins or their levels are abnormal or in the presence of substances that inhibit protein binding (such as uremic toxins).[23] Measurement of Free T4 *via* equilibrium dialysis and radioimmunoassay can overcome this limitation by separating bound and free T4 and measuring the hormone directly.[24]

HYPOTHYROIDISM AS A COMPLICATION OF CHRONIC KIDNEY DISEASE

Although normal kidney development and function is dependent on a euthyroid state, it is well known that thyroid dysfunction, specifically subclinical and overt hypothyroidism, is more common in patients with CKD.[25,26] In over 14,000 participants in the Third National Health and Nutritional Examination Survey, patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 had twice the risk of hypothyroidism (defined as TSH greater than 4.5 mIU/L or treatment with levothyroxine) compared with patients with eGFRs >90 mL/min/1.73 m^2.[27]

There are several mechanisms by which CKD may lead to thyroid dysfunction. The metabolic acidosis commonly present in patients with CKD may result in thyroid hormone laboratory changes. Selenium is an important cofactor in the synthesis of thyroid hormone, and selenium deficiency is common in CKD patients. Iodine retention (from iodinated contrast[28] or high iodine diets[29]) because of impaired kidney function may also contribute to the development of hypothyroidism. Finally, heavy urinary protein losses in nephrotic syndrome may lead to total body thyroid hormone depletion, because most circulating thyroid hormone is protein-bound.[30]

Because both hypothyroidism and subclinical hypothyroidism are more common in patients with CKD, it is unclear whether treatment of patients with these conditions benefits kidney function. The benefit of treatment of subclinical hypothyroidism in general is widely debated in various clinical contexts. Historically, thyroid hormone deficiency was thought to be an adaptation to CKD, in that it allowed the body to conserve metabolism in catabolic renal patients.[31] However, more recent studies implicate an association between hypothyroidism and increased mortality in dialysis patients.[32] Some observational studies have shown that treatment with thyroid hormone replacement decreased CKD progression.[33] However, treatment with thyroid hormone does have a narrow therapeutic window. Overtreatment causing thyrotoxicosis could easily exacerbate protein catabolism, loss of bone mineral density, and increased risk of arrhythmia in an already vulnerable CKD patient population. Therefore, randomized trials evaluating the effect of thyroid hormone replacement in CKD patients are needed.

CORTISOL ABNORMALITIES IN CKD

The metabolism of adrenal hormones is also affected in CKD, although these abnormalities do not appear to be mediated through the HP axis. Kidneys metabolize cortisol and its metabolites, which are water soluble. The kidney is an important site of the conversion of active to inactive cortisol *via* 11-ß hydroxysteroid dehydrogenase type 2 (11-ßHSD2), which prevents unrestrained activation of the mineralocorticoid receptor by cortisol. In CKD, 11-ßHSD2 activity is reduced, and thus the half-life of cortisol is extended.[34] Free cortisol levels in plasma are disproportionately higher than total cortisol levels in patients with CKD, suggesting less binding of the hormone to albumin[35] and corticosteroid-binding globulin.

Higher levels of cortisol may be responsible for loss of bone density with resulting osteopenia or osteoporosis, redistribution of fat, and increased catabolism of protein

in CKD patients.[36] In addition, prehemodialysis patients with higher levels of cortisol were at higher risk of hospitalizations and malnutrition.[37] Because baseline levels of cortisol are higher in patients with CKD, it is reasonable to assume that evaluation of adrenal function may be affected in such patients. Cosyntropin stimulation testing with 1, 5, or 250 mcg of cosyntropin is normal in patients with CKD, as the diurnal variation in cortisol release is preserved.[38]

Testing for adrenal hyperfunction (hypercortisolism) is not reliable in patients with CKD. Therefore, the diagnosis of Cushing syndrome in patients with CKD is challenging. In patients without CKD, screening for hypercortisolism may be performed using urine, saliva, or serum. However, because urinary free cortisol (UFC) reflects glomerular filtration, 24-hour values are significantly lower in patients with CKD. Therefore, 24-hour urine collections for UFC levels are not reliable in CKD, as a falsely low UFC level can occur even at a GFR of 60 mL/min/1.73 m^2.[39] Although studies have shown preserved salivary cortisol levels in CKD patients,[40] midnight salivary cortisol tests to evaluate possible Cushing syndrome have not been validated in this population. Dexamethasone suppression with serum cortisol testing may be helpful in diagnosing hypercortisolism in patients with CKD, but it may require higher doses of dexamethasone to suppress the patients' cortisol level.[41]

Exogenous steroid metabolism is also altered in patients with CKD. Plasma protein binding of both dexamethasone and prednisolone is reduced. Dexamethasone clearance is increased, whereas prednisolone has decreased clearance. Although there are no adjustments provided in the drug labeling, attention should be paid to diminished dexamethasone or enhanced prednisolone clinical efficacy and adverse effects in CKD patients. The clearance of methylprednisolone is unchanged in patients with CKD.[42]

ADIPOSE TISSUE AND CKD

Adipose tissue is recognized as an endocrine organ, due to its production of a variety of biologically active substances, adipokines, which function as classically circulating hormones. Several adipokines have abnormal levels in patients with CKD, with varying clinical effects. Adiponectin is the most plentiful adipokine in the human circulation, acting as a cardioprotective protein, improving insulin sensitivity, and protecting the vascular system by suppressing the production of reactive oxygen species.[43] Despite the cardioprotective effects of adiponectin, however, elevated levels are a marker of increased mortality in patients with stage 3 and 4 CKD.[44] The mechanism underlying this association is unknown.

Leptin is also produced in adipocytes, and leptin levels are elevated in patients with CKD.[45] High levels of leptin are associated with vascular dysfunction and CV disease *via* reactive oxygen species and nitric oxide metabolites.[46] Furthermore, incomplete clearance of leptin by the kidneys leads to accumulation of proinflammatory cytokines, which may enhance renal damage.

Resistin is an adipokine that is increased in patients with CKD, principally due to reduced renal clearance. Resistin is found in the visceral adipose tissue—resident macrophages and is associated with inflammation, insulin resistance, and endothelial damage.[47] Serum levels of resistin are negatively associated with GFR.[48] Resistin promotes the expression of adhesion molecules, endothelin, and matrix metalloproteinases, leading to systemic vascular dysfunction.[49] High resistin levels were an independent risk factor for mortality in patients treated with hemodialysis.[50]

GROWTH HORMONE AXIS IN CKD

The growth hormone (GH) axis regulates the release of insulin-like growth factor (IGF), and is important in kidney development and disease.[51,52] Secretion of GH from the anterior pituitary is stimulated by GH-releasing hormone (GHRH) and inhibited by GH inhibiting hormone (GHIH, or somatostatin), which are then regulated *via* negative feedback from circulating GH. This axis affects renal plasma flow and sodium retention and volume expansion, through multiple mechanisms, likely through stimulation of the renin—angiotensin—aldosterone system. IGF-1 also plays a critical role in childhood growth and has anabolic effects in adults. GH deficient patients have been shown to have decreased total body water and extracellular volume, which corrects when they are treated with GH replacement. Similarly, patients with acromegaly and elevated GH levels have been found to have increased extracellular volume that normalizes after surgical removal of the GH-producing adenoma.[53]

Many derangements in the GH axis occur in CKD. Plasma GH levels may be normal or elevated in individuals with CKD. However, as in the case with gonadotropins, there is evidence of GH resistance at target organ sites. Children with CKD show growth retardation, and adults exhibit accelerated protein catabolism and protein malnutrition as a result of this resistance,[51] which is likely in part related to increased levels of circulating insulin-like growth factor binding proteins (IGFBPs) as well as impaired GH signal transduction through the JAK-STAT pathway.[54] In the setting of

CKD, production of IGFBPs in the liver is increased, and renal clearance of IGFBPs is diminished, leading to increased circulating levels. Given that insulin-like growth factor-1 (IGF-1) has a higher affinity for IGFBP than the IGF-1 receptor, high levels of IGFBP lead to decreased bioavailability of IGF-1.[55]

These effects are a particularly important clinical issue in children with CKD, where exogenous recombinant GH therapy should be considered for patients with eGFR <75 mL/min/1.73 m^2 and height in the third percentile, in whom other factors for poor growth including metabolic acidosis, hypothyroidism, and malnutrition have been excluded.[56]

CONCLUSION

Abnormalities in the HP axis, as well as altered target organ effects, are common as kidney function declines. Decreased clearance, changes in transport and metabolism, abnormal end-organ responses, and alterations in feedback mechanisms all play a role in the development of endocrinopathies, with both laboratory and clinical manifestations. Endocrine disorders also comprise many of the manifestations of the uremic syndrome, including protein calorie malnutrition, sexual dysfunction, and menstrual abnormalities. Clinicians caring for patients with CKD must be aware of these effects, as well as the increased prevalence of endocrine disorders in these patients. More research is needed to determine the optimal treatment of endocrine disorders in this population.

References

1. Iglesias P, Carrero JJ, Diez JJ. Gonadal dysfunction in men with chronic kidney disease: clinical features, prognostic implications and therapeutic options. *J Nephrol* 2012;**25**(1):31–42.
2. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an endocrine Society clinical Practice Guideline. *J Clin Endocrinol Metab* 2018;**103**(5):1715–44.
3. Carrero JJ, Stenvinkel P. The vulnerable man: impact of testosterone deficiency on the uraemic phenotype. *Nephrol Dial Transplant* 2012; **27**(11):4030–41.
4. Yilmaz MI, Sonmez A, Qureshi AR, et al. Endogenous testosterone, endothelial dysfunction, and cardiovascular events in men with nondialysis chronic kidney disease. *Clin J Am Soc Nephrol* 2011; **6**(7):1617–25.
5. Doumouchtsis KK, Perrea DN, Doumouchtsis SK. The impact of sex hormone changes on bone mineral deficit in chronic renal failure. *Endocr Res* 2009;**34**(3):90–9.
6. Bao Y, Johansen KL. Diagnosis and treatment of low testosterone among patients with end-stage renal disease. *Semin Dial* 2015; **28**(3):259–65.
7. Cochrane R, Regan L. Undetected gynaecological disorders in women with renal disease. *Hum Reprod* 1997;**12**(4):667–70.
8. Sievertsen GD, Lim VS, Nakawatase C, Frohman LA. Metabolic clearance and secretion rates of human prolactin in normal subjects and in patients with chronic renal failure. *J Clin Endocrinol Metab* 1980;**50**(5):846–52.
9. Lim VS, Henriquez C, Sievertsen G, Frohman LA. Ovarian function in chronic renal failure: evidence suggesting hypothalamic anovulation. *Ann Intern Med* 1980;**93**(1):21–7.
10. Naves Diaz M, Rodriguez Rodriguez A, Fernandez Martin JL, Serrano Arias M, Menendez Rodriguez P, Cannata Andia JB. Effects of estradiol, calcitriol and both treatments combined on bone histomorphometry in rats with chronic kidney disease and ovariectomy. *Bone* 2007;**41**(4):614–9.
11. Ishani A, Blackwell T, Jamal SA, Cummings SR, Ensrud KE, Investigators M. The effect of raloxifene treatment in postmenopausal women with CKD. *J Am Soc Nephrol* 2008;**19**(7):1430–8.
12. Carrero JJ, de Jager DJ, Verduijn M, et al. Cardiovascular and noncardiovascular mortality among men and women starting dialysis. *Clin J Am Soc Nephrol* 2011;**6**(7):1722–30.
13. Carrero JJ, Kyriazis J, Sonmez A, et al. Prolactin levels, endothelial dysfunction, and the risk of cardiovascular events and mortality in patients with CKD. *Clin J Am Soc Nephrol* 2012;**7**(2):207–15.
14. Mejia-Rodriguez O, Herrera-Abarca JE, Ceballos-Reyes G, et al. Cardiovascular and renal effects of bromocriptine in diabetic patients with stage 4 chronic kidney disease. *BioMed Res Int* 2013; **2013**:104059.
15. Mariani LH, Berns JS. The renal manifestations of thyroid disease. *J Am Soc Nephrol* 2012;**23**(1):22–6.
16. Gheissari A, Hashemipour M, Khosravi P, Adibi A. Different aspects of kidney function in well-controlled congenital hypothyroidism. *J Clin Res Pediatr Endocrinol* 2012;**4**(4):193–8.
17. Li X, Misik AJ, Rieder CV, Solaro RJ, Lowen A, Fliegel L. Thyroid hormone receptor alpha 1 regulates expression of the Na+/H+ exchanger (NHE1). *J Biol Chem* 2002;**277**(32):28656–62.
18. Schmitt R, Klussmann E, Kahl T, Ellison DH, Bachmann S. Renal expression of sodium transporters and aquaporin-2 in hypothyroid rats. *Am J Physiol Renal Physiol* 2003;**284**(5):F1097–104.
19. Michael UF, Barenberg RL, Chavez R, Vaamonde CA, Papper S. Renal handling of sodium and water in the hypothyroid rat. Clearance and micropuncture studies. *J Clin Investig* 1972;**51**(6): 1405–12.
20. Wang W, Li C, Summer SN, Falk S, Schrier RW. Polyuria of thyrotoxicosis: downregulation of aquaporin water channels and increased solute excretion. *Kidney Int* 2007;**72**(9):1088–94.
21. Song SH, Kwak IS, Lee DW, Kang YH, Seong EY, Park JS. The prevalence of low triiodothyronine according to the stage of chronic kidney disease in subjects with a normal thyroid-stimulating hormone. *Nephrol Dial Transplant* 2009;**24**(5):1534–8.
22. Meuwese CL, Dekkers OM, Stenvinkel P, Dekker FW, Carrero JJ. Nonthyroidal illness and the cardiorenal syndrome. *Nat Rev Nephrol* 2013;**9**(10):599–609.
23. Langton JE, Brent GA. Nonthyroidal illness syndrome: evaluation of thyroid function in sick patients. *Endocrinol Metab Clin N Am* 2002;**31**(1):159–72.
24. Soldin O. Measuring serum thyroid-stimulating hormone, thyroid hormones, thyroid-directed antibodies and transport proteins. In: Wilkens LW, editor. *Werner and Ingbar's the thyroid*; 2013. p. 279–97.
25. Lo JC, Chertow GM, Go AS, Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. *Kidney Int* 2005;**67**(3):1047–52.

26. Chonchol M, Lippi G, Salvagno G, Zoppini G, Muggeo M, Targher G. Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2008;**3**(5):1296–300.
27. Rhee CM, Kalantar-Zadeh K, Streja E, et al. The relationship between thyroid function and estimated glomerular filtration rate in patients with chronic kidney disease. *Nephrol Dial Transplant* 2015;**30**(2):282–7.
28. Takeda S, Michigishi T, Takazakura E. Iodine-induced hypothyroidism in patients on regular dialysis treatment. *Nephron* 1993; **65**(1):51–5.
29. Sanai T, Inoue T, Okamura K, et al. Reversible primary hypothyroidism in Japanese patients undergoing maintenance hemodialysis. *Clin Nephrol* 2008;**69**(2):107–13.
30. Feinstein EI, Kaptein EM, Nicoloff JT, Massry SG. Thyroid function in patients with nephrotic syndrome and normal renal function. *Am J Nephrol* 1982;**2**(2):70–6.
31. Lim VS. Thyroid function in patients with chronic renal failure. *Am J Kidney Dis* 2001;**38**(4 Suppl. 1):S80–4.
32. Rhee CM, Alexander EK, Bhan I, Brunelli SM. Hypothyroidism and mortality among dialysis patients. *Clin J Am Soc Nephrol* 2013;**8**(4):593–601.
33. Shin DH, Lee MJ, Kim SJ, et al. Preservation of renal function by thyroid hormone replacement therapy in chronic kidney disease patients with subclinical hypothyroidism. *J Clin Endocrinol Metab* 2012;**97**(8):2732–40.
34. Quinkler M, Zehnder D, Lepenies J, et al. Expression of renal 11beta-hydroxysteroid dehydrogenase type 2 is decreased in patients with impaired renal function. *Eur J Endocrinol* 2005; **153**(2):291–9.
35. Rosman PM, Benn R, Kay M, Wallace EZ. Cortisol binding in uremic plasma. II. Decreased cortisol binding to albumin. *Nephron* 1984;**37**(4):229–31.
36. Niemczyk S, Niemczyk L, Romejko-Ciepielewska K. Basic endocrinological disorders in chronic renal failure. *Endokrynol Pol* 2012; **63**(3):250–7.
37. Himmelfarb J, Holbrook D, McMonagle E, Robinson R, Nye L, Spratt D. Kt/V, nutritional parameters, serum cortisol, and insulin growth factor-1 levels and patient outcome in hemodialysis. *Am J Kidney Dis* 1994;**24**(3):473–9.
38. Ramirez G. Endocrine and metabolic function in renal failure: abnormalities in teh hypothalamic-hypophyseal axes in patients with chronic renal failure. *Semin Dial* 1994;**7**(2):138–46.
39. Kidambi S, Raff H, Findling JW. Limitations of nocturnal salivary cortisol and urine free cortisol in the diagnosis of mild Cushing's syndrome. *Eur J Endocrinol* 2007;**157**(6):725–31.
40. Cardoso EM, Arregger AL, Budd D, Zucchini AE, Contreras LN. Dynamics of salivary cortisol in chronic kidney disease patients at stages 1 through 4. *Clin Endocrinol* 2016;**85**(2):313–9.
41. Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an endocrine Society clinical Practice Guideline. *J Clin Endocrinol Metab* 2008;**93**(5):1526–40.
42. Jusko WJ, Milad MA, Ludwig EA, Lew KH, Kohli RK. Methylprednisolone pharmacokinetics and pharmacodynamics in chronic renal failure. *Clin Nephrol* 1995;**43**(Suppl. 1):S16–9.
43. Sharma K, Ramachandrarao S, Qiu G, et al. Adiponectin regulates albuminuria and podocyte function in mice. *J Clin Investig* 2008; **118**(5):1645–56.
44. Menon V, Li L, Wang X, et al. Adiponectin and mortality in patients with chronic kidney disease. *J Am Soc Nephrol* 2006;**17**(9): 2599–606.
45. Ruster C, Wolf G. Adipokines promote chronic kidney disease. *Nephrol Dial Transplant* 2013;**28**(Suppl. 4):iv8–14.
46. Beltowski J, Jamroz-Wisniewska A, Wojcicka G, Lowicka E, Wojtak A. Renal antioxidant enzymes and glutathione redox status in leptin-induced hypertension. *Mol Cell Biochem* 2008;**319**(1–2): 163–74.
47. Steppan CM, Bailey ST, Bhat S, et al. The hormone resistin links obesity to diabetes. *Nature* 2001;**409**(6818):307–12.
48. Axelsson J, Bergsten A, Qureshi AR, et al. Elevated resistin levels in chronic kidney disease are associated with decreased glomerular filtration rate and inflammation, but not with insulin resistance. *Kidney Int* 2006;**69**(3):596–604.
49. Dimitriadis K, Tsioufis C, Selima M, et al. Independent association of circulating resistin with glomerular filtration rate in the early stages of essential hypertension. *J Hum Hypertens* 2009;**23**(10): 668–73.
50. Chi PJ, Liou HH, Hsu BG, Tasi JP. Relationship between resistin and mortality in maintenance hemodialysis patients. *Clin Nephrol* 2016;**86**(9):125–31.
51. Zha Y, Qian Q. Protein nutrition and malnutrition in CKD and ESRD. *Nutrients* 2017;**9**(3).
52. Sun DF, Zheng Z, Tummala P, Oh J, Schaefer F, Rabkin R. Chronic uremia attenuates growth hormone-induced signal transduction in skeletal muscle. *J Am Soc Nephrol* 2004;**15**(10):2630–6.
53. Moller J. Effects of growth hormone on fluid homeostasis. Clinical and experimental aspects. *Growth Hormone IGF Res* 2003;**13**(2–3): 55–74.
54. Schaefer F, Chen Y, Tsao T, Nouri P, Rabkin R. Impaired JAK-STAT signal transduction contributes to growth hormone resistance in chronic uremia. *J Clin Investig* 2001;**108**(3):467–75.
55. Roelfsema V, Lane MH, Clark RG. Insulin-like growth factor binding protein (IGFBP) displacers: relevance to the treatment of renal disease. *Pediatr Nephrol* 2000;**14**(7):584–8.
56. Mahan JD, Warady BA, Consensus C. Assessment and treatment of short stature in pediatric patients with chronic kidney disease: a consensus statement. *Pediatr Nephrol* 2006;**21**(7):917–30.

QUESTIONS AND ANSWERS

Question 1

Which of the following is a cause of infertility in men with CKD?

A. Low GnRH levels
B. Decreased FSH levels resulting in low testosterone
C. Elevated levels of gonadotropins (FSH and LH) resulting in high testosterone (hypergonadism)
D. Hyperprolactinemia resulting in loss of pulsatile release of GnRH and resistance to gonadotropins
E. Decreased pulsatile release of GnRH resulting in low gonadotropin and testosterone levels

Answer: D

CKD results in hyperprolactinemia, which inhibits the pulsatile release of GnRH as well as causing resistance to the gonadotropin hormones themselves. GnRH and gonadotropin levels are increased, not decreased, in CKD, therefore A, B, and E are not correct. Although FSH and LH are increased in CKD, testosterone levels are low (hypergonadotropic hypogonadism), likely due to resistance to the gonadotropins, therefore C is not correct.

Question 2

Which of the following is TRUE regarding women with CKD?

A. Hypoprolactinemia causes ovarian dysfunction women with CKD
B. Hypoestrogenemia may explain the increased risk of CV disease in women with CKD compared to women without CKD
C. Hypoestrogenemia has not been shown to increase the risk of bone disease in women with CKD
D. Bromocriptine, a dopamine agonist, has been shown to restore gonadotropin response in women with CKD
E. Hyperprolactinemia is common but is not associated with worse outcomes or infertility

Answer: B

In the general population, premenopausal women have a lower risk of CV disease compared to men. However, this difference is not seen in women with CKD, possibly due to hypoestrogenemia. Women with CKD tend to have hyperprolactinemia, rather than hypoprolactinemia, from both reduced renal clearance, as well as upregulation of hormone production due to CKD-related inhibition of dopaminergic activity in the pituitary gland, therefore A is not correct. Hypoestrogenemia is also a well-known risk factor for bone disease in women with CKD, therefore C is not correct. Bromocriptine (a dopamine agonist) lowers prolactin levels but does not restore gonadotropin response, suggesting that hyperprolactinemia is not the sole cause of ovarian dysfunction in women with CKD. Therefore, D is not correct. Finally, hyperprolactinemia is associated with both infertility and CV risk in women (E).

Question 3

Thyroid hormones have been found to have all of the following effects on the kidney EXCEPT:

A. Decreased renal blood flow
B. Upregulation of renin–angiotensin–aldosterone system
C. Increased sodium reabsorption
D. Increased water and solute clearance
E. Increased GFR

Answer: A

Thyroid hormones have both direct renal and indirect CV effects, resulting in increased GFR, sodium retention, water and solute clearance, and upregulation of the renin–angiotensin–aldosterone system, therefore B, C, D, and E are all true. Renal blood flow is increased, not decreased, by thyroid hormones through these mechanisms, therefore the correct answer is A.

Question 4

Which of the following is TRUE regarding thyroid function and patients with CKD?

A. Thyroid function tests can be interpreted the same way in patients with CKD as patients without CKD
B. Hypothyroidism is less prevalent in the CKD population than the general population
C. Thyroid replacement in patients with CKD and hypothyroidism have been shown to be efficacious in decreasing CKD progression in randomized clinical trials
D. CKD may increase risk of thyroid disease through iodine retention and urinary protein loss
E. Hypothyroidism is not associated with increased mortality in patients with CKD

Answer: D

Reduced iodine clearance as well as urinary protein loss of thyroid hormone may both contribute to the development of thyroid dysfunction due to CKD (Answer D). Thyroid function tests must be interpreted in caution in patients with CKD, as the typical analog assays of free T4 depend on protein binding and may not be reliable when circulating proteins levels are abnormal or in the presence of uremic toxins that inhibit protein binding, therefore A is not correct.

Hypothyroidism is more prevalent, not less prevalent, in CKD compared to the general population, and is associated with increased mortality, therefore B and E are not correct. Finally, although observational studies have shown that treatment with thyroid hormone replacement decreased CKD progression, randomized trials are lacking (therefore, answer C is not correct).

Question 5

All of the following statements are true regarding cortisol and CKD EXCEPT:

A. Cortisol levels are higher in patients with CKD due to decreased metabolism and increased half-life
B. Cortisol binding to albumin and corticosteroid binding globulin is altered in CKD, resulting in disproportionately higher free cortisol levels
C. Testing for Cushing syndrome in patients with CKD can be performed accurately using urine, saliva, or serum levels
D. Dexamethasone suppression tests may require higher doses of dexamethasone to suppress cortisol levels in patients with CKD
E. Clinical efficacy and adverse effects should be evaluated carefully in patients with CKD receiving exogenous steroids given the difference in clearance

Answer: C

Testing for Cushing syndrome in patients with CKD is challenging, as UFC may be falsely low due to decreased clearance and dexamethasone suppression testing may require higher doses, therefore C is the correct answer. Answers A, B, D, and E are all true statements.

Question 6

All of the following statements are true about hormone disorders in CKD EXCEPT:

A. Elevated adiponectin levels are associated with increased mortality
B. Circulating levels of growth hormone levels may be elevated in CKD, but there is impaired GH signal transduction *via* the JAK−STAT pathway
C. Children with GH deficiency and CKD should not be treated with GH
D. Resistin is elevated in CKD and is associated with insulin resistance, inflammation, and endothelial damage
E. Growth hormone has a role in renal function in adults as well as children with CKD

Answer: C

Growth hormone deficiency is particularly relevant in children with CKD, who should be considered for GH replacement therapy when other modifiable factors for short stature have been optimized, therefore C is the correct answer. Although treatment with GH is not indicated in adults with CKD, it does play a role in renal plasma flow and sodium retention, therefore answer E is a true statement. Answers A and D are also true statements.

CHAPTER

35

Chronic Kidney Disease–Mineral and Bone Disorders

Keith A. Hruska[a,b], *Matthew J. Williams*[a], *Toshifumi Sugatani*[a]

[a]Division of Pediatric Nephrology, Department of Pediatrics, Washington University, St. Louis, MO, United States;
[b]Departments of Medicine and Cell Biology, Washington University, St. Louis, MO, United States

Abstract

The disruption of a multiorgan systems biology produced by renal injury in early stages of kidney injury and disease was unrecognized until its elucidation during the investigation of the chronic kidney disease–mineral bone disorder (CKD-MBD). The disordered systems biology causes the CKD-MBD and contributes major components of increased cardiovascular risk for CKD patients. The outcome of the syndrome, in addition to previously recognized renal osteodystrophy (ROD), is increased cardiovascular mortality in CKD patients. The inception of the CKD-MBD was only recently realized to be with the early effects of kidney disease. Its pathophysiology involves circulating factors produced by renal repair and newly discovered hormones, such as fibroblast growth factor 23 (FGF-23) and cleaved klotho. Progressing from its inception, the disruption of the multiorgan system leads to the pathophysiology previously recognized as secondary hyperparathyroidism, hyperphosphatemia, calcitriol deficiency, and ROD that are now incorporated into the CKD-MBD syndrome, along with vascular disease (especially calcification) and cardiac disease (especially hypertrophy and heart failure). The new pathophysiology brings attention to extreme need for advances in treatment of the CKD-MBD, which is currently focused on the late components of the syndrome, and which have been shown in clinical trials not to affect the mortality associated with the syndrome.

INTRODUCTION

In 2006, the disorders of mineral and bone metabolism in CKD were enshrined in a new syndrome called the chronic kidney disease–mineral bone disorder (CKD-MBD). The CKD-MBD name was coined by the Kidney Disease: Improving Global Outcomes (KDIGO) foundation[1,2] for the syndrome associated with CKD in which disorders of mineral metabolism and renal osteodystrophy (ROD) are key contributors to excess mortality.[3–6] The pandemic of CKD and end-stage renal disease (ESRD) and the role of the CKD-MBD in the associated mortality make the syndrome a major health issue for Americans and all developed societies.[5,7–10] Recent advances define the CKD-MBD as a uniform complication of renal injury with wide variation in severity. The syndrome begins with renal injury early in CKD and contributes to the high mortality rates associated with CKD.[11] This chapter reviews recent pathophysiologic advances in the CKD-MBD and the classic pathophysiology of secondary hyperparathyroidism and ROD of CKD that have been incorporated into the syndrome. The result is the new understanding of a disordered systems biology involving the kidney, vasculature, heart, skeleton, and parathyroid glands, in CKD, contributing mortality risk beyond that due to kidney disease itself (Figure 35.1).[12]

PATHOBIOLOGY

Vascular

Abnormalities of the vasculature found in early CKD produce vascular stiffness and contribute to the development of left ventricular hypertrophy (LVH).[13,14] In addition, studies show that osteoblastic transition in arterial walls during early CKD progresses to vascular calcification,[15,16] a common phenomenon in the aging population that is accelerated in CKD to the highest level seen in clinical medicine. Vascular calcification further intensifies stiffness and development of LVH, all processes that contribute to cardiovascular risk and excess cardiac mortality. However, CKD directly

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00035-8

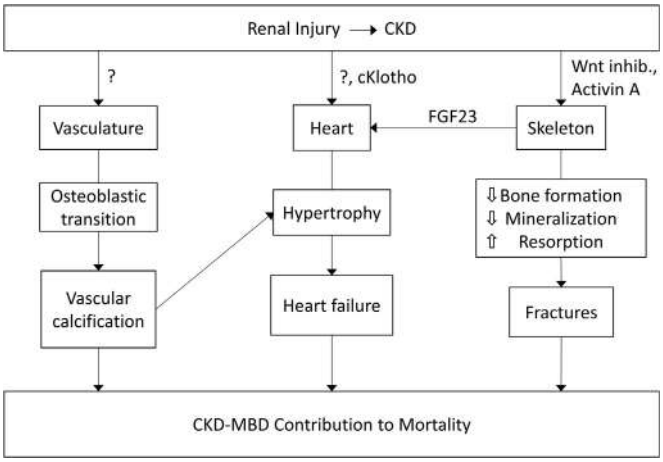


FIGURE 35.1 The disordered systems biology of the CKD-MBD. A multiorgan systems biology "wired" together in part by circulating communications is disordered in CKD. Renal injury increases circulating levels of factors affecting multiple organs peripheral to the kidneys. Key among these is the vasculature, affected very early in kidney disease by osteoblastic transition of cells in vessel walls. The heart's cardiomyocytes undergo hypertrophy due to a multitude of factors, including (1) unknown in nature and reductions in cKlotho; (2) due to vascular stiffness produced in part by vascular calcification; and (3) by high levels of FGF-23 acting through FGFR4.[89] The skeleton is immediately impacted during attempted renal repair by inhibitors of bone formation such as Dickkopf-1 and other Wnt inhibitors. The effects of peripheral organ damage lead to secondary pathologies of vascular calcification, cardiac hypertrophy, and renal osteodystrophy, culminating in the contributions of the CKD-MBD to the exaggerated mortality of CKD. *CKD-MBD*, chronic kidney disease—mineral bone disorder; *FGF-23*, fibroblast growth factor 23.

stimulates cardiac hypertrophy independent of arterial stiffness, further contributing to mortality.[17]

The pathogenesis of vascular calcification in CKD is complex.[18] Pathologically vascular calcification includes two types: neointimal and arterial medial. The pathogenesis of atherosclerotic neointimal calcification is multifactorial, but it involves activation of an osteoblastic differentiation program in cells of the neointima of atherosclerotic plaques and in cells of the arterial media.[19–22] Diffuse calcification of the arterial tunica media is referred to as Mönckeberg's sclerosis.[23] CKD is the most common cause of Mönckeberg's sclerosis, especially when it complicates diabetes mellitus. In translational models of atherosclerosis and diabetes (*ldlr−/−* with high fat feeding) mild renal insufficiency (equivalent to human stage 2 CKD) reduces the levels of aortic proteins involved in the contractile apparatus of smooth muscle.[15] This, coupled with evidence that vascular smooth muscle cells move into a dedifferentiated synthetic state from their normal contractile differentiated state,[24] represents significant evidence of large artery smooth muscle dedifferentiation in very early diabetic CKD.[25] Within the developmental program of mesenchymal stem cells and early progenitor cells, dedifferentiated vascular smooth muscle cells are susceptible to transition to the differentiation program of osteoblasts, which causes vascular calcification in CKD.[23,26] Osteoblastic transition of cells in the arterial walls produces CKD-stimulated calcification of atherosclerotic plaques and the vascular media.[16,19,23,27–29] The source of these cells may be mesenchymal progenitors from the adventitia moving into the media and expressing both smooth muscle and osteoblastic transcriptional programs,[30] although other lineage tracing studies support the role of vascular smooth muscle cells.[22,31]

Cardiac

Cardiac hypertrophy is highly prevalent in CKD patients. We found in a cohort of patients with CKD stage 3 from a single center clinic and a mean estimated glomerular filtration rate (eGFR) of 50 mL/min/1.73 m^2, an 80% incidence of LVH by CT scanning.[32] This is in concert with the results of larger population studies.[7,17] Cardiac hypertrophy is an early stage of cardiovascular disease leading to high rates of heart failure, sudden death, and even ischemic myocardial infarction.[7] The causes of cardiac hypertrophy in CKD are multifactorial, including vascular stiffness, fibroblast growth factor 23 (FGF-23),[33] and decreased αklotho—all components of the CKD-MBD (Figure 35.2). Vascular stiffness is a result of vascular calcification. The high levels of FGF-23 causing cardiomyocyte hypertrophy are also late in CKD compared with the early elevations in FGF-23.[34] We have found a new and novel cause of cardiac hypertrophy in our studies of activin receptor stimulation in CKD.[16,35] In three models of CKD in mice, cardiac hypertrophy develops during CKD, with reductions in GFR equivalent to human CKD stage 3. Inhibition of activin receptor type 2A prevents cardiac hypertrophy despite not affecting FGF-23 levels or fully restoring αklotho.[16,35] The mechanism of this effect will introduce a new therapeutic target for cardiovascular disease in CKD and the CKD-MBD.

Skeletal

Abnormalities of bone in the CKD-MBD begin with the renal response to injury due to activation of Wingless/Integration 1 (Wnt, a portmanteau of Wg and int) pathways in the kidney.[36,37] Canonical Wnt signaling transcriptionally stimulates production of multiple Wnt inhibitors which are secreted systemic factors.[38,39] As a result, kidney injury directly inhibits bone remodeling which is homeostatically Wnt dependent (Figure 35.2).[40–42] Skeletal inhibition of Beta catenin signaling and increased expression of osteocytic FGF-23

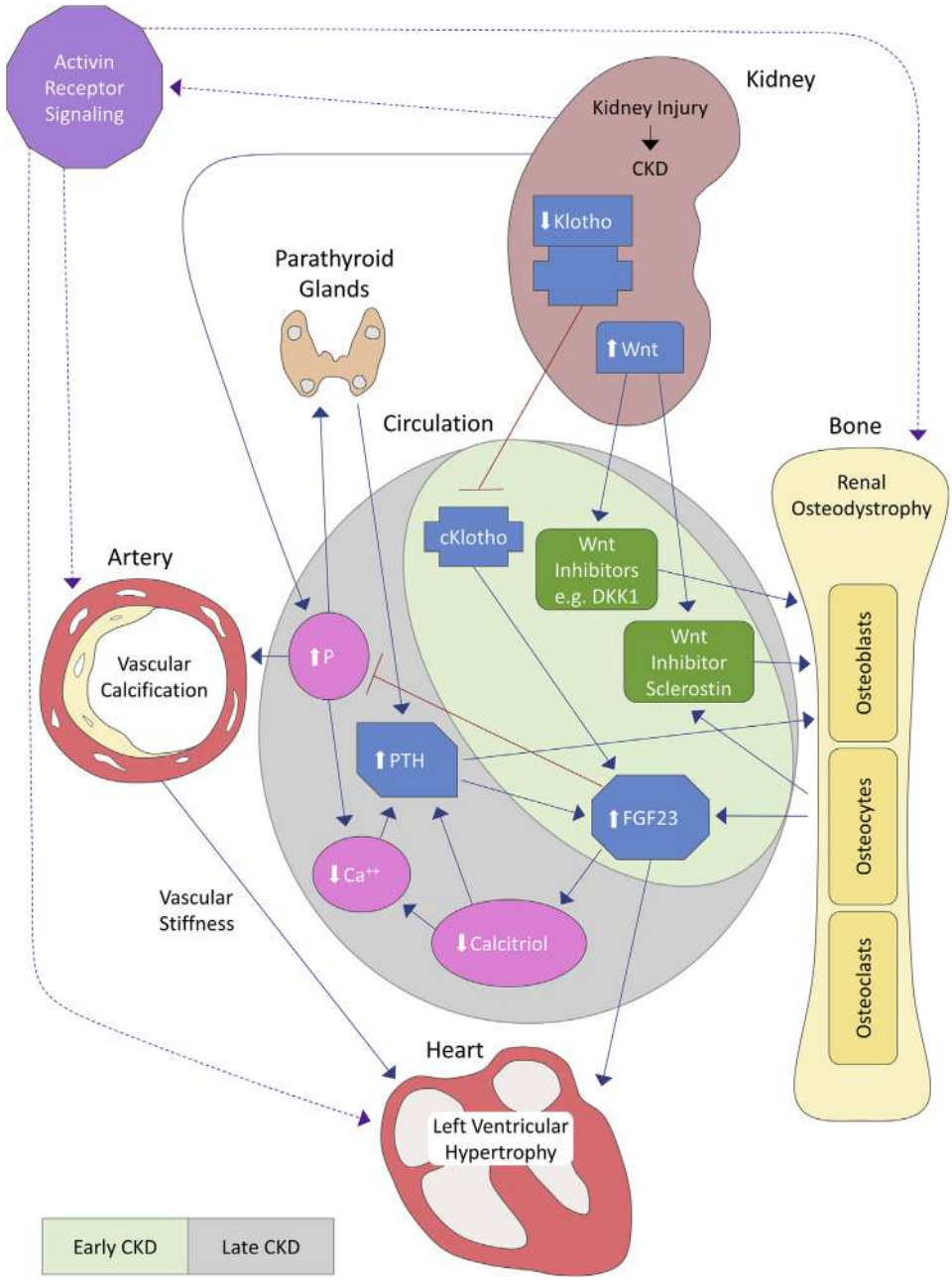


FIGURE 35.2 The disordered systems biology of the CKD-MBD. A multiorgan systems biology "wired" together in part by circulating communications is disordered in CKD. Kidney injury (*early CKD*) leading to CKD increases levels of some factors reaching the circulation, such as the Wnt inhibitor family, and decreases others, such a αklotho. Renal αklotho is a transmembrane protein, whose extracellular domain is cleaved by ADAMS 10 and 17,[80] producing circulating klotho (cklotho), whose hormonal functions include regulation of FGF-23 secretion by skeletal osteocytes.[79,80] The decrease in αklotho produced by renal injury immediately disorders regulation of FGF-23 secretion. The increased FGF-23 affects proximal tubular phosphate excretion and calcitriol production through activation of FGFR1C through the coreceptor function of αklotho.[185,186] The loss of klotho disorders phosphate excretion[100,187] leading to the development of hyperphosphatemia, calcitriol deficiency, hypocalcemia, and hyperparathyroidism as kidney disease progresses. Hyperphosphatemia stimulates vascular calcification already in progress from osteoblastic transition.[107,188] CKD activation of activin receptor signaling systemically contributes to vascular calcification, decreased bone formation, increased bone resorption, and cardiac hypertrophy, without affecting FGF-23 but increasing αklotho.[16,35,47] *CKD-MBD*, chronic kidney disease—mineral bone disorder; *FGF-23*, fibroblast growth factor 23.

are seen after a relatively mild reduction in the GFR, at stage 2 CKD.[43–45] These abnormalities affect cortical bone predominately in early CKD and progress to decreased cortical bone volume and porosity.[15] Abnormalities of remodeling, mineralization, and the material properties of bone develop in CKD, leading to major decreases in structural strength, fractures, and deformity associated with long-term disease (Figure 35.1).[46]

Recent studies demonstrate the progressive development of a remodeling imbalance during CKD due to stimulation of osteoclast number and function, and a relative decrease in osteoblast function in view of increased osteoblast number that fails to increase bone formation as expected.[16,47] This is fueled by hyperparathyroidism in collaboration with activin/activin receptor type II signaling (Figure 35.2).[16] The progression of the skeletal remodeling disorder in CKD to the familiar high-turnover state related to hyperparathyroidism begins from a low-turnover state produced by CKD-induced Wnt inhibition in early CKD.[39,44,45]

Plasma

In early CKD, before detectable changes in the S[P], S[Ca], or calcitriol levels, elevated FGF-23 and sclerostin levels largely from osteocytes (although the diseased kidney produces sclerostin[48]) and elevated parathyroid hormone (PTH) levels are observed[49–51] The early increase in FGF-23 in CKD[43,49] makes it a powerful biomarker, indicating that renal injury has affected osteocyte function and secretion.[43] If the hyperparathyroidism of early CKD is prevented, the prevalence of a low-turnover osteodystrophy (the adynamic bone disorder (ABD)) increases, further demonstrating the effects of kidney injury on the skeleton.[52] By the time ESRD develops, skeletal pathology is nearly universally present.[53]

PATHOGENESIS

Renal injuries produce circulating signals that affect the vasculature, the skeleton, and the myocardium. The skeleton is affected in at least two ways. One produces changes in remodeling and material properties. The second causes changes in the secretory properties of skeletal osteocytes (Figure 35.1). Renal injury and disease produce reactivation of developmental programs of nephrogenesis in an attempt at kidney repair. These programs are generally silent in the normal adult human kidney. The best studied example is the reactivation of the Wnt pathway[54,55] that controls tubular epithelial differentiation, proliferation, and polarity during nephrogenesis[56–60] and is a driving force in renal fibrosis in disease.[61–63] In the canonical Wnt signaling pathway, the transcriptional targets include a complex family of inhibitory proteins,[64] the Wnt inhibitors, including Dickkopf,[65] soluble frizzled-related proteins, and sclerostin.[48] Although Wnts are strictly autocrine/paracrine factors,[66] the Wnt inhibitors are secreted/circulating proteins.[67] The role of Wnt in renal development largely precedes the invasion of the microcirculation forming the glomerulus and the peritubular capillaries. Thus, the Wnt inhibitors were not designed as circulating humoral substances produced by the normal kidney. Their release into the circulation during kidney injury/repair represents a systemic pathologic insult inhibiting the physiologic roles of Wnt in the rest of the body. So far, this has been shown to have major consequences in the vasculature and the skeleton.[39,45,68]

The role of the Wnt inhibitor families in vascular function during early kidney disease was recently demonstrated by finding significantly increased renal expression of Wnt inhibitors in the injured kidney,[39,54] their increased presence in the circulation,[39] and the inhibition of one, Dickkopf 1 (Dkk1), by a monoclonal antibody.[39] Dkk1 neutralization was sufficient to decrease the CKD-stimulated dedifferentiation of the vasculature. Dedifferentiation was shown by decreased expression levels of proteins involved in smooth muscle contraction. Dkk1 neutralization increased smooth muscle contractile protein levels and inhibited osteoblastic transition. The levels of Runx2, the critical osteoblast transcription factor, and its transcriptional targets were decreased by Dkk1 neutralization, and the expression of klotho was increased. The result was that Dkk1 neutralization inhibited stimulation of vascular calcium levels in an atherosclerotic calcification model stimulated by early CKD.[15,39]

The skeleton is especially sensitive to circulating Wnt inhibition. Wnts have been shown to be the major stimuli of normal skeletal remodeling.[69] Genetic diseases are also produced by activating mutations in the Wnt coreceptor proteins, low-density lipoprotein receptor–related proteins 5 and 6 (LRP5/6),[42,70] and by inactivating mutations in Wnt inhibitor proteins, such as sclerostin, involved in the pathogenesis of sclerosteosis[71,72] and van Buchem's disease.[73] Wnts are also critical factors of the hematopoietic stem cell niche.[66,74,75] Their inhibition through circulating Wnt inhibitors is not tolerable, leading to adaptive production of another niche factor, PTH.[76,77] The adaptive increase in PTH prevents the expected inhibition of skeletal remodeling produced by circulating Wnt inhibitors.[45] Therefore, low-turnover osteodystrophy is not a generalized observation in early CKD, but it is observed when the increase in PTH is prevented.[52] In a preclinical model of atherosclerosis and type 2 diabetes, early CKD additively suppressed bone formation rates, especially in cortical bone. The effect was reversed by Dkk1 neutralization.[39]

Early CKD stimulates osteocyte production of FGF-23 and sclerostin.[43,49] Neutralization of Dkk1 did not affect increased FGF-23 levels, but decreasing urinary phosphate excretion without changing normal S[P] levels inhibited FGF-23 levels.[39] This is in agreement with

studies showing that the combination of dietary phosphate restriction and phosphate binders decreased FGF-23 levels in early CKD with normophosphatemia.[78] The concept that changes in urinary (tubular fluid) phosphate regulates osteocytic FGF-23 secretion is in agreement with the demonstrated hormonal function of cleaved klotho.[79] Thus, the physiologic paradigm is that regulation of disintergin metalloproteases ADAMS 10 and 17 by tubular fluid phosphate affects cleavage of membrane klotho producing the hormone, cleaved klotho, which regulates osteocyte secretion of FGF-23 (Figure 35.2).[79,80] The problem with the physiologic system is that CKD decreases tubular epithelial membrane klotho levels[81] eliminating the adaptive potential of increasing cleaved klotho levels in CKD and relegating regulation of FGF-23 secretion to increases in S[P] and other factors such as iron status and inflammation.[82,83] Stimulation of FGF-23 and sclerostin in early CKD produces an inhibition to skeletal remodeling that becomes a background as adaptive hyperparathyroidism maintains and even increases bone remodeling rates.[45,84] In addition to FGF-23, the increases in Dickkopf 1 and sclerostin, powerful inhibitors of Wnt signaling in early CKD, represent biomarker evidence of skeletal inhibition produced by renal injury. The loss of skeletal anabolism in CKD occurs in the presence of normal PTH, vitamin D, S[Ca], and S[P] levels. It is, however, not usually observed as the ABD because disturbed homeostasis in these factors stimulate PTH secretion. The sustained increase in PTH levels produced through adaptation to CKD increases remodeling rates and eventually produces an unwanted high-turnover disorder of skeletal remodeling, osteitis fibrosa.

Pathogenic Factors in the CKD-MBD

FGF-23

FGF-23 is the original phosphatonin (phosphate excretion regulating hormone) discovered in studies of autosomal-dominant hypophosphatemic rickets and oncogenic osteomalacia.[85,86] The principal hormonal functions identified for FGF-23 are regulation of proximal tubular [P] excretion, inhibition of CYP27B1, the 1α-hydroxylase synthesizing calcitriol in the proximal tubule, and stimulating the 25-hydroxyvitamin D3 24R-hydroxylase, 24-(OH) hydroxylase, CYP24A1. FGF-23 levels are stimulated by mild renal injury[49,87] and progressively rise during the course of CKD, due to increased secretion by osteocytes and decreased catabolism by the diseased kidney (Figure 35.2). FGF-23 contributes to maintenance of phosphate homeostasis during early CKD and causes vitamin D deficiency through increased catabolism. Hormonal FGF-23 is produced by osteocytes and osteoblasts, although it is expressed elsewhere in disease.[15] FGF-23 levels strongly associate with clinical outcomes of CKD,[88] especially with the intermediate surrogate, LVH.[33] Extremely high FGF-23 levels in CKD cause cardiac myocyte hypertrophy independent of klotho coreceptor function.[89] FGF-23 represents direct bone–kidney and bone–parathyroid and bone–heart connections in the systems biology involved in the CKD-MBD (Figure 35.2). The early stimulation of osteocyte FGF-23 secretion by renal injury is an example of kidney–bone communication, perhaps through regulation of AMP-activated kinase,[90] and preceding changes in S[P], calcitriol or PTH and proinflammatory cytokines, TNFα, or IL-1.

Klotho

FGF-23 signaling through FGF receptors requires the coreceptor function of alpha Klotho.[91] High Klotho expression has very limited tissue distribution, defining the tissue targets of FGF-23 as a hormone.[92,93] These targets are the proximal and distal renal tubules, the parathyroid glands, and the brain.[92,94] Secondly, Klotho is a single transmembrane pass protein with a large extracellular domain that possesses homology with glycosidases and functions as a glucuronidase, and a sialidase.[95,96] Thirdly, cleavage of the extracellular domain of klotho[80] and its shedding into the urine and blood suggested hormonal function of the protein,[97,98] which was shown to function in FGF-23 secretion by osteocytes.[79]

FGF-23 suppresses PTH secretion, and PTH gene expression through FGFR/Klotho signaling,[94] and PTH affects FGF-23 secretion. This physiologic system of osteocyte–parathyroid and parathyroid–osteocyte regulation does not operate appropriately in CKD.[99] The kidney–osteocyte, osteocyte–kidney signaling for phosphate homeostasis is not adaptive in CKD, due to the major decrease in klotho expression produced by renal injury,[100,101] limiting the role of cleaved klotho in osteocyte regulation, and leaving hyperphosphatemia as the main regulator of FGF-23 secretion in CKD. Furthermore, the loss of klotho expression in CKD limits FGF-23-stimulated signal transduction through FGF receptor/klotho complexes. One result is the loss of negative feedback to FGF-23 secretion and the continual production of FGF-23 and secretion by the osteocyte. In late CKD, the very high levels of FGF-23 permit anomalous FGF receptor activation independent of Klotho. This results in FGF-23-stimulated pathologic stimuli such as cardiac myocyte hypertrophy (Figure 35.2).[89]

Hyperphosphatemia

As renal injury decreases nephron number, phosphate excretion is maintained by reductions in the fraction of filtered phosphate reabsorbed by the remaining nephrons under the influence of FGF-23 and PTH.[102] The effects of FGF-23 stimulated by cleaved klotho before changes in

S[P] are limited by the loss of proximal tubular klotho.[100] The combination of FGF-23 and PTH effects to decrease proximal tubular phosphate reabsorption is sufficient to maintain phosphate homeostasis through stages 3–4 CKD when hyperphosphatemia ensues.[99] This is at the cost of higher PTH and FGF-23 levels. In stage 4 and 5 CKD, when renal injury is severe enough that the GFR reaches levels of less than 30% of normal, hyperphosphatemia develops due to decreased renal [P] excretion despite high PTH and FGF-23 levels.[99,103]

Failure of calcium and phosphorus deposition into the skeleton or excess resorption of the skeleton also contribute to abnormal S[P] and S[Ca] levels in CKD and ESRD.[104–106] The skeleton contributes to the pathogenesis of vascular calcification through contributing to hyperphosphatemia.[14,104] Signals deriving from the skeleton are direct causes of vascular mineralization. The best documented signal deriving from the skeleton is hyperphosphatemia.[107,108] Hyperphosphatemia stimulates osteoblastic transition in the vasculature[107,109] and directly contributes to mineralization through the calcium-phosphorus product (Figure 35.2).[108] Phosphorus is a signaling mechanism working through the Pit 1 and 2 sodium phosphate cotransport proteins as receptors for stimulation of MAP kinase signal transduction and stimulation of heterotopic mineralization of the vasculature in CKD.[108,110]

Hyperphosphatemia also decreases S[Ca] through physicochemical complexation (Figure 35.2) and suppresses 1α-hydroxylase activity, which results in further lowering of circulating calcitriol levels. Moreover, a direct stimulatory effect of phosphorus on parathyroid gland cells, independent of S[Ca] and calcitriol levels, produces increased secretion and nodular hyperplasia of parathyroid gland cells.[111,112] A direct stimulatory effect of inorganic phosphate, perhaps in the exchangeable inorganic phosphate pool, regulates osteocyte FGF-23 secretion.

Calcitriol Deficiency

The physiologic actions of FGF-23 from the osteocyte include inhibition of proximal tubular CYP27B1, 25-OH vitamin D 1α hydroxylase, and stimulation of CYP24A1, vitamin D 24-hydroxylase, decreasing calcitriol production, and producing vitamin D deficiency in early CKD. As CKD advances, the functioning nephron mass is decreased and this, combined with an increased phosphate load in the remaining nephrons and increased FGF-23 levels, results in calcitriol deficiency.[113] Calcitriol deficiency in turn decreases intestinal calcium absorption and leads to the development of hypocalcemia. Calcitriol deficiency in cases of advanced CKD in turn diminishes tissue levels of vitamin D receptors (VDRs), in particular, the VDR of parathyroid gland cells.[114] Because the chief cell VDR suppresses the expression of pre-pro-PTH mRNA, lower circulating calcitriol levels, together with a low number of VDRs in patients with ESRD result in stimulation of both synthesis and secretion of PTH[115] and resistance to the effects of calcitriol. The hypocalcemia in CKD stage 5 resulting from these pathophysiologic processes, unchecked by medical intervention is severe and resistant to therapy with calcium and calcitriol supplementation due to VDR deficiency.

Hypocalcemia

As CKD progresses, hypocalcemia develops due to decreased intestinal Ca absorption. Low blood levels of ionized calcium stimulate, whereas high S[Ca] suppresses PTH secretion. The action of calcium on parathyroid gland chief cells is mediated through a calcium sensor (CASR), a G-protein coupled plasma membrane receptor expressed in chief cells, kidney tubular epithelia, and widely throughout the body at lower levels.[116,117] The short-term stimulation of PTH secretion induced by low S[Ca] is due to exocytosis of PTH packaged in granules. Longer-term stimulation results from an increase in the number of cells that secrete PTH. More prolonged hypocalcemia induces changes in intracellular PTH degradation and mobilization of a secondary storage pool. Within days or weeks of the onset of hypocalcemia, pre-pro-PTH mRNA expression is stimulated. This effect is exerted through a negative calcium response element located in the upstream flanking region of the gene for PTH. Expression of the calcium receptor is suppressed by calcitriol deficiency and stimulated by calcitriol administration, suggesting an additional regulatory mechanism of the active vitamin D metabolite on PTH production. The decreased number of calcium-sensing receptors (CaSRs) with low circulating calcitriol may, at least in part, explain the relative insensitivity of parathyroid gland cells to calcium in patients undergoing dialysis.

Hyperparathyroidism

All of the mechanisms discussed above result in increased production of PTH and nodular hyperplasia of the parathyroid glands in CKD. The size of the parathyroid glands progressively increases during CKD and in dialyzed patients paralleling serum PTH levels. This increase in gland size is mainly due to diffuse cellular hyperplasia. Monoclonal chief cell growth also develops, resulting in the formation of nodules. Nodular hyperplastic glands have fewer VDR and CaSRs compared with diffusely hyperplastic glands, promoting parathyroid gland resistance to calcitriol and calcium. Sustained elevation in PTH levels, while adaptive to maintain osteoblast surfaces, produce an abnormal phenotype of osteoblast function and osteocyte stimulation, with relatively less type 1 collagen

and more RANKL ligand production than anabolic osteoblasts. A key component of the RANKL stimulation is osteocytic in origin. This leads to a high-turnover osteodystrophy, PTH receptor desensitization, and excess bone resorption.

Hypogonadism

Patients with ESRD have various states of gonadal dysfunction.[118–120] Estrogen and testosterone deficiency significantly contribute to the pathogenesis of ROD.[121,122]

Other Factors

Inflammatory mediators, acidosis,[123,124] aluminum, leptin, and retained catabolites are all potentially critical factors in the CKD-MBD that have not been well studied, or recently have become less important clinically. Some patients with CKD are treated with glucocorticoids, which affect bone metabolism. Patients maintained on chronic dialysis have retention of β2-microglobulin. Additionally, alterations in growth factors and other hormones involved in the regulation of bone remodeling may be disordered in CKD and ESRD, thus affecting bone remodeling and contributing to the development of ROD.

PATHOLOGY OF RENAL OSTEODYSTROPHY

With the advent of the CKD-MBD syndrome, the term ROD is restricted to the skeletal pathology of CKD and the modeling/remodeling disorders it causes. ROD is not a uniform disease. Depending on the relative contribution of the different pathogenic factors discussed above and their treatment, various pathologic patterns of bone remodeling are expressed in CKD and ESRD patients.[125]

Predominant Hyperparathyroidism Bone Disease, High-Turnover ROD, and Osteitis Fibrosa

Sustained excess PTH action results in increased bone turnover.[125–129] Osteoclasts, osteoblasts, and osteocytes are found in abundance. Disturbed osteoblastic activity results in a disorderly production of collagen, which results in formation of woven bone.[130] Accumulation of fibroblastic osteoprogenitors not in the osteoblastic differentiation program results in collagen deposition, and the development of fibrosis in the peritrabecular and marrow space.[28,125,131] The nonmineralized component of bone, osteoid, is increased, and the normal three-dimensional architecture of osteoid is frequently lost.[132] Osteoid seams no longer exhibit their usual birefringence under polarized light. Instead, a disorderly arrangement of woven osteoid and woven bone with a typical crisscross pattern under polarized light is seen. The mineral apposition rate and number of actively mineralizing sites are increased, as documented under fluorescent light after the administration of time-spaced fluorescent (tetracycline) markers.[133]

Low-Turnover Bone Disease, Adynamic Bone Disorder

Low-turnover uremic osteodystrophy is the other end of the spectrum of ROD.[134] The histologic hallmark of these disorders is a profound decrease in bone turnover, due to a low number of active remodeling sites, and suppression of bone formation and resorption.[135,136] Bone resorption is not as decreased as formation. The result is a low-turnover osteopenic condition. The majority of trabecular bone is covered by lining cells, with few osteoclasts and osteoblasts. Bone structure is predominantly lamellar. The extent of mineralizing surfaces is markedly reduced. Usually only a few thin, single tetracycline labels are observed. Two subgroups can be identified in this type of ROD, depending on the cause of events leading to a decline in osteoblast activity: first, the ABD and, secondly, low-turnover osteomalacia from aluminum intoxication, bisphosphonate administration, or other factors.[137–139]

We postulated that the ABD was caused by loss of skeletal anabolic activity,[125] which has subsequently shown to be true. First, we demonstrated that following renal injury, if S[Ca], S[P], PTH, and calcitriol were maintained normal, the ABD resulted,[52] and that it was corrected by a skeletal anabolic factor made in the normal kidney. Subsequently, we demonstrated that renal diseases increase inhibitors of Wnt in the systemic circulation,[39] and Sabbagh et al. showed that skeletal Wnt activity was suppressed in early CKD.[45] We showed that neutralization of a key Wnt inhibitor, Dkk1, was sufficient to correct the low-turnover osteodystrophy seen in a model of type 2 diabetes and early CKD.[39] In this model with further aging, resistance to PTH action is overcome by very high PTH levels and the osteodystrophy begins to convert into higher turnover rates. Thus, the complex pathophysiology of ROD has been further clarified.

Low-turnover osteomalacia is characterized by an accumulation of unmineralized matrix in which a diminution in mineralization precedes or is more pronounced than the inhibition of collagen deposition.[140–143] Unmineralized bone represents a sizable fraction of trabecular bone volume. The increased lamellar osteoid volume is due to the presence of wide osteoid seams that cover a large portion of the trabecular surface. The occasional

presence of woven bone buried within the trabeculae indicates past high bone turnover. When osteoclasts are present, they are usually seen within trabecular bone or at the small fraction of trabecular surface left without osteoid coating.

Mixed Uremic Osteodystrophy, High-Turnover ROD plus a Mineralization Defect

Mixed uremic osteodystrophy is caused primarily by hyperparathyroidism and defective mineralization with or without increased bone formation.[133,136,140] These features may coexist in varying degrees in different patients. Increased numbers of heterogeneous remodeling sites can be seen. The number of osteoclasts is usually increased. Because active foci with numerous cells, woven osteoid seams, and peritrabecular fibrosis coexist next to lamellar sites with a more reduced activity, greater production of lamellar or woven osteoid causes an accumulation of osteoid with normal or increased thickness of osteoid seams. While active mineralizing surfaces increase in woven bone with a higher mineralization rate and diffuse labeling, mineralization surfaces may be reduced in lamellar bone with a decreased mineral apposition rate.

ASSOCIATED FEATURES

Osteoporosis and Osteosclerosis

With progressive loss of renal function, cancellous bone volume may be increased along with a loss of cortical bone. This is in part due to deposition of woven immature collagen fibrils instead of lamellar fibrils. Thus, bone strength suffers despite the increase in mass detected by dual energy x-ray absorptiometry. Patients undergoing chronic dialysis might have a loss or gain in bone volume depending on bone balance. When the bone balance is positive, osteosclerosis may be observed when osteoblasts are active in depositing new bone, especially woven bone, thus superseding bone resorption. This is rare in the 21st century due to improved therapy of secondary hyperparathyroidism.[130]

In the case of negative bone balance, bone loss occurs in cortical and cancellous bone and is more rapid when bone turnover is high. In those cases, bone densitometry will detect osteopenia or osteoporosis.[144,145] The prevalence of osteoporosis in the population with CKD exceeds the prevalence in the general population.[146–148] Osteoporosis is observed in CKD before dialysis is required for ESRD.[149] When bone turnover is high, as in secondary hyperparathyroidism with osteitis fibrosa, bone resorption rates are in excess of bone formation, and osteopenia progressing to osteoporosis may result. When bone turnover is low, although both bone formation rates and bone resorption may be reduced, resorption exceeds bone formation, and loss of bone mass occurs. Thus, osteoporosis may be observed with either high-turnover[149–152] or low-turnover[153] forms of osteodystrophy. When bone resorption exceeds bone formation rates in CKD, positive phosphorus and calcium balance results in the development of hyperphosphatemia and hypercalcemia without an increase in skeletal mineral deposition, but with a stimulation of heterotopic mineralization, especially of the vasculature. The failure of the skeleton to absorb positive phosphate balance in CKD is an important stimulus to heterotopic mineralization and links the skeleton and osteoporosis in CKD to cardiovascular events and mortality.[107]

It is apparent that four forms of osteoporosis associate with the CKD-MBD: high-turnover ROD causing osteoporosis, low-turnover ROD causing osteoporosis, osteoporosis preexisting CKD, and osteoporosis due to gonadal hormone deficiency. In patients with osteoporosis and decreased eGFR, it is important to determine the presence of CKD, and the state of the CKD-MBD.

Bone Aluminum, Iron, Lanthanum, and Bisphosphonate Accumulation

Aluminum, iron, lanthanum,[154] and bisphosphonates accumulate in bone at the mineralization front, at the cement lines, or diffusely. The extent of stainable aluminum at the mineralization front correlates with histologic abnormalities in mineralization. Aluminum deposition is most severe in cases of low-turnover osteomalacia. Aluminum deposition, however, can be observed in all histologic forms of ROD. In patients in whom an increased aluminum burden develops, bone mineralization and bone turnover progressively decrease. These abnormalities are reversed with removal of the aluminum. Iron also accumulates at the mineralization front and can cause low-turnover forms of ROD and fractures[155,156] similar to aluminum, although much less is known regarding skeletal iron intoxication compared with aluminum intoxication.

Lanthanum has been added as a rare earth ion administered to CKD and ESRD patients as a phosphate binder. It is poorly absorbed, and its levels in bone are much lower than aluminum and not clinically relevant.[157] Therapy with lanthanum has not been shown to have long-term toxic effects, and studies suggest skeletal efficacy of lanthanum therapy.[158–160] Eight-year data suggest that the levels of skeletal accumulation remain below those associated with any biologic or toxic effects.[161] Lanthanum disappearance from bone deposits is slow, but not as slow as bisphosphonate disappearance.[157]

Bisphosphonates are drugs used in the treatment of osteoporosis and hypercalcemia.[162,163] There are increasing instances of bisphosphonate use in patients with CKD and ESRD especially for treatment of vascular calcification.[164] Many patients in the multiple bisphosphonate registration trials were retrospectively found to have reduced eGFR.[165,166] Generally, these were elderly women who most likely did not have kidney disease or the CKD-MBD because they did not have elevated PTH levels. Therefore, there is concern extrapolating data from these trials to patients with osteoporosis and CKD. The nature of the bone remodeling abnormalities in CKD, especially with woven bone formation and mineralization defects, conveys a high level of risk for skeletal deposition of a substance that once deposited may not be removed. Such a risk of long-term retention of an active drug inhibiting bone turnover is now being recognized with use of bisphosphonates in osteogenesis imperfecta, as is the rare side effect of the drugs, resulting in osteonecrosis of the jaw and atypical femoral fractures.[164,167] The FDA has added to its bisphosphonate warnings, due to the nephrotoxicity of potent bisphosphonates.[162]

Clinical Manifestations

Patients with early stage CKD are rarely symptomatic due to ROD and its skeletal pathology, but they are usually hypertensive. If the CKD-MBD contributes to hypertension, the pulse pressure may be high due to vascular stiffness and increased pulse wave velocity.[168] However, fracture risk for CKD patients is increased more than twofold above age-matched cohorts without CKD.[169,170] Stimulation of vascular calcification in the setting of disordered skeletal remodeling is a life-threatening complication of the CKD-MBD.[171,172] Vascular calcification produces vascular stiffness.[13] Vascular stiffness in CKD causes an increase in systolic blood pressure, a widening of the pulse pressure, and an increase in pulse wave velocity. All of these can lead to cardiac hypertrophy, heart failure, and cardiovascular mortality.[173]

Heterotopic Mineralization, Calciphylaxis, and Tumoral Calcinosis

Heterotopic tissue calcification may occur in the eyes and manifest as band keratopathy in the sclera or induce an inflammatory response, known as the red eye syndrome, in the conjunctiva. Calcium deposits are also found in the lungs, leading to restrictive lung disease. Deposits in the myocardium might cause arrhythmias, annular calcifications, valvular calcification, or myocardial dysfunction. Calcification of the kidney may contribute to the progression of CKD. Most soft tissue calcifications are attributed to the increased calcium phosphate product contributed to by ROD and excess bone resorption.

The syndrome of calciphylaxis is characterized by vascular calcification in the tunica media of peripheral arteries.[174,175] These calcifications induce painful violaceous skin lesions that progress to ischemic necrosis.[176] This syndrome is associated with serious complications and often death.

Tumoral calcinosis is a form of soft tissue calcification that involves the periarticular tissues. Calcium deposits may grow to enormous size and interfere with the function of adjacent joints and organs. Although this type of calcification is usually associated with high calcium phosphate products, its exact pathogenesis is poorly understood. The discoveries of three single gene mutations in FGF-23, Klotho, and GALNT3 causing inherited tumoral calcinosis shed light on the role of hyperphosphatemia in the pathogenesis of tumoral calcinosis.[177–179] The role of GALNT3 in hyperphosphatemia is associated with enzymatic degradation of FGF-23.

Bone Pain, Fractures, and Skeletal Deformities

Symptoms of ROD related to the skeleton appear in patients with advanced CKD.[180] Clinical manifestations are preceded, however, by an abnormal biochemical profile that should alert the physician and prompt steps to prevent more severe complications. When symptoms related to the skeleton occur, they are usually insidious, subtle, nonspecific, and slowly progressive.

Bone pain is usually vague, ill defined, and deep seated. Bone pain may be diffuse or localized in the lower part of the back, hips, knees, or legs. Weight bearing and changes in position commonly aggravate bone pain. Bone pain may progress slowly to the degree that patients are completely incapacitated. Bone pain in patients with ESRD usually does not cause physical signs. Local tenderness, however, may be apparent with pressure. Occasionally, pain can occur suddenly at one joint of the lower extremities and mimic acute arthritis or periarthritis not relieved by heat or massage. A sharp chest pain may indicate rib fracture. Spontaneous fractures or fractures after minimal trauma may also occur in vertebrae (crush fractures) and in tubular bones.

Bone pain and bone fractures can be observed in all patients with ESRD independent of the underlying histologic bone disease, especially when osteoporosis is present.[146] However, low-turnover osteomalacia and aluminum-related bone disease are associated with the most severe bone pain and the highest incidence of fractures and incapacity.

Skeletal deformities can be observed in children and adults. Most children with ESRD have growth

retardation, and bone deformities may develop from vitamin D deficiency (rickets) or secondary hyperparathyroidism.[123] In rickets, bowing of the long bones is seen, especially the tibiae and femora, with typical genu valgum that becomes more severe with adolescence. Long-standing secondary hyperparathyroidism in children may be responsible for slipped epiphyses secondary to impaired transformation of growth cartilage into regular metaphyseal spongiosa. This complication most commonly affects the hips, becomes obvious in preadolescence, and causes limping but is usually painless. When the radius and ulna are involved, ulnar deviation of the hands and local swelling may occur. In adults, skeletal deformities can be observed in cases of severe osteomalacia or osteoporosis and include lumbar scoliosis, thoracic kyphosis, and recurrent rib fractures.[181]

CONCLUSION

CKD produces a complex syndrome of disrupted systems biology that affects the vasculature, heart, skeleton, muscle, and mineral metabolism which contributes to mortality. The advances in our understanding of the CKD-MBD syndrome and its pathogenesis bring into focus the great need for new therapeutics. The 2017 update of clinical practice guidelines by KDIGO[6] demonstrates that our therapies are focused on the late components of the syndrome and have not improved its mortality in clinical trials (EVOLVE, OPERA, PRIMO) despite control of secondary hyperparathyroidism.[182–184] Thus, there is great need for discoveries related to therapeutic targets for the CKD-MBD cardiovascular components and development of therapeutic agents.

Acknowledgments

The writing of this chapter was supported by NIH grants DK070790 and DK089137 to KAH.

References

1. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006;**69**(11): 1945–53.
2. Olgaard K. KDIGO: clinical guide to bone and mineral metabolism in CKD. In: Olgaard K, editor. National Kidney Foundation; 2006.
3. Stevens LA, Djurdjev O, Cardew S, Cameron EC, Levin A. Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: evidence for the complexity of the association between mineral metabolism and outcomes. *J Am Soc Nephrol* 2004;**15**(3):770–9.
4. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium X phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998;**31**(4):607–17.
5. Slinin Y, Foley RN, Collins AJ, cartographers. Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: the USRDS waves 1, 3, and 4 study. *J Am Soc Nephrol* 2005;**16**.
6. Group KDIGOKC-MUW. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2017;**7**(1):1–59.
7. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; **32**(5 Suppl. 3):S112–9.
8. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 2005; **352**(20):2049–60.
9. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension* 2003;**42**:1050–65.
10. Peralta CA, Shlipak MG, Judd S, Cushman M, McClellan W, Zakai NA, et al. Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. *J Am Med Assoc* 2011;**305**:1545–52.
11. Tyson CC, Smith PJ, Sherwood A, Mabe S, Hinderliter AL, Blumenthal JA. Association between normal or mildly reduced kidney function, cardiovascular risk and biomarkers for atherosclerosis: results from the ENCORE trial. *Clin Kidney J* 2017; **10**(5):666–71.
12. Graciolli FG, Neves KR, Barreto F, Barreto DV, dos Reis LM, Canziani ME, et al. The complexity of chronic kidney disease-mineral and bone disorder across stages of chronic kidney disease. *Kidney Int* 2017;**91**(6):1436–46.
13. Ix JH, de Boer IH, Peralta CA, Adeney KL, Duprez DA, Jenny NS, et al. Serum phosphorus concentrations and arterial stiffness among individuals with normal kidney function to moderate kidney disease in MESA. *Clin J Am Soc Nephrol* 2009; **4**:609–15.
14. Mitsnefes MM, Kimball TR, Kartal J, Witt SA, Glascock BJ, Khoury PR, et al. Cardiac and vascular adaptation in pediatric patients with chronic kidney disease: role of calcium-phosphorus metabolism. *J Am Soc Nephrol* 2005;**16**:2796–803.
15. Fang Y, Ginsberg C, Sugatani T, Faugere MC, Malluche H, Hruska KA. Early chronic kidney disease-mineral bone disorder stimulates vascular calcification. *Kidney Int* 2014;**85**(1):142–50.
16. Williams MJ, Sugatani T, Agapova OA, Fang Y, Gaut JP, Faugere M-C, et al. The activin receptor is stimulated in the skeleton, vasculature, heart, and kidney during chronic kidney disease. *Kidney Int* 2018;**93**(1):147–58.
17. Di Lullo L, Gorini A, Russo D, Santoboni A, Ronco C. Left ventricular hypertrophy in chronic kidney disease patients: from pathophysiology to treatment. *Cardiorenal Med* 2015;**5**(4):254–66.
18. Shanahan CM, Crouthamel MH, Kapustin A, Giachelli CM. Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. *Circ Res* 2011;**109**:697–711.
19. Shanahan CM, Cary NRB, Metcalfe JC, Weissberg PL. High expression of genes for calcification-regulating proteins in human atherosclerotic plaques. *J Clin Investig* 1994;**93**:2393–402.
20. Demer LL. A skeleton in the atherosclerosis closet. *Circulation* 1995;**92**:2029–32.

21. Moe SM, Duan D, Doehle BP, O'Neill KD, Chen NX. Uremia induces the osteoblast differentiation factor Cbfa1 in human blood vessels. *Kidney Int* 2003;**63**:1003–11.
22. Speer MY, Yang HY, Brabb T, Leaf E, Look A, Lin WL, et al. Smooth muscle cells give rise to osteochondrogenic precursors and chondrocytes in calcifying arteries. *Circ Res* 2009;**104**:733–41.
23. Shanahan CM, Cary NRB, Salisbury JR, Proudfoot D, Weissberg PL, Edmonds ME. Medial localization of mineralization-regulating proteins in association with Monckeberg's sclerosis: evidence for smooth muscle cell-mediated vascular calcification. *Circulation* 1999;**100**:2168–76.
24. Kokubo T, Ishikawa N, Uchida H, Chasnoff SE, Xie X, Mathew S, et al. CKD accelerates development of neointimal hyperplasia in arteriovenous fistulas. *J Am Soc Nephrol* 2009;**20**:1236–45. PMCID: PMC2689906.
25. Towler DA, Bidder M, Latifi T, Coleman T, Semenkovich CF. Diet-induced diabetes activates an osteogenic gene regulatory program in the aortas of low density lipoprotein receptor-deficient mice. *J Biol Chem* 1998;**273**:30427–34.
26. Steitz SA, Speer MY, Curinga G, Yang H-Y, Haynes P, Aebersold R, et al. Smooth muscle cell phenotypic transition associated with calcification. *Circ Res* 2001;**89**:1147–54.
27. Giachelli CM, Bae N, Almeida M, Denhardt DT, Alpers CE, Schwartz SM. Osteopontin is elevated during neointima formation in rat arteries and is a novel component of human atherosclerotic plaques. *J Clin Investig* 1993;**92**:1686–96.
28. Davies MR, Lund RJ, Hruska KA. BMP-7 is an efficacious treatment of vascular calcification in a murine model of atherosclerosis and chronic renal failure. *J Am Soc Nephrol* 2003;**14**:1559–67.
29. Moe SM, O'Neill KD, Duan D, Ahmed S, Chen NX, Leapman SB, et al. Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins. *Kidney Int* 2002;**61**: 638–47.
30. Kramann R, Goettsch C, Wongboonsin J, Iwata H, Schneider Rebekka K, Kuppe C, et al. Adventitial MSC-like cells are progenitors of vascular smooth muscle cells and drive vascular calcification in chronic kidney disease. *Cell Stem Cell* 2016; **19**(5):628–42.
31. Durham AL, Speer MY, Scatena M, Giachelli CM, Shanahan CM. Role of smooth muscle cells in vascular calcification: implications in atherosclerosis and arterial stiffness. *Cardiovasc Res* 2018;**114**(4): 590–600.
32. Seifert ME, dlF L, Ginsberg C, Rothstein M, Dietzen DJ, Cheng SC, Ross W, Windus D, Dávila-Román VG, Hruska KA. Progressive increase in left ventricular mass in stage 3 CKD despite stable kidney function. *Am J Nephrol* 2014;**39**:392–9.
33. Gutierrez OM, Januzzi JL, Isakova T, Laliberte K, Smith K, Collerone G, et al. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. *Circulation* 2009;**119**: 2545–52.
34. Chmielewski M, Carrero JJ, Stenvinkel P, Lindholm B. Metabolic abnormalities in chronic kidney disease that contribute to cardiovascular disease, and nutritional initiatives that may diminish the risk. *Curr Opin Lipidol* 2009;**20**(1):3–9.
35. Agapova OA, Fang Y, Sugatani T, Seifert ME, Hruska KA. Ligand trap for the activin type IIA receptor protects against vascular disease and renal fibrosis in mice with chronic kidney disease. *Kidney Int* 2016;**89**(6):1231–43.
36. Zhou D, Tan RJ, Fu H, Liu Y. Wnt/β-catenin signaling in kidney injury and repair: a double-edged sword. *Lab Investig* 2016;**96**(2): 156–67.
37. Surendran K, Schiavi SC, Hruska K. A putative Wnt antagonist secreted frizzled-related protein 4 (sFRP4) suppresses the progression of renal fibrosis follwoing unilateral ureteral obstruction. *J Am Soc Nephrol* 2004;**15**:245A.
38. Aaron M. Wnt signalling: antagonistic dickkopfs. *Curr Biol* 2001; **11**:R592–5.
39. Fang Y, Ginsberg C, Seifert M, Agapova O, Sugatani T, Monier-Faugere MC, et al. CKD-induced wingless/integration1 inhibitors and phosphorus cause the CKD-mineral and bone disorder. *J Am Soc Nephrol* 2014;**25**(8):1760–3.
40. Bafico A, Liu G, Yaniv A, Gazit A, Aaronson SA. Novel mechanism of Wnt signalling inhibition mediated byDickkopf-1 interaction with LRP6/arrow. *Nat Cell Biol* 2001;**3**:683–6.
41. Gong Y, Slee RB, Fukai N, Rawadi G, Roman-Roman S, Reginato AM, et al. LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development. *Cell* 2001;**107**:513–23.
42. Little RD, Carulli JP, DelMastro RG, Dupuis J, Osborne M, Folz C, et al. A mutation in the LDL receptor-related protein 5 gene results in the autosomal dominant high-bone-mass trait. *Am J Hum Genet* 2002;**70**:11–9.
43. Pereira RC, Juppner H, Azucena-Serrano CE, Yadin O, Salusky IB, Wesseling-Perry K. Patterns of FGF-23, DMP1 and MEPE expression in patients with chronic kidney disease. *Bone* 2009;**45**(6): 1161–8.
44. Graciolli FG, de Oliveira RB, dos Reis LM, Cancela ALE, Cuppari L, Canziani MEF, et al. Wnt pathway inhibition: another actor in CKD-MBD pathophysiology? *J Am Soc Nephrol* 2010;**21**: 774A.
45. Sabbagh Y, Graciolli FG, O'Brien S, Tang W, dos Reis LM, Ryan S, et al. Repression of osteocyte Wnt/β-catenin signaling is an early event in the progression of renal osteodystrophy. *J Bone Miner Res* 2012;**27**(8):1757–72.
46. Moe SM, Nickolas TL. Fractures in patients with CKD: time for action. *Clin J Am Soc Nephrol* 2016;**11**(11):1929–31.
47. Sugatani T, Agapova OA, Fang Y, Berman AG, Wallace JM, Malluche HH, et al. Ligand trap of the activin receptor type IIA inhibits osteoclast stimulation of bone remodeling in diabetic mice with chronic kidney disease. *Kidney Int* 2017;**91**(1):86–95.
48. Hruska KA, Sugatani T, Agapova O, Fang Y. The chronic kidney disease — mineral bone disorder (CKD-MBD): advances in pathophysiology. *Bone* 2017;**100**:80–6.
49. Isakova T, Wahl P, Vargas GS, Gutierrez OM, Scialla J, Xie H, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int* 2011; **79**(12):1370–8.
50. Craver L, Marco MP, Martinez I, Rue M, Borras M, Martin ML, et al. Mineral metabolism parameters throughout chronic kidney disease stages 1-5–achievement of K/DOQI target ranges. *Nephrol Dial Transplant* 2007;**22**(4):1171–6.
51. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int* 2006;**71**:31–8.
52. Lund RJ, Davies MR, Brown AJ, Hruska KA. Successful treatment of an adynamic bone disorder with bone morphogenetic protein-7 in a renal ablation model. *J Am Soc Nephrol* 2004;**15**(2):359–69.
53. Malluche HH, Faugere MC. Renal bone disease 1990: challenge for nephrologists. *Kidney Int* 1990;**38**:193–211.
54. Surendran K, Schiavi S, Hruska KA. Wnt-dependent- β-catenin signaling is activated after unilateral ureteral obstruction, and recombinant secreted frizzled-related protein 4 alters the progression of renal fibrosis. *J Am Soc Nephrol* 2005;**16**:2373–84.
55. Terada Y, Tanaka H, Okado T, Shimamura H, Inoshita S, Kuwahara M, et al. Expression and function of the developmental gene Wnt-4 during experimental acute renal failure in rats. *J Am Soc Nephrol* 2003;**14**:1223–33.
56. Kispert A, Vainio S, McMahon AP. Wnt-4 is a mesenchymal signal for epithelial transformation of metanephric mesenchyme in the developing kidney. *Development* 1998;**125**:4225–34.

57. Lin Y, Liu A, Zhang S, Ruusunen T, Kreidberg JA, Peltoketo H, et al. Induction of ureter branching as a response to Wnt-2b signaling during early kidney organogenesis. *Dev Dynam* 2001; **2001**:26–39.
58. Stark K, Vainio S, Vassileva G, McMahon AP. Epithelial transformation of metanephric mesenchyme in the developing kidney regulated by Wnt-4. *Nature* 1994;**372**:679–83.
59. Herzlinger D, Qiao J, Cohen D, Ramakrishna N, Brown AMC. Induction of kidney epithelial morphogenesis by cells expressing Wnt-1. *Dev Biol* 1994;**166**:815–8.
60. Iglesias DM, Hueber P-A, Chu L, Campbell R, Patenaude A-M, Dziarmaga AJ, et al. Canonical WNT signaling during kidney development. *Am J Physiol Renal Physiol* 2007;**293**(2):F494–500.
61. Surendran K, McCaul SP, Simon TC. A role for Wnt-4 in renal fibrosis. *Am J Physiol Renal Physiol* 2002;**282**:F431–41.
62. He W, Dai C, Li Y, Zeng G, Monga SP, Liu Y. Wnt/{beta}-Catenin signaling promotes renal interstitial fibrosis. *J Am Soc Nephrol* 2009;**20**:765–76.
63. Kawakami T, Ren S, Duffield JS. Wnt signalling in kidney diseases: dual roles in renal injury and repair. *J Pathol* 2013;**229**(2): 221–31.
64. Jho E, Zhang T, Domon C, Joo CK, Freund JN, Costantini F. Wnt/{beta}-Catenin/Tcf signaling induces the transcription of Axin2, a negative regulator of the signaling pathway. *Mol Cell Biol* 2002;**22**: 1172–83.
65. Niida A, Hiroko T, Kasai M, Furukawa Y, Nakamura Y, Suzuki Y, et al. DKK1, a negative regulator of Wnt signaling, is a target of the β-catenin/TCF pathway. *Oncogene* 2004;**23**:8520–6.
66. Reya T, Duncan AW, Ailles L, Domen J, Scherer DC, Willert K, et al. A role for Wnt signalling in self-renewal of haematopoietic stem cells. *Nature* 2003;**423**:409–14.
67. Pietilä I, Ellwanger K, Railo A, Jokela T, Barrantes IB, Shan J, et al. Secreted Wnt antagonist Dickkopf-1 controls kidney papilla development coordinated by Wnt-7b signalling. *Dev Biol* 2011; **353**(1):50–60.
68. de Oliveira RB, Graciolli FG, dos Reis LM, Cancela ALE, Cuppari L, Canziani ME, et al. Disturbances of Wnt/β-catenin pathway and energy metabolism in early CKD: effect of phosphate binders. *Nephrol Dial Transplant* 2013;**28**(10):2510–7.
69. Kramer I, Halleux C, Keller H, Pegurri M, Gooi JH, Weber PB, et al. Osteocyte Wnt/β-catenin signaling is required for normal bone homeostasis. *Mol Cell Biol* 2010;**30**(12):3071–85.
70. Boyden LM, Mao J, Belsky J, Mitzner L, Farhi A, Mitnick MA, et al. High bone density due to a mutation in LDL-receptor-related protein 5. *N Engl J Med* 2002;**346**:1513–21.
71. Balemans W, Ebeling M, Patel N, Van Hul E, Olson P, Dioszegi M, et al. Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). *Hum Mol Genet* 2001; **10**:537–43.
72. Brunkow ME, Gardner JC, Van Ness J, Paeper BW, Kovacevich BR, Proll S, et al. Bone dysplasia sclerosteosis results from loss of the SOST gene product, a novel cystine knot-containing protein. *Am J Hum Genet* 2001;**2001**:577–89.
73. Staehling-Hampton K, Proll S, Paeper BW, Zhao L, Charmley P, Brown A, et al. A 52-kb deletion in the SOST-MEOX1 intergenic region on 17q12-q21 is associated with van Buchem disease in the Dutch population. *Am J Med Genet* 2002;**110**(2):144–52.
74. Reya T, Clevers H. Wnt signalling in stem cells and cancer. *Nature* 2005;**434**(7035):843–50.
75. ten Berge D, Kurek D, Blauwkamp T, Koole W, Maas A, Eroglu E, et al. Embryonic stem cells require Wnt proteins to prevent differentiation to epiblast stem cells. *Nat Cell Biol* 2011;**13**(9):1070–5.
76. Calvi LM, Adams GB, Weibrecht KW, Weber JM, Olson DP, Knight MC, et al. Osteoblastic cells regulate the haematopoietic stem cell niche. *Nature* 2003;**425**:841–6.
77. Kuznetsov SA, Riminucci M, Ziran N, Tsutsui TW, Corsi A, Calvi L, et al. The interplay of osteogenesis and hematopoiesis: expression of a constitutively active PTH/PTHrP receptor in osteogenic cells perturbs the establishment of hematopoiesis in bone and of skeletal stem cells in the bone marrow. *J Cell Biol* 2004; **167**:1113–22.
78. Isakova T, Barchi-Chung A, Enfield G, Smith K, Vargas G, Houston J, et al. Effects of dietary phosphate restriction and phosphate binders on FGF23 levels in CKD. *Clin J Am Soc Nephrol* 2013; **8**(6):1009–18.
79. Smith RC, O'Bryan LM, Farrow EG, Summers LJ, Clinkenbeard EL, Roberts JL, et al. Circulating αKlotho influences phosphate handling by controlling FGF23 production. *J Clin Investig* 2012;**122**(12):4710–5.
80. Chen C-D, Podvin S, Gillespie E, Leeman SE, Abraham CR. Insulin stimulates the cleavage and release of the extracellular domain of Klotho by ADAM10 and ADAM17. *Proc Natl Acad Sci USA* 2007;**104**(50):19796–801.
81. Hu MC, Shi M, Zhang J, Qui+Ýones H, Griffith C, Kuro-o M, et al. Klotho deficiency causes vascular calcification in chronic kidney disease. *J Am Soc Nephrol* 2011;**22**:124–36.
82. David V, Martin A, Isakova T, Spaulding C, Qi L, Ramirez V, et al. Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production. *Kidney Int* 2016;**89**(1):135–46.
83. Singh S, Grabner A, Yanucil C, Schramm K, Czaya B, Krick S, et al. Fibroblast growth factor 23 directly targets hepatocytes to promote inflammation in chronic kidney disease. *Kidney Int* 2016; **90**(5):985–96.
84. Moe SM, Radcliffe JS, White KE, Gattone VH, Seifert MF, Chen X, et al. The pathophysiology of early-stage chronic kidney disease–mineral bone disorder (CKD-MBD) and response to phosphate binders in the rat. *J Bone Miner Res* 2011;**26**(11):2672–81.
85. White KE, Evans WE, O'Riordan JLH, Speer MC, Econs MJ, Lorenz-Depiereux B, et al. Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. *Nat Genet* 2000;**26**:345–8.
86. White KE, Jonsson KB, Carn G, Hampson G, Spector TD, Mannstadt M, et al. The autosomal dominant hypophosphatemic rickets (ADHR) gene is a secreted polypeptide overexpressed by tumors that cause phosphate wasting. *J Clin Endocrinol Metab* 2001;**86**(2):497–500.
87. Larsson T, Nisbeth U, Ljunggren O, Juppner H, Jonsson KB. Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. *Kidney Int* 2003;**64**(6):2272–9.
88. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008; **359**:584–92.
89. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, et al. FGF23 induces left ventricular hypertrophy. *J Clin Investig* 2011; **121**(11):4393–408.
90. Glosse P, Feger M, Mutig K, Chen H, Hirche F, Hasan AA, et al. AMP-activated kinase is a regulator of fibroblast growth factor 23 production. *Kidney Int* 2018;**94**(3):491–501.
91. Kurosu H, Ogawa Y, Miyoshi M, Yamamoto M, Nandi A, Rosenblatt KP, et al. Regulation of fibroblast growth factor-23 signaling by klotho. *J Biol Chem* 2006;**281**(10):6120–3.
92. Kuro-o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, et al. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature* 1997;**390**:45–51.
93. Imura A, Tsuji Y, Murata M, Maeda R, Kubota K, Iwano A, et al. α-klotho as a regulator of calcium homeostasis. *Science* 2007;**316**: 1615–8.

94. Ben-Dov IZ, Galitzer H, Lavi-Moshayoff V, Goetz R, Kuro-o M, Mohammadi M, et al. The parathyroid is a target organ for FGF23 in rats. *J Clin Investig* 2007;**117**(12):4003–8.
95. Chang Q, Hoefs S, van der Kemp AW, Topala CN, Bindels RJ, Hoenderop JG. The β-glucuronidase klotho hydrolyzes and activates the TRPV5 channel. *Science* 2005;**310**:490–3.
96. Cha SK, Ortega B, Kurosu H, Rosenblatt KP, Kuro-o M, Huang CL. Removal of sialic acid involving klotho causes cell-surface retention of TRPV5 channel via binding to galectin-1. *Proc Natl Acad Sci USA* 2008;**105**:9805–10.
97. Kurosu H, Yamamoto M, Clark JD, Pastor JV, Nandi A, Gurnani P, et al. Suppression of aging in mice by the hormone klotho. *Science* 2005;**309**(5742):1829–33.
98. Imura A, Iwano A, Tohyama O, Tsuji Y, Nozaki K, Hashimoto N, et al. Secreted klotho protein in sera and CSF: implication for post-translational cleavage in release of klotho protein from cell membrane. *FEBS Lett* 2004;**565**(1–3):143–7.
99. Silver J, Rodriguez M, Slatopolsky E. FGF23 and PTH—double agents at the heart of CKD. *Nephrol Dial Transplant* 2012;**27**(5): 1715–20.
100. Hu MC, Shi M, Zhang J, Pastor J, Nakatani T, Lanske B, et al. Klotho: a novel phosphaturic substance acting as an autocrine enzyme in the renal proximal tubule. *FASEB J* 2010;**24**:3438–50.
101. Koh N, Fujimori T, Nishiguchi S, Tamori A, Shiomi S, Nakatani T, et al. Severely reduced production of klotho in human chronic renal failure kidney. *Biochem Biophys Res Commun* 2001;**280**: 1015–20.
102. Slatopolsky E, Gradowska L, Kashemsant C. The control of phosphate excretion in uremia. *J Clin Investig* 1966;**45**:672–7.
103. Slatopolsky E, Robson AM, Elkan I, Bricker NS. Control of phosphate excretion in uremic man. *J Clin Investig* 1968;**47**(8):1865–74.
104. Davies MR, Lund RJ, Mathew S, Hruska KA. Low turnover osteodystrophy and vascular calcification are amenable to skeletal anabolism in an animal model of chronic kidney disease and the metabolic syndrome. *J Am Soc Nephrol* 2005;**16**(4):917–28.
105. Kurz P, Monier-Faugere MC, Bognar B, Werner E, Roth P, Vlachojannis J, et al. Evidence for abnormal calcium homeostasis in patients with adynamic bone disease. *Kidney Int* 1994;**46**(3): 855–61.
106. Block GA, Bone HG, Fang L, Lee E, Padhi D. A single-dose study of denosumab in patients with various degrees of renal impairment. *J Bone Miner Res* 2012;**27**(7):1471–9.
107. Mathew S, Tustison KS, Sugatani T, Chaudhary LR, Rifas L, Hruska KA. The mechanism of phosphorus as a cardiovascular risk factor in chronic kidney disease. *J Am Soc Nephrol* 2008; **19**(6):1092–105.
108. Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, et al. Phosphate regulation of vascular smooth muscle cell calcification. *Circ Res* 2000;**87**(7):e10–7.
109. El-Abbadi MM, Pai AS, Leaf EM, Yang HY, Bartley BA, Quan KK, et al. Phosphate feeding induces arterial medial calcification in uremic mice: role of serum phosphorus, fibroblast growth factor-23, and osteopontin. *Kidney Int* 2009;**75**:1297–307.
110. Li X, Yang HY, Giachelli CM. Role of the sodium-dependent phosphate cotransporter, pit-1, in vascular smooth muscle cell calcification. *Circ Res* 2006;**98**(7):905–12.
111. Moallem E, Kilav R, Silver J, Naveh-Many T. RNA-protein binding and post-transcriptional regulation of parathyroid hormone gene expression by calcium and phosphate. *J Biol Chem* 1998; **273**(9):5253–9.
112. Naveh-Many T, Rahamimov R, Livni N, Silver J. Parathyroid cell proliferation in normal and chronic renal failure rats. *J Clin Investig* 1995;**4**:1786–93.
113. Goodman WG, Quarles LD. Development and progression of secondary hyperparathyroidism in chronic kidney disease: lessons from molecular genetics. *Kidney Int* 2007:276–88.
114. Naveh-Many T, Marx R, Keshet E, Pike JW, Silver J. Regulation of 1,25-dihydroxyvitamin D3 receptor gene expression by 1,25-dihydroxyvitamin D3 in the parathyroid in vivo. *J Clin Investig* 1990;**86**(6):1968–75.
115. Silver J, Russell J, Sherwood LM. Regulation by vitamin D metabolites of messenger ribonucleic acid for preproparathyroid hormone in isolated bovine parathyroid cells. *Proc Natl Acad Sci USA* 1985;**82**(12):4270–3.
116. Brown EM, Gamba G, Riccardi D, Lombardi M, Butters R, Kifor O, et al. Cloning and characterization of an extracellular Ca2+-sensing receptor from bovine parathyroid. *Nature* 1993; **366**(6455):575–80.
117. Brown EM, Hebert SC. A cloned Ca2+-sensing receptor; a mediator of direct effects of extracellular Ca2+ on renal function? *J Am Soc Nephrol* 1995;**6**(6):1530–40.
118. Handelman DJ. Hypothalamic-Pituitary gonadal dysfunction in renal failure, dialysis and renal transplantation. *Endocr Rev* 1985; **6**(2):151–82.
119. Lim VS, Fang VS. Gonadal dysfunction in uremic men: a study of the hypothalamo-pituitary-testicular axis before and after renal transplantation. *Am J Med* 1975;**58**(5):655–62.
120. Lindberg J. The effects of hypogonadism and kidney failure on renal osteodystrophy. *Contemp Dial Nephrol* 1994;**15**:22–4.
121. Saito O. *Menopause*. USA: Nova Science Publishers Inc.; 2012.
122. Gluhovschi GH, Gluhovschi A, Anastasiu D, Petrica L, Gluhovschi C, Velciov S. Chronic kidney disease and the involvment of estrogen hormones in its pathogenesis and progression. *Rom J Intern Med* 2012;**50**(2):135–44.
123. Bacchetta J, Harambat J, Cochat P, Salusky IB, Wesseling-Perry K. The consequences of chronic kidney disease on bone metabolism and growth in children. *Nephrol Dial Transplant* 2012;**27**(8):3063–71.
124. Bushinsky DA. The contribution of acidosis to renal osteodystrophy. *Kidney Int* 1995;**47**:1816–32.
125. Hruska KA, Teitelbaum SL. Renal osteodystrophy. *N Engl J Med* 1995;**333**:166–75.
126. Hruska KA, Teitelbaum SL, Kopelman R, Richardson CA, Miller P, Debman J, et al. The predictability of the histological features of uremic bone disease by non-invasive techniques. *Metab Bone Dis Relat Res* 1978;**1**(1):39–44.
127. Bordier PHJ, Marie PJ, Arnaud CD. Evolution of renal osteodystrophy: correlation of bone histomorphometry and serum mineral and immunoreactive parathyroid hormone values before and after treatment with calcium carbonate or 25-hydroxycholecalciferol. *Kidney Int* 1975;**7**(Suppl. l):S102–12.
128. Wang M, Hercz G, Sherrard DJ, Maloney NA, Segre GV, Pei Y. Relationship between intact 1-84 parathyroid hormone and levels for bone turnover in patients on chronic maintenance dialysis. *Am J Kidney Dis* 1995;**26**:836–44.
129. Malluche HH, Monier-Faugere MC. Risk of adynamic bone disease in dialyzed patients. *Kidney Int* 1992;**38**:S62–7.
130. Malluche HH, Ritz E, Lange HP. Bone histology in incipient and advanced renal failure. *Kidney Int* 1976;**9**(4):355–62.
131. Gonzalez EA, Lund RJ, Martin KJ, McCartney JE, Tondravi MM, Sampath TK, et al. Treatment of a murine model of high-turnover renal osteodystrophy by exogenous BMP-7. *Kidney Int* 2002;**61**:1322–31.
132. Malluche HH, Mawad HW, Monier-Faugere MC. Renal osteodystrophy in the first decade of the new millennium: analysis of 630 bone biopsies in black and white patients. *J Bone Miner Res* 2011; **26**(6):1368–76.
133. Malluche H, Faugere M. Renal osteodystrophy. *N Engl J Med* 1989; **321**(5):317–9.
134. Moriniere P, Cohen-Solal M, Belbrik S. Disappearance of aluminic bone disease in a long-term asymptomatic dialysis population restricting Al(OH)3 intake: emergence of an idiopathic adynamic bone disease not related to aluminum. *Nephron* 1989;**53**:93–101.

135. Sherrard DJ. Renal osteodystrophy. *Semin Nephrol* 1986;**6**:56–67.
136. Sherrard DJ, Hercz G, Pei Y, Maloney NA, Greenwood C, Manuel A, et al. The spectrum of bone disease in end-stage renal failure: an evolving disorder. *Kidney Int* 1993;**43**:436–42.
137. Hodsman AB, Sherrard DJ, Wong EGC. Vitamin D resistant osteomalacia in hemodialysis patients lacking secondary hyperparathyroidism. *Ann Intern Med* 1981;**94**:629–37.
138. Hercz G, Pei Y, Greenwood C, Manuel A, Saiphoo C, Goodman WG, et al. Aplastic osteodystrophy without aluminum: the role of "suppressed" parathyroid function. *Kidney Int* 1993;**44**: 860–6.
139. Coburn J, Slatopolsky E. Vitamin D, PTH and renal osteodystrophy. In: Brenner B, Rector F, editors. *The kidney*. Philadelphia: Saunders; 1981. p. 2213.
140. Ott SM, Maloney NA, Coburn JW. The prevalence of bone aluminum deposition in renal osteodystrophy and its relation to the response to calcitriol therapy. *N Engl J Med* 1982;**307**:709–13.
141. Andress DL, Sherrard DJ. The osteodystrophy of chronic renal failure. In: Schrier RW, editor. *Diseases of the kidney and urinary tract*. Lippincott Williams & Wilkins; 2001. p. 2735–67.
142. Andreoli SP, Bergstein JM, Sherrard DJ. Aluminum intoxication from aluminum-containing phosphate binders in children with axotemia not undergoing dialysis. *N Engl J Med* 1984;**310**:1079–84.
143. Coburn JW, Sherrard DJ, Brickman AS. A skeletal mineralizing defect in dialysis patients: a syndrome resembling osteomalacia but unrelated to vitamin D. *Contrib Nephrol* 1980;**18**:172–83.
144. West S, Lok C, Jamal S. Fracture risk assessment in chronic kidney disease, prospective testing under real World Environments (FRACTURE): a prospective study. *BMC Nephrol* 2010;**11**(1):17.
145. Jamal S, Gilbert J, Gordon C, Bauer D. Cortical pQCT measures are associated with fractures in dialysis patients. *J Bone Miner Res* 2006;**21**(4):543–8.
146. Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, et al. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int* 2000;**58**(1):396–9.
147. Cunningham J, Sprague SM, Cannata-Andia J, Coco M, Cohen-Solal M, Fitzpatrick L, et al. Osteoporosis in chronic kidney disease. *Am J Kidney Dis* 2004;**43**(3):566–71.
148. Stehman-Breen C. Osteoporosis and chronic kidney disease. *Semin Nephrol* 2004;**24**(1):78–81.
149. Rix M, Andreassen H, Eskildsen P, Langdahl B, Olgaard K. Bone mineral density and biochemical markers of bone turnover in patients with predialysis chronic renal failure. *Kidney Int* 1999;**56**(3): 1084–93.
150. Bonyadi M, Waldman SD, Liu D, Aubin JE, Grynpas MD, Stanford WL. Mesenchymal progenitor self-renewal deficiency leads to age-dependent osteoporosis in Sca-1/Ly-6A null mice. *Proc Natl Acad Sci USA* 2003;**100**(10):5840–5.
151. Stehman-Breen C. Bone mineral density measurements in dialysis patients. *Semin Dial* 2001;**14**(3):228–9.
152. Stehman-Breen C, Sherrard D, Walker A, Sadler R, Alem A, Lindberg J. Racial differences in bone mineral density and bone loss among end-stage renal disease patients. *Am J Kidney Dis* 1999;**33**(5):941–6.
153. Coco M, Rush H. Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. *Am J Kidney Dis* 2000;**36**(6):1115–21.
154. Behets GJ, Verberckmoes SC, Oste L, Bervoets AR, Salome M, Cox AG, et al. Localization of lanthanum in bone of chronic renal failure rats after oral dosing with lanthanum carbonate1. *Kidney Int* 2005;**67**:1830–6.
155. Norrdin RW, Hoopes KJ, O'Toole D. Skeletal changes in hemochromatosis of Salers cattle. *Vet Pathol* 2004;**41**(6):612–23.
156. VandeVyver F, Visses WJ, D'Hesse P, DeBroe ME. Iron overload and bone disease in chronic dialysis patients. *Nephrol Dial Transplant* 1990;**5**:781–7.
157. Spasovski GB, Sikole A, Gelev S, Masin-Spasovska J, Freemont T, Webster I, et al. Evolution of bone and plasma concentration of lanthanum in dialysis patients before, during 1 year of treatment with lanthanum carbonate and after 2 years of follow-up. *Nephrol Dial Transplant* 2006;**21**. gfl146.
158. Freemont T, Malluche HH. Utilization of bone histomorphometry in renal osteodystrophy: demonstration of a new approach using data from a prospective study of lanthanum carbonate. *Clin Nephrol* 2005;**63**:138–45.
159. D'Haese PC, Spasovski GB, Sikole A, Hutchison A, Freemont TJ, Sulkova S, et al. A multicenter study on the effects of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients. *Kidney Int* 2003;**63**:S73–8.
160. Malluche HH, Siami GA, Swanepoel C, Wang GH, Mawad H, Confer S, et al. Improvements in renal osteodystrophy in patients treated with lanthanum carbonate for two years. *Clin Nephrol* 2008;**70**:284–95.
161. Hutchison AJ, Maes B, Vanwalleghem J, Asmus G, Mohamed E, Schmieder R, et al. Long-term efficacy and tolerability of lanthanum carbonate: results from a 3-year study. *Nephron Clin Pract* 2006;**102**:c61–71.
162. Whitaker M, Guo J, Kehoe T, Benson G. Bisphosphonates for osteoporosis — where do we go from here? *N Engl J Med* 2012;**366**(22): 2048–51.
163. Berenson JR. Treatment of hypercalcemia of malignancy with bisphosphonates. *Semin Oncol* 2002;**29**(6 Suppl. 21):12–8.
164. Toussaint ND, Elder GJ, Kerr PG. Bisphosphonates in chronic kidney disease; balancing potential benefits and adverse effects on bone and soft tissue. *Clin J Am Soc Nephrol* 2009;**4**(1):221–33.
165. Miller PD. Is there a role for bisphosphonates in chronic kidney disease? *Semin Dial* 2007;**20**:186–90.
166. Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. *J Bone Miner Res* 2005;**20**:2105–15.
167. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American society for bone and mineral research. *J Bone Miner Res* 2007;**22**(10): 1479–91.
168. James MA, Watt PAC, Potter JF, Thurston H, Swales JD. Pulse pressure and resistance artery structure in the elderly. *Hypertension* 1995;**26**(2):301–6.
169. Nickolas TL, Leonard MB, Shane E. Chronic kidney disease and bone fracture: a growing concern. *Kidney Int* 2008;**74**(6):721–31.
170. Yenchek RH, Ix JH, Shlipak MG, Bauer DC, Rianon NJ, Kritchevsky SB, et al. Bone mineral density and fracture risk in older individuals with CKD. *Clin J Am Soc Nephrol* 2012;**7**(7): 1130–6.
171. Goodman WG, London G, Amann K, Block GA, Giachelli C, Hruska KA, et al. Vascular calcification in chronic kidney disease. *Am J Kidney Dis* 2004;**43**(3):572–9.
172. London GM, Marty C, Marchais SJ, Guerin AP, Metivier F, de Vernejoul MC. Arterial calcifications and bone histomorphometry in end-stage renal disease. *J Am Soc Nephrol* 2004;**15**:1943–51.
173. London GM, Pannier B, Guerin AP, Blacher J, Marchais SJ, Darne B, et al. Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: follow-up of an interventional study. *J Am Soc Nephrol* 2001;**12**:2759–67.
174. Hafner J, Keusch G, Wahl C, Sauter B, Hurlimann A, von Weisacker F, et al. Uremic small-artery disease with medical calcification and intimal hyperplasia (so-called calciphylaxis): a complication of chronic renal failure and benefit from parathyroidectomy. *J Am Acad Dermatol* 1995;**33**:954–62.
175. Selye H. *Calciphylaxis*. Chicago: University of Chicago Press; 1962.

176. Edwards RB, Jaffe W, Arrowsmith J, Henderson HP. Calciphylaxis: a rare limb and life threatening cause of ischaemic skin necrosis and ulceration. *Br J Plast Surg* 2000;**53**:253–4.
177. Ichikawa S, Imel EA, Kreiter ML, Yu X, Mackenzie DS, Sorenson AH, et al. A homozygous missense mutation in human KLOTHO causes severe tumoral calcinosis. *J Clin Investig* 2007; **117**(9):2684–91.
178. Ichikawa S, Lyles KW, Econs MJ. A novel GALNT3 mutation in a pseudoautosomal dominant form of tumoral calcinosis: evidence that the disorder is autosomal recessive. *J Clin Endocrinol Metab* 2005;**90**(4):2420–3.
179. Benet-Pages A, Orlik P, Strom TM, Lorenz-Depiereux B. An FGF23 missense mutation causes familial tumoral calcinosis with hyperphosphatemia. *Hum Mol Genet* 2005;**14**(3):385–90.
180. Martin KJ, González EA. Metabolic bone disease in chronic kidney disease. *J Am Soc Nephrol* 2007;**18**(3):875–85.
181. Applbaum Y. *Chapter 12: imaging the skeleton and joints in CKD*. 2nd ed. 2010. Oxford.
182. Thadhani R, Appelbaum E, Pritchett Y, Chang Y, Wenger J, Tamez H, et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease. *J Am Med Assoc* 2012; **307**(7):674–84.
183. Investigators TET. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012;**367**(26):2482–94.
184. Wang AY-M, Fang F, Chan J, Wen Y-Y, Qing S, Chan IH-S, et al. Effect of paricalcitol on left ventricular mass and function in CKD—the OPERA trial. *J Am Soc Nephrol* 2014;**25**(1):175–86.
185. Shimada T, Urakawa I, Yamazaki Y, Hasegawa H, Hino R, Yoneya T, et al. FGF-23 transgenic mice demonstrate hypophosphatemic rickets with reduced expression of sodium phosphate cotransporter type IIa. *Biochem Biophys Res Commun* 2004;**314**: 409–14.
186. Larsson T, Marsell R, Schipani E, Ohlsson C, Ljunggren O, Tenenhouse HS, et al. Transgenic mice expressing fibroblast growth factor 23 under the control of the α1 (I) collagen promoter exhibit growth retardation, osteomalacia, and disturbed phosphate homeostasis. *Endocrinology* 2004;**145**:3087–94.
187. Hu MC, Shi M, Gillings N, Flores B, Takahashi M, Kuro-o M, et al. Recombinant α-Klotho may be prophylactic and therapeutic for acute to chronic kidney disease progression and uremic cardiomyopathy. *Kidney Int* 2017;**91**(5):1104–14.
188. Giachelli CM, Speer MY, Li X, Rajachar RM, Yang H. Regulation of vascular calcification: roles of phosphate and osteopontin. *Circ Res* 2005;**96**:717–22.

QUESTIONS AND ANSWERS

Question 1

A 46-year-old man with S[Cr] 2.9 mg/dL and eGFR 22 mL/min/1.73 m^2 is seen in clinic. The patient has small echogenic kidneys on renal ultrasound. One year earlier, S[Cr] was 2.13 mg/dL, S[Ca] was 9.1 mg/dL, and PTH was 105 pg/mL. His blood pressure is 150/94 mm Hg. Blood pressure medications include amlodipine 5 mg daily and lisinopril 20 mg daily. On these medications, the blood pressure was normal one year ago. The following blood tests are available:

S[Ca] 10.9 mg/dL
Ionized calcium 5.68 mg/dL (normal 4.64–5.16 mg/dL)
S[P] 3.8 mg/dL
PTH 8 pg/mL (normal 14–72 pg/mL)
25-Vitamin D 34 ng/mL (goal 30–80 ng/mL)
1,25-Vitamin D 20 pg/mL (normal 19–72 pg/mL)
S[Na] 138 mEq/L
S[K] 4.4 mEq/L
S[Cl] 94 mEq/L
S[HCO_3] 34 mEq/L

Which of the following statements regarding the hypercalcemia is most likely?

A. The hypercalcemia is due to severe secondary hyperparathyroidism from renal failure
B. The hypercalcemia is from primary hyperparathyroidism
C. The hypercalcemia is from exogenous calcium ingestion
D. The hypercalcemia is from an undiagnosed granulomatous disease
E. Vitamin D intoxication should be suspected

Answer: C

PTH is suppressed from hypercalcemia, which does not occur in either severe secondary hyperparathyroidism or primary hyperparathyroidism. Rather the high PTH drives the hypercalcemia in these conditions. Last year, the patient had a mildly elevated PTH and normal S[Ca] which would be compatible with secondary hyperparathyroidism from renal failure. Hypercalcemia with renal failure from a granulomatous disease such as sarcoidosis is sometimes seen, but the cause is an elevated 1,25-vitamin D value, which was not present in this case. The normal 25-vitamin D shows that the patient is not ingesting excessive amounts of vitamin D. The patient is also not taking a thiazide diuretic, which infrequently contributes to the development of hypercalcemia. The correct answer is that the hypercalcemia is from exogenous calcium ingestion, which is known as the milk alkali syndrome. The major clue is the elevated serum bicarbonate concentration. Renal failure in the absence of an exogenous source of bicarbonate is associated with metabolic acidosis because of a decreased capacity to excrete an acid load. Finally, the capacity to excrete an exogenous calcium load is decreased in renal failure because of decreased calcium filtration due to the deceased GFR.

Question 2

A 34-year-old male with stage 4 CKD, S[Cr] 3.5 mg/dL (eGFR 19 mL/min/1.73 m^2), and with urinary protein excretion less than 1 g/24 h is seen in your clinic. The blood pressure is controlled and the patient is asymptomatic. The following blood work is obtained:

S[Ca] 7.4 mg/dL
Ionized calcium 3.76 mg/dL (normal 4.64–5.16 mg/dL)
S[P] 6.6 mg/dL
PTH 629 pg/mL (normal 10–65 pg/mL)
1,25-Vitamin D 14 pg/mL (normal 19–72 pg/mL)
25-Vitamin D 16 ng/mL (goal >30 ng/mL)

Which of the following should be done first to treat the elevated PTH?

A. Begin treatment with a calcium-based phosphate binder and have the patient see a dietician to restrict dietary phosphate
B. Begin treatment with 1,25-vitamin D (calcitriol) to reduce the PTH and increase serum calcium (S[Ca])
C. Start cholecalciferol (vitamin D_3) at 2000 IU/day
D. Begin treatment with the calcimimetic cinacalcet to reduce the PTH value
E. Begin treatment with sevelamer

Answer: A

An approach to initiating treatment requires a firm understanding of the pathophysiology of hyperparathyroidism. The first step in treating an elevated PTH in a patient with CKD is to correct the abnormal serum phosphate (S[P]), (S[Ca]), and vitamin D values. Hypocalcemia stimulates PTH secretion contributing to the elevated PTH. Hyperphosphatemia exacerbates the hypocalcemia by increasing the calcemic resistance to PTH. Thus, the first step to treat hyperparathyroidism in this patient is to begin with a calcium-based phosphate binder which not only lowers the S[P] but also increases the S[Ca]. In addition, such an elevated S[P] in stage 4 CKD is somewhat unusual and suggests the patient is eating a high phosphate diet and would benefit from seeing a dietician. Starting treatment with 1,25-vitamin D (calcitriol) is not correct because it increases intestinal phosphate absorption, making the hyperphosphatemia worse. Starting treatment with cinacalcet

is also incorrect because marked hypocalcemia is already present and cinacalcet will lower S[Ca] further. In addition, in CKD patients not on dialysis, lowering PTH with cinacalcet decreases phosphate excretion which increases S[P]. Starting cholecalciferol to increase 25OHD to greater than 30 ng/mL is desirable, but not the best answer because it takes time for 25OHD values to increase, and the reduction in PTH is generally modest. As a general rule, 1000 IU of cholecalciferol will increase 25OHD values by approximately 10 ng/mL. Treatment with sevelamer would lower the S[P], which would improve the calcemic action of PTH, but in the presence of marked hypocalcemia, a calcium-based phosphate binder would serve the dual purpose of lowering S[P] and decreasing PTH levels by increasing S[Ca]. Once the hyperphosphatemia has been corrected, then 1,25-vitamin D (calcitriol) could be used to treat the hyperparathyroidism if hypocalcemia is still present.

Question 3

After the first generation PTH assay was developed in the late 1960s, elevated PTH values were shown to accompany the parathyroid gland hyperplasia known to be present in CKD. In the early 1970s, Slatopolsky and Bricker proposed the "trade-off" hypothesis, which stated that as a result of decreased renal function, phosphate retention would cause transient reductions in S[Ca] which would be corrected by increased PTH secretion, restoring the S[Ca] and S[P] to normal. The "trade-off" was maintenance of normal circulating calcium and phosphate concentration by a progressive increase in PTH levels and parathyroid gland hyperplasia. Subsequent studies with dietary phosphate loading and restriction established a central role for phosphate in PTH secretion and parathyroid gland hyperplasia. In azotemic animals, dietary phosphate loading increased PTH secretion and parathyroid gland hyperplasia, whereas dietary phosphate restriction had the opposite effect. Later studies showed that both the VDR and CaSR were present in the parathyroid gland.

Which of the following statements about parathyroid gland hyperplasia is not correct?

A. The progressive decrease in the VDR seen as parathyroid gland hyperplasia contributes to the development of parathyroid gland hyperplasia
B. Nodular hyperplasia precedes the development of diffuse parathyroid gland hyperplasia
C. A decrease in the CaSR is seen in parathyroid gland hyperplasia
D. High dietary phosphate given to azotemic rats increases PTH levels and PCNA positive cells, a marker of cell proliferation, in parathyroid gland
E. Clonal analysis of parathyroid nodules has shown that each nodule arises from a single clone of cells

Answer: B

As parathyroid gland hyperplasia develops, an increase in the number of secretory cells is followed by the development of diffuse hyperplasia. With continuing hyperplasia, the next stage is early nodularity, followed by multiple nodules in the parathyroid gland, which can evolve into a single nodule. During this evolution, the mass of the parathyroid gland continues to increase. By the time the weight of the parathyroid gland exceeds 500 mg (normal weight <40 mg), the vast majority of parathyroid glands have some form of nodularity. Individual parathyroid glands greater than 5000 mg can be seen, and asymmetry of the different parathyroid glands in a single patient is common. Diffuse parathyroid gland hyperplasia has a polyclonal origin, whereas nodular hyperplasia has a monoclonal origin. As progressive parathyroid gland hyperplasia develops, there is a decrease in both the VDR and CaSR which contributes to loss of sensitivity (suppressive effect) to vitamin D (calcitriol) and calcium. Because of the decrease in the CaSR, there were questions regarding whether azotemic patients with advanced secondary hyperparathyroidism (presumably nodular hyperplasia) would respond to the calcimimetic cinacalcet, which suppresses PTH secretion through its actions on the CaSR. For the above statements, B is incorrect because diffuse hyperplasia precedes nodular hyperplasia. A progressive decrease in the VDR and CaSR is seen as parathyroid gland hyperplasia progresses from diffuse to nodular hyperplasia. Finally, a high phosphate diet in azotemic rats has been shown to increase PTH levels and parathyroid cell proliferation.

Question 4

A 60-year-old man is referred to your office for evaluation of CKD. The past history is unremarkable except for stage 1 hypertension for 10 years, mild obesity, and benign prostatic hypertrophy. His eGFR has deteriorated over the past 12 months from 100 mL/min/1.73 m^2 to 45 mL/min/1.73 m^2. Several urinalyses obtained during the past year were bland except for trace protein by dipstick. A renal ultrasound obtained 3 months ago was unremarkable, with normal sized kidneys and no significant postvoid residual. He did not

use nonsteroidal antiinflammatory agents or herbal medications and reported no lower urinary tract symptoms.

The following:

S[Na] 140 mEq/L
S[K] 4.2 mEq/L
S[Cl] 107 mEq/L
S[HCO3] 25 mEq/L
S[Ca] 9.8 mg/dL
S[P] 7.0 mg/dL
BUN 35 mg/dL
S[Cr] 1.8 mg/dL
eGFR 45 mL/min/1.73 m^2

Which one of the following is true about his condition?

A. He should be started on a low phosphate diet
B. He needs to start on a calcium-containing phosphate binder
C. He needs to be started on a noncalcium-containing phosphate binder
D. The S[P] is elevated due to resistance to FGF-23
E. Free light chains should be measured

Answer: E

Hyperphosphatemia in CKD does not usually occur until the GFR is below 30 mL/min. In addition, S[Ca] is usually low normal or decreased when the S[P] is increased. In this case, the S[P] is high and S[Ca] is high normal. This profile can be seen in cases of pseudohyperphosphatemia, in which S[P] is actually normal, but appears elevated due to laboratory methodology. Dysproteinemias, such as multiple myeloma, are a common cause of pseudohyperphosphatemia. Excessive serum protein as seen in multiple myeloma may produce excessive turbidity and interfere with the colorimetric assay used to measure S[P]. Restricting dietary phosphate and using phosphate binders in the presence of pseudohyperphosphatemia can result in significant hypophosphatemia. Resistance to FGF-23 does occur with stage 3 CKD, but FGF-23 levels rise along with PTH levels in compensation, resulting in the maintenance of S[P] in the normal range.

Question 5

You are asked to consult on a 75-year-old man with worsening hyperphosphatemia. His past history is remarkable for hypertension, gastroesophageal reflux, elevated prostate-specific antigen (PSA), intermittent constipation, and schizophrenia. He has had stable CKD, with urinary protein excretion less than 1 g/24 h, following an episode of AKI 10 years ago, with a residual eGFR of 45 mL/min/1.73 m^2. His S[Ca] has fluctuated between 9.1–9.3 mg/dL and S[P] between 4.2 and 4.6 mg/dL. Because of an increasing PSA, he has undergone an extensive urologic evaluation during the past 6 months, including an MRI of the prostate, prostate biopsy, and transurethral prostatectomy. His only complaint is intermittent constipation. His estimated dietary phosphorus intake is approximately 700 mg per day. His medications include amlodipine, atorvastatin, doxazosin, omeprazole, and quetiapine.

The following laboratory data are obtained:

S[Ca] 8.2 mg/dL
S[P] 8.0 mg/dL
eGFR 35 mL/min/1.73 m^2

What would be the next appropriate steps in the management of the patient's hyperphosphatemia?

A. Reduce dietary phosphorus
B. Start calcium-containing phosphate binder
C. Start noncalcium-containing phosphate binder
D. Obtain further history regarding bowel habits and prostate procedures
E. Obtain CBC, CPK
F. D and E

Answer: F

The dietary phosphorus intake in this patient is relatively low and is unlikely to be the cause of the patients worsening hyperphosphatemia. He has had a decline in renal function which may be a factor contributing to the increased S[P], but his GFR is still at a level that is typically not associated with significant hyperphosphatemia. In this case, it would be important to look for additional endogenous or exogenous sources of phosphate. Hemolysis or rhabdomyolysis can result in an increased endogenous phosphate load. The patient is on a statin, which is a relatively common cause of rhabdomyolysis, which is associated with a rise in S[P] and decline in renal function. Some patients with schizophrenia can be obsessed with bowel cleansing and may use phosphate purges. In addition, the patient had recently undergone an extensive urological evaluation. Phosphate enemas are commonly used for bowel cleansing before urological procedures such as the prostate MRI, prostate biopsy, and transurethral resection. Although the small intestine is the primary intestinal site for phosphate absorption, the large bowel may also absorb phosphate, particularly if there is prolonged retention of the enema or bowel irritation. The use of phosphate purgatives may also explain the deterioration in renal function by inducing an interstitial nephritis from calcium-phosphate precipitation. Therefore, obtaining a careful history regarding the possible use of phosphate purgatories would be important in this case, particularly with the complaint of constipation. The use of phosphate binders would have little impact

in this case if the source of excessive phosphate load is endogenous or from the use of phosphate enemas.

Question 6

A 78-year-old man is admitted to the hospital with acute abdominal pain and vomiting. The patient has a history of congestive heart failure with an ejection fraction of 30% and is treated with furosemide 40 mg twice daily. On admission, the patient is somnolent and the systolic blood pressure is 90 mm Hg with a pulse of 46 bpm. He has a distended and tender abdomen. Pertinent laboratory results include white blood cell count 6900×10^9/L, hemoglobin 10.5 g/dL, S[Na] 140 mEq/L, S[K] 3.4 mEq/L, S[Cl] 104 mEq/L, S[Ca] 8.1 mg/dL, S[Alb] 4.2 g/dL, S[Cr] 2.1 mg/dL (baseline 1.5 mg/dL), and BUN 42 mg/dL. CT exam of the abdomen shows dilated loops of bowel and air fluid levels compatible with an ileus. The electrocardiogram shows prolonged PR and QT intervals and an increase in QRS duration. After your initial evaluation, you find the family in the waiting room. The family tells you that the patient was being prepared for colonoscopy to be performed that same day, but they did not know the medication he was taking. After obtaining that information, you measure the S[P] and S[Mg]. The S[P] is 2.2 mg/dL and the S[Mg] is 9.2 mg/dL. What are the two best answers?

A. Give intravenous furosemide
B. Give intravenous calcium
C. Give intravenous phosphate to correct the hypophosphatemia
D. Dialyze the patient
E. Wait for the magnesium load to be excreted

Answers: B and D

Magnesium citrate was given as the bowel preparation. 450 mL of magnesium citrate was prescribed to be taken at 7 pm and another 450 mL was prescribed to be taken in the morning 5 hours before the scheduled colonoscopy. The total elemental magnesium load is almost 9 g, while the recommended intake of elemental magnesium is approximately 350−400 mg daily. Thus, elderly patients with decreased renal function are clearly at risk for developing hypermagnesemia with toxic manifestations when give a magnesium load. The two best answers are B and D. Calcium is an antagonist of magnesium which acts as a calcium channel blocker. Calcium administration can reverse cardiac arrhythmias, hypotension, and other manifestations of hypermagnesemia. Hemodialysis with a magnesium free dialysate is an effective treatment because it rapidly lowers the magnesium concentration, reversing its toxicity. The Answer A, furosemide, is correct in patients with good cardiac and renal function and mild to moderate hypermagnesemia. Furosemide is often given with normal saline to enhance magnesium excretion at its primary excretory site in the thick ascending limb of Henle. However, the combination of furosemide and saline is not a good choice in this patient because of his congestive heart failure and decreased renal function. To measure the S[P] after learning the patient was given a bowel preparation was important because phosphate bowel preps are common and are associated with nephrotoxicity in older patients with decreased renal function. In addition, the observed hypocalcemia associated with phosphate toxicity would be consistent with the hypocalcemia seen in this patient. But the mild hypophosphatemia present in this patient immediately after taking the bowel prep essentially eliminates phosphate bowel preparation as the cause of this patient's illness. Even though mild hypophosphatemia is present, there is no indication to give phosphate, which could exacerbate the hypocalcemia. Finally, it is unlikely that the patient would spontaneously excrete his magnesium load before progressive complications occur.

CHAPTER

36

Sleep Disorders in Chronic Kidney Disease

Lee K. Brown[a,b,c,d], *Mark L. Unruh*[a,e]

[a]Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, NM, United States; [b]University of New Mexico Health Sciences Center, Albuquerque, NM, United States; [c]University of New Mexico School of Engineering, Albuquerque, NM, United States; [d]University of New Mexico Health System Sleep Disorders Centers, Albuquerque, NM, United States; [e]Nephrology Section, New Mexico Veterans Hospital, Albuquerque, NM, United States

Abstract

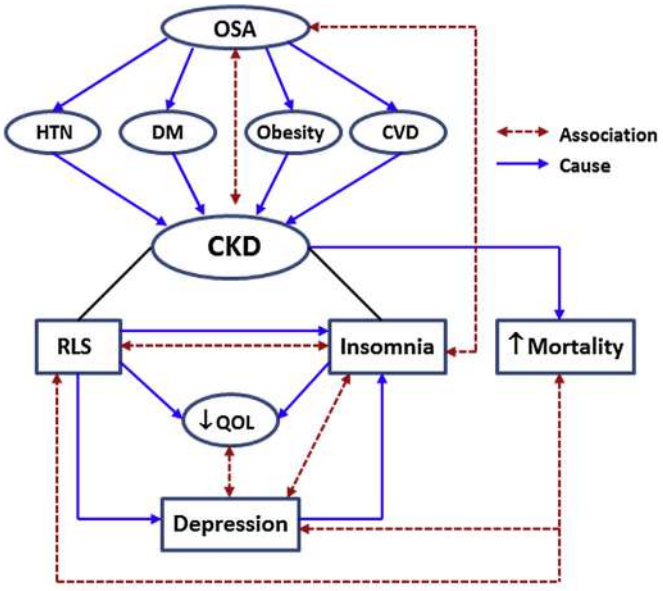
Sleep is an essential function of life. Sleep clearly serves a crucial role in the promotion of health and performance. Poor sleep quality and sleep disorders have been a recurrent finding in patients with chronic kidney disease (CKD). Sleep disorders such as obstructive sleep apnea (OSA) can contribute to hypertension, diabetes (type 2 diabetes mellitus [T2DM]), cardiovascular disease (CVD), and worsen obesity, all of which are implicated in the etiology of CKD. CKD itself may lead to OSA. Mechanisms specific to OSA could hasten decline in renal function in and of themselves. OSA, in spite of its high prevalence, remains underdiagnosed and undertreated in CKD patients. Optimal sleep duration and quality play a significant role in improving control of T2DM. Insufficient sleep has been shown to increase the risk of obesity. Restless legs syndrome (RLS) and insomnia worsen health-related quality of life in CKD patients. RLS and depression are associated with increased mortality in CKD patients. There is emerging evidence linking insomnia and RLS to an increased risk of CVD, which is an important cause of mortality in CKD patients, and insomnia is increasingly recognized as having a causal link to dementia and white matter disease. Addressing sleep disorders could help to prevent not only the development but also the progression of CKD.

INTRODUCTION

Sleep is an essential function of life, consuming approximately one-third of our existence and clearly serving a crucial role n the promotion of health and performance. Sleep has been described behaviorally as "a reversible behavioral state of perceptual disengagement from, and unresponsiveness to, the environment."[1] Sleep appears to exert a restorative effect on the brain by allowing recovery of CNS neurons that undergo one or more reversible changes during wakeful activation. Recent work suggests that sleep facilitates the clearance of β amyloid by the glymphatic system.[2] Similar to diet and activity, sleep serves as an important regulator of somatic growth, maturation, and health. Moreover, sleep is an important enabler of protein synthesis and body repair. The negative effects of sleep deprivation include defects in cognition, vigilance, emotional stability, risk-taking, and possibly moral reasoning as well as an increase in appetite, and glucose intolerance.[3–6] Procedural, declarative, and emotional memory are impaired by lack of sleep, and functional MRI shows profound changes in regional cerebral activity related to attention and memory.[7] Widespread alterations of immune function and inflammatory regulators can also be seen.[5] Sleep and sleep quality may be impaired among those with chronic illnesses, particularly among individuals with chronic kidney disease (CKD).

In the past decade, CKD has been increasingly linked with poor sleep quality and a variety of sleep disorders. Sleep disorders such as obstructive sleep apnea (OSA) can contribute to hypertension, diabetes, cardiovascular disease, and obesity, all of which are implicated in the etiology of CKD (Figure 36.1). Although hypertension, diabetes, and obesity are risk factors for CKD, the causal relationship between sleep disorders and CKD is not yet well established. Although several risk factors for CKD are also commonly linked to sleep disorders such as OSA, OSA alone may also accelerate the progression of CKD. Thus, although it appears highly likely that a unidirectional or bidirectional relationship between CKD and OSA exists, the increased prevalence of both of these

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00036-X



Abbreviations: OSA= obstructive sleep apnea; HTN = hypertension; DM = diabetes; CVD = cardiovascular disease; CKD = chronic kidney disease; RLS = restless leg syndrome; QOL = quality of life

FIGURE 36.1 Significance of sleep disorders in CKD patients.

disorders and their associated risk factors has made the direction of causality and underlying mechanisms difficult to ascertain. Certainly, this subject warrants further understanding because it is likely that clinicians must recognize and treat sleep disorders in CKD patients to slow the progression to renal replacement therapy. The aim of this chapter is to describe the important role sleep plays in patients with CKD. Three specific sleep disorders in CKD patients, insomnia, OSA, and restless legs syndrome (RLS), will be discussed (including their prevalence, pathogenesis, impact, and treatment).

INSOMNIA

Insomnia is defined as difficulty falling asleep, staying asleep, and/or the perception of inadequate sleep along with daytime consequences that cannot be attributed to another sleep disorder. The International Classification of Sleep Disorders [ICSD-3] diagnostic criteria for insomnia are shown in Table 36.1. In comparison with previous editions of the ICSD, insomnia is now classified as either Chronic Insomnia Disorder or Short-term Insomnia Disorder. The latter encompasses time-limited insomnia that is a result of a stressful event, whereas the former is further subdivided into insomnia disorders with distinct clinical and pathophysiologic correlates. Specific criteria for eight individual disorders associated with the symptom of insomnia are listed in the ICSD-3.

In the general population, insomnia symptoms occur in 30–40% of adults. Specific insomnia disorders occur in 5–10% of adults.[9] Studies in CKD patients have shown a wide range of estimates of chronic insomnia disorder, with a high prevalence of insomnia reported early in the course of CKD,[10] suggesting that this may be an important factor in the difficulty CKD patients have coping with their illness. Moreover, the prevalence of chronic insomnia disorder is higher with lower levels of kidney function.[11] Although chronic illnesses are a significant risk factor for insomnia, the presence of concurrent depressive symptoms is an even stronger risk factor. Moreover, the relationship between insomnia and depression is thought to be bidirectional. Longitudinal studies have shown insomnia to be a substantial risk factor for the subsequent development of depression, and this risk appears to extend over a large portion of a person's life.[12,13] Patients with CKD have an increased prevalence of both insomnia and depression, and therefore the presence of insomnia presumably would additively increase their risk of depression, nonresponse to treatment for depression, and any subsequent recurrence.

There remains some uncertainty regarding the prevalence of clinical insomnia in CKD patients, as most studies have relied on self-report rather than evaluation by a skilled practitioner. Several studies have reported a wide range of insomnia prevalence (14–85%) in CKD patients, based on patient reported questionnaires.[14–23] Cohen et al. reported that 69% of patients with CKD experienced pain; 55% had disordered sleep with scores on the Pittsburgh Sleep Quality Inventory (PSQI) >5.[17] Kurella et al. reported a prevalence of insomnia of 5–20% for all CKD patients, and in Caucasian and Asian subjects, lower kidney disease quality of life (KDQoL) scores were seen in advanced stages of CKD compared to early stages of CKD.[16] Interestingly, self-reported insomnia seemed to persist even after renal transplantation in two studies.[23,24] Another relevant question relates to whether insomnia symptoms differ with respect to dialysis modality. Knezevic et al. used the Insomnia Severity Index questionnaire to compare HD techniques consisting of online polysulfone bicarbonate hemodiafiltration (n = 43), high-flux polysulfone bicarbonate hemodialysis (HD) (n = 39), and low-flux polysulfone bicarbonate HD (n = 40).[25] Their data suggested a beneficial effect on insomnia symptoms by using high-flux membranes. Yet another controversy has been raised regarding whether sleep is disturbed by nocturnal treatment for end-stage renal disease (ESRD) by means of automated peritoneal dialysis (APD). Losso et al. examined this possibility using a battery of questionnaires administered to patients on HD, home-based continuous ambulatory peritoneal dialysis (CAPD), and APD.[26] Their data indicated that the

TABLE 36.1 International Classification of Sleep Disorders, Third Edition: Diagnostic and Coding Manual Diagnostic Criteria for Chronic Insomnia Disorder*

A	A complaint of difficulty initiating sleep, difficulty maintaining sleep, or waking up too early, sleep that is chronically nonrestorative or poor in quality, or (in children), resistance to an appropriate bedtime, or difficulty falling asleep without adult intervention.
B	At least one of the following forms of daytime consequences related to the nighttime sleep difficulty is reported by the patient:
	1. Fatigue or malaise
	2. Poor attention or concentration
	3. Social or vocational/educational dysfunction
	4. Abnormal mood or excessive irritability
	5. Inappropriate sleepiness
	6. Reduced motivation or energy
	7. Increased errors or accidents
	8. Impulsivity, hyperactivity, aggression, or other changes in behavior
	9. Concerns or worries about sleep duration, continuity, or quality
C	The insomnia symptom(s) occur in the setting of an adequate amount of time allotted for sleep and an environment conducive to sleep
D/E	Symptoms occur at least three times per week for at least 3 months
F	Symptoms are not better explained by another sleep disorder

* *Adapted from reference 8.*

prevalence of insomnia was similar between the HD (85 %), CAPD (81%), and APD (84%) groups ($p = 0.83$). Studies incorporating a thorough clinical history with a focus on the items listed in the ICSD-3 or a similar nosology are warranted to determine a more precise estimate of the rate of chronic insomnia disorder in CKD patients.

In addition to self-reported symptoms of insomnia, CKD patients have reduced sleep efficiency and poor sleep quality measured by actigraphy and polysomnographic (PSG) testing. Parker et al. reported PSG measures of sleep in 8 later-stage CKD patients and 16 patients on chronic HD.[27] In this study, both groups had reduced total sleep time and sleep efficiency in comparison with normative data. Analysis of quality of life (QOL) scores showed that CKD patients had lower psychological, spiritual, health, and functioning scores compared to HD patients, suggesting that the impact of having untreated CKD in and of itself is marked. The prospect of CKD progression and the eventual need for renal replacement therapy appeared to adversely affect sleep and QOL in the CKD patients. Roumelioti et al. also demonstrated delayed sleep onset and short and disrupted sleep in the CKD and ESRD population.[28] Agarwal and Light[29] and Barmer et al.[30] studied CKD patients using wrist actigraphy, demonstrating reduced sleep efficiency and poor sleep quality using this semi-quantitative technique. Disrupted sleep was associated with a decline in daytime activity, both in duration as well as in intensity, and poor QOL.

Importantly, the quality of sleep has been reported to decrease even in the early stages of CKD.[15] Sabbatini reported that progression of CKD was accompanied by progressive worsening of sleep quality. Over a 3-year time period, decline in both sleep quality as well as the expected worsening of kidney function were reported.[18] Ezzat et al. performed nocturnal PSGs in three groups of patients: those with CKD, those with ESRD treated with HD, and normal controls. In the ESRD group, PSGs were performed on the night of their HD, whereas the CKD subjects were age- and gender-matched, and metabolically comparable.[19] Both CKD and ESRD patients had reduced total sleep time and sleep efficiency in comparison with controls. The CKD group had normal sleep latency, whereas the HD group exhibited sleep latencies almost twice as long. HD patients exhibited significantly less REM sleep and an increase in brief arousals, which may have been a consequence of this group demonstrating more frequent apneas (despite attempts to limit the likelihood of sleep-disordered breathing in the subjects) and limb

movements. Additional analyses revealed inverse correlations between sleep disorders and levels of circulating hemoglobin and albumin, as well as creatinine clearance, and a positive correlation between disordered sleep and serum phosphate concentration (S[P]). In summary, CKD patients have an increased prevalence of insomnia and depression, decreased health-related quality of life (HRQOL), decreased daytime activity, and a progressive decline in sleep quality and kidney function.

Pathogenesis

Although it is unknown if there is a shared propensity for hyperarousal in CKD, it has been shown that CKD patients suffer marked socioeconomic and health-related stress as well as distress that could lead to the same result.[31] Converging evidence from physiological and psychological studies suggest that hyperarousal is common to individuals with insomnia.[32] Worry and rumination about life stresses result in hyperarousal, disrupted sleep, and foster insomnia. It is also likely that interplay exists between a genetic vulnerability to an imbalance between arousing and sleep-inducing brain activity, psychosocial/medical stressors, and perpetuating mechanisms, including improper sleep behaviors, learned sleep-preventing associations, and the tendency to worry and ruminate.[33] Insomnias were found to have a higher heart rate, decreased heart rate variability, and increased lower frequency spectral power—all characteristics of increased sympathetic activity that could then increase cardiovascular risk.[34] Patients with insomnia have increased cerebral glucose metabolism in pertinent CNS regions when studied by positron emission tomography scans,[35] characteristic of failure of arousal mechanisms to decrease in activity from wake to sleep states.

Impact

Insomnia in CKD patients has been shown to be independently associated with self-reported comorbidity, depression, RLS symptoms, and increased risk for OSA as assessed by the Berlin questionnaire. These observations are consistent with relationships observed in the general population. Insomnia has been associated with decrements in HRQOL, increased costs of care, poor work performance, and depression in the general population. Patients with severe insomnias have also been reported to have more medical problems, more physician office visits, more frequent hospitalizations, and more medication use compared to good sleepers, creating a significant economic burden.[36–38] Simon and Von Korff reported that mean total health care expenditures were 60% higher in insomniacs compared to controls.[39] Insomniacs report decreased alertness and fatigue[40] and show psychomotor performance deficits compared to normal sleepers during objective testing.[41] Meta-analysis of longitudinal epidemiological studies (spanning the years 1980–2010) demonstrate patients with insomnia have a twofold increased risk of developing depression compared to good sleepers.[42] Another longitudinal study by Laugsand et al.[43] reported a link between insomnia symptoms and subsequent risk of acute myocardial infarction over a 11-year time period in a sample of more than 50,000 individuals in Norway. Despite some study limitations, their results and other observational data[44–46] support the need for future studies to determine whether improving poor sleep quality might improve cardiovascular outcomes. Depression alone, which contributes to the incidence of insomnia, has already been associated with a substantially increased risk of death in CKD patients.[47]

Insomnia also appears to promote the occurrence and progression of CKD. In an ancillary study of the CRIC cohort, shorter and fragmented sleep using wrist actigraphy was associated with greater declines in kidney function and increased levels of proteinuria.[48] In arguably one of the most robust studies on this subject, patients in Japan exhibiting both short sleep and long sleep as well as poor sleep quality had an associated increased rate of progression to ESRD.[49] Huang et al., in a population-based retrospective study, demonstrated an increased incidence of CKD in individuals with non-apnea (e.g. insomnia) sleep disorders.[50] A similar study by Lin et al. reported similar results with respect to incident CKD in patients aged less than 65 years.[51] Yet another study, by Li et al., followed 11,040 Chinese adults and found that lower overall sleep quality was associated with higher odds of being at high to very high risk for CKD and proteinuria.[52] Lu et al. used a database incorporating 1,639,090 US Veterans and found that chronic insomnia was associated with a greater risk of both the initial development and the progression of CKD, but, interestingly, not of progression to ESRD.[53] The fact that these individuals tended not to progress to ESRD seems counterintuitive. Sasaki et al. found an association with the incidence of CKD in patients with insomnia, but only in those who were shift-workers, a hazard of shift work that has not heretofore been reported.[54]

Diagnosis and Treatment

Specific recommendations for the diagnosis and treatment of insomnia among patients with CKD are difficult to make because few studies of insomnia have focused

on this population. In general, a thorough clinical history is a foundation of chronic insomnia evaluation, and it should include a detailed interview with a focus on a description of the sleep disturbance experienced during the night, sleep habits, lifestyle patterns, sleep schedule, variability in sleep timing from day to day, daytime consequences of the sleep disturbance (including alterations in mood, subjective sleepiness, and fatigue), associated medical and psychiatric illness, intake of caffeine, alcohol, and medications that interfere with sleep. The specific cause for underlying insomnia, if identified, should be initially treated and then the patient should be reevaluated. Following the general principles of sleep hygiene will almost always be beneficial. These include exercising during the day (but not in the evening), reducing or eliminating caffeine intake, avoidance of alcohol and nicotine near bedtime, establishing a regular bedtime and *especially* a wake up time, avoiding eating close to bedtime, and use of the bedroom and bed for sleep and intimacy only.

Short-term (adjustment) insomnia lasts for a relatively brief time period, usually occurs in a temporal relationship with an identifiable stressor, and in most cases the patient will sleep better once the stressor resolves. Hypnotic agents are a treatment option in such cases, particularly if sleepiness from insomnia is causing impaired driving or represents a danger in operation of hazardous machinery in the workplace.[55] Guidelines promulgated by the American Academy of Sleep Medicine may be used as the basis of both nonpharmacologic and pharmacologic treatment for chronic insomnia, although the latter must be interpreted with due regard to those hypnotics that may be contraindicated or require more careful dosing in patients with CKD or ESRD.[56,57] In chronic insomnia disorder, cognitive behavioral therapy for insomnia (CBT-I) works equally well for both sleep onset as well as for maintenance insomnia. Cognitive behavioral therapy for insomnia includes stimulus control and sleep restriction therapies, training in relaxation techniques (including biofeedback and paradoxical intention) and cognitive reorientation of patient attitudes to reduce the anxiety experienced over an episode of poor sleep. CBT-I is grounded in the behavioral construct of insomnia pathogenesis, which holds that faulty attitudes toward sleep and unproductive strategies for dealing with disturbed sleep lead to perpetuation of the disorder.[55] According to two meta-analyses,[58,59] CBT-I treated patients fell asleep faster than 81% of controls and slept longer than 74% of their untreated controls. CBT-I has long-lasting efficacy that aids in the prevention of insomnia recurrences[60,61] and benefits patients with insomnia when it is comorbid with other disorders such as depression.[62] Although CBT-I has been of known benefit to insomnia patients, its implementation has been difficult, due to lack of provider time. Recently however, randomized controlled trials (RCTs) of CBT-I show effectiveness in more time-efficient settings, such as group therapy, and with lower-intensity interventions such as brief telephone consultation followed by internet-based fully automated therapeutic regimens.[63] The availability of internet-based or computer-based CBT-I has expanded greatly in the last few years, as has a variety of "self-help" treatment modalities, including written materials. Most have been validated experimentally. Ho et al. published a meta-analysis of these therapeutic modalities in 2015 and concluded that they demonstrated a reasonable degree of therapeutic efficacy overall.[64] Effect sizes, based on sleep diaries, indicated that sleep efficiency, sleep onset latency, and wake after sleep onset at immediate posttreatment were 0.80, 0.66, and 0.55, respectively, compared to waiting-list controls. Not included in this meta-analysis was a recent RCT of a specific CBT-I product that also demonstrated efficacy for insomnia treatment.[65]

The use of CBT-I has not been studied in patients with CKD or ESRD. However, numerous studies of CBT applied to patients with CKD and/or ESRD in general have suggested salutary effects with respect to depression and anxiety, which would therefore be expected to help ameliorate insomnia. These have included both internet-based CBT[66–68] and in-person CBT administered by trained personnel.[69,70] In addition, a RCT comparing CBT to sertraline for the treatment of depression in ESRD has been completed.[71,72] This investigation showed both treatments resulted in improvement of depressive symptoms, with scores modestly better with sertraline compared to CBT.[72]

When CBT-I fails or is not practical, the newer nonbenzodiazepine hypnotic agents (the so-called z-drugs: zolpidem, zaleplon, and zopiclone) have no significant adverse effects on sleep architecture, are less likely to result in tolerance, and are only infrequently associated with rebound insomnia on withdrawal, compared to benzodiazepines or most other hypnotics. The elimination of all three drugs and their metabolites involve almost exclusively nonrenal mechanisms. There was no accumulation of zolpidem in ESRD patients and no alteration in pharmacokinetics.[73,74] Eszopiclone in a dose of 3 mg has been shown to retain efficacy for over 6 months in one study.[75] Studies have shown improvement in HRQOL of patients with both depression and insomnia, when they were given eszopiclone 3 mg (for insomnia) along with fluoxetine for depression.[76] Clonazepam was more effective than zolpidem for disturbed sleep; however, zolpidem was better tolerated, in a sample of ESRD patients.[73] Another small study showed a trend toward improvement in the PSQI in ESRD patients treated with CBT-I and a small dose of hypnotic.[77]

Ramelteon is a melatonin receptor agonist with a Federal Drug Administration (FDA)-approved indication for the treatment of insomnia. Its elimination does not involve renal mechanisms. It theoretically may be of utility in CKD patients with insomnia. However, no information has appeared with respect to its use in this population. More recently, a new hypnotic, suvorexant, received FDA approval, but the utility in patients with CKD or ESRD is yet to be determined. Suvorexant acts *via* a novel mechanism as an orexin receptor antagonist, but it is not yet available on the market. Studies of suvorexant metabolism indicated that 66% of the drug is eliminated through the gastrointestinal tract, and 23% in urine, primarily as oxidative metabolites.[78] Despite the involvement of CYP3a enzymes in the oxidation of suvorexant, significant drug interactions *via* induction or inhibition of these enzymes were not felt to be of concern.[78] Several sedating antidepressant medications have been reformulated, or are prescribed off-label, as hypnotics including trazodone, doxepin, mirtazapine, and amitriptyline. Some of these agents have bioactive metabolites, long elimination half-lives, and/or are renally excreted. Little information is available concerning their utility in CKD patients with insomnia, and their use is discouraged.

Given the increased prevalence of insomnia in CKD patients and its impact, nephrologists should be vigilant in looking for symptoms of insomnia and depression in their patients, and at least should implement simple sleep hygiene measures for those with complaints of disturbed sleep. Clinicians should have a low clinical threshold for referral to sleep medicine physicians when more complicated issues arise. Given that cognitive behavioral therapy has efficacy in the treatment of major depression and insomnia in kidney failure patients,[72,79] it is a reasonable expectation that appropriate CKD patients may also benefit from CBT for insomnia.

SLEEP-DISORDERED BREATHING

OSA is highly prevalent and likely contributes to the substantial morbidity observed in the CKD population. OSA may also directly and indirectly contribute to the progression of CKD. OSA can contribute to systemic hypertension (HTN), type 2 diabetes mellitus (T2DM), and worsen obesity, all of which are associated with CKD. OSA has been described as "characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation."[80] An apnea is the cessation of airflow for more than 10 seconds despite continued inspiratory efforts. The definition of hypopnea as required by the Centers for Medicare and Medicaid Services is a 30% decrease in airflow or chest wall movement for at least 10 seconds, accompanied by oxyhemoglobin desaturation (by pulse oximetry) of 4% or greater.[81] An alternative definition of hypopnea, felt by most experts in the field to be more clinically relevant and recommended by the American Academy of Sleep Medicine, is a 30% decrease in airflow or chest wall movement from baseline for at least 10 seconds, accompanied by either a 3% or greater desaturation or EEG evidence of arousal. The presence of OSA is confirmed when the apnea–hypopnea index (AHI) is at least 5 per hour (total of apneas plus hypopneas divided by total sleep time). Various obstructive events must also be differentiated from central apneas, characterized by absent inspiratory effort as well as cessation of airflow, and mixed apneas where a central apnea concludes with one or more obstructed breaths.

Although somewhat less common, patients with CKD may also have central sleep apnea (CSA). CSA is a subtype of sleep-disordered breathing with a repetitive pattern of cessations (or reductions) and resumptions (or increases) of respiratory effort usually not accompanied by significant upper airway obstruction. The pattern of CSA may take the form of abrupt cessations of respiration or may assume the waxing and waning pattern of Hunter–Cheyne–Stokes breathing (HCSB). For all intents and purposes, the two phenotypes do not appear to differ with respect to pathogenesis, clinical significance, or treatment.

Establishing a diagnosis of OSA or CSA is best accomplished using in-center PSG, although home sleep apnea testing using portable equipment can be appropriate when adhering to published guidelines.[82] It is important to emphasize that these definitions rely on physiological recordings only and do not require the presence of symptoms of sleepiness, which may be less characteristic of OSA in the CKD population. Specifically, screening questionnaires for OSA that incorporate these and other variables have been shown to lack sensitivity in patients with CKD.[83] Intermittent hypoxia and increased sympathetic activity associated with OSA may be expected to lead to CKD, suggesting that OSA should be addressed by clinicians not just in ESRD but also in CKD patients. CSA is frequently even less symptomatic, particularly in patients who also suffer from heart failure. Such individuals are thought to suffer from sympathetic overactivity that prevents the perception of sleepiness.

Prevalence

The reported prevalence of OSA in CKD populations ranges between 27% and 71%.[27,28,84–96] Table 36.2 presents a summary of OSA studies in CKD patients. Risk factors for OSA in the general population, such as older

TABLE 36.2 Obstructive Sleep Apnea (OSA) Prevalence in Chronic Kidney Disease (CKD) Populations

Study	Participants	Findings
Canales[87]	508 elderly male >67 years.	Association of reduced renal function (as defined by higher cystatin-C concentration) with higher RDI did not persist after correction for BMI, sex, age (p for trend 0.34). When CKD was identified using Mayo clinic formula only, there was twofold greater OR of moderate to severe OSA. Association between CKD and OSA is not clear given the inconsistency of findings across different measures of renal function.
Canales[92]	2696 patients	S[Cr] measured an average of 3.4 year prior to PSG. Men >72 years of age, eGFR < 65 was not associated with increasing RDI. In men <72 years of age, eGFR < 65, association between RDI and eGFR was not statistically significant when corrected for BMI (p for trend 0.3)
Nicholl[90] Canada.	46CKD + OSA/73CKD alone. 46CKD + OSA/230OSA alone. CKD defined as eGFR < 60 mL/min/1.73 m^2	MVRA: only male gender was significantly associated with OSA in CKD patients. Daytime sleepiness was higher in CKD+OSA (39%/19%) compared to CKD only. Prevalence of sleep-related symptoms was lower in CKD+OSA compared to OSA alone suggesting MD should have low threshold to obtain PSG in CKD patients. Kidney function not assessed in 230 patients. Because respiratory effort assessment was not done, cannot distinguish if the apnea was obstructive or central.
Nicholl[91] Canada.	55 CKD 1−2/124 CKD 3−4/75 ESRD.	Increased prevalence of old age, BMI, CVA, and CHF in their patients, all of which increase risk of OSA. After MVA, only ESRD was associated with presence of SA. Because respiratory effort assessment was not done, cannot distinguish if the apnea was obstructive or central.
Fleischmann[86]	70(n GFR)/70 CKD 2/18 CKD 3	Prevalence of sleep apnea same between groups 80%/86%/94%. Type of apnea differed significantly. Number of central sleep apnea (CSA) in CKD 3 was 6 times >compared to CKD 2. Prevalence of OSA did not differ between groups. MRA: CKD 3, NYHA class ≥ 3 predicted CSA. Patients studied were referred because of suspected apnea.
Roumelioti[28]	89 CKD (GFR ≤ 40 mL/min/1.73 m^2)/75 HD/224.	Controls, CKD patient had higher median total sleep time and efficiency compared to HD patients. Presence of advanced CKD associated with 2.4 fold higher risk of severe OSA (AHI > 30) compared to control group whose kidney function was unknown.
Parker[27]	8 CKD (4−5)/16 HD.	CKD pt reported significantly poorer functional and psychological quality of life. All patients had reduced total sleep time and efficiency compare to normative data. HD pt had higher brief arousal index, trend toward higher RDI. Small sample size.
Sim[88]	1,102,089.	Prevalence of sleep apnea 2.54%. Diagnosis of SA was identified from database using ICD-9 codes. BMI data not provided so adjustment for obesity not possible. Average OR for SA by eGFR is 1.34. Their low prevalence compared to other smaller studies raise suspicion for underdiagnosis in their population.
Markou[85] Greece.	35 CKD Group A: CKD-4/Group B: CKD-5 not on HD.	Mild OSA in 54%, moderate OSA in 31%. No significant difference in AHI between group A and B. Group B had significantly low slow wave sleep. OSA unrelated to daytime sleepiness. Small sample. No control group. AHI did not correlate with kidney function except in nondiabetics.
Sakaguchi[89] Japan.	100 CKD (1−3), Median BMI 23	Mild OSA 32%, Moderate OSA 25%, Severe 8%. MLRA: 10 mL/min/1.73m^2 decrease in GFR associated with 42% increase in OR of OSA. Adjusted eGFR inversely correlated with AHI.
Iseki[93] Japan.	1624 OSA, 7454 control CKD defined as GFR < 60	CKD detected in 31% of OSA patients compared to 9% in control. In contrast to control group, prevalence of CKD decreased in OSA group as BMI increased, suggesting that physicians should have lower threshold in nonobese OSA patients for CKD. In Japan, where obesity is less prevalent, craniofacial bone structure difference may be a more important risk factor for OSA.
Chou[94] Taiwan.	40 patients c/o snoring.	Prospective study. No DM, HTN. Mild OSA 15%, Moderate 8%, severe 70%. Prevalence of CKD 18% in severe OSA patients. 37 patients had OSA of which 5 (14%) had CKD. All had severe OSA (5 out of 23, 18%). MVRA: AHI and desaturation index were independent predictors of UACR and eGFR respectively. Small sample.
Marrone Italy[96]	7700 in sleep centers across 26 sleep centers	OSA severity and lowest SpO2 were associated with moderate CKD

AHI, apnea hypopnea index; *BMI*, body mass index; *CSA*, central sleep apnea; *CHF*, congestive heart failure; *CKD*, chronic kidney disease; *CVA*, cerebrovascular disease; *DM*, diabetes mellitus; *eGFR*, estimated glomerular filtration rate; *ESRD*, end-stage renal disease; *HD*, hemodialysis; *HTN*, hypertension; *MLRA*, multiple linear regression analysis; *MRA*, multiple regression analysis; *MVA*, multivariate analysis; *MVRA*, multivariate regression analysis; *NYHA*, New York Heart Association; *OR*, odds ratio; *OSA*, obstructive sleep apnea; *PSG*, polysomnography; *RDI*, respiratory disturbance index; *S[Cr]*, Serum creatinine concentration; *SA*, sleep apnea; *UACR*, urine albumin:creatinine ratio; *Type II*, comprehensive portable PSG (unattended); *Type III*, modified portable sleep apnea testing (unattended; minimum of 4 channels including ventilation [at least 2 channels of respiratory movement or a combination of respiratory; movement and airflow]); heart rate or electrocardiography (ECG); and oxygen saturation; *Type IV*, continuous single- or dual-bioparameter recording (unattended).

age, diabetes, obesity, male gender, and smoking, are also prevalent in the CKD population.[97,98] The wide variation in prevalence estimates may be due to small sample sizes, selective recruitment, and imprecise definitions of sleep apnea and CKD. In addition, for patients with ESRD already on dialysis, Huang et al. found differences in the incidence of OSA that varied with the type of dialysis treatment.[99] The incidence rate of OSA was higher in the peritoneal dialysis (PD) cohort than the HD and control cohorts. Independent risk factors for OSA were, not surprisingly, also present, including age, gender, coronary artery disease, lipid disorders, chronic obstructive pulmonary disease, and hypertension. The severity of OSA was higher in PD patients than HD patients.

A relatively low prevalence of CSA in CKD patients has been reported.[28] However, most studies of sleep-disordered breathing prevalence in CKD have failed to distinguish between CSA events and OSA events, often due to the limited technology used to ascertain the presence of respiratory events during sleep. A recent systematic review by Nigram et al. estimated a point prevalence of about 10%, but acknowledged that the extant literature reports prevalence varying between an astounding 0 and 75%.[100]

Proteinuria

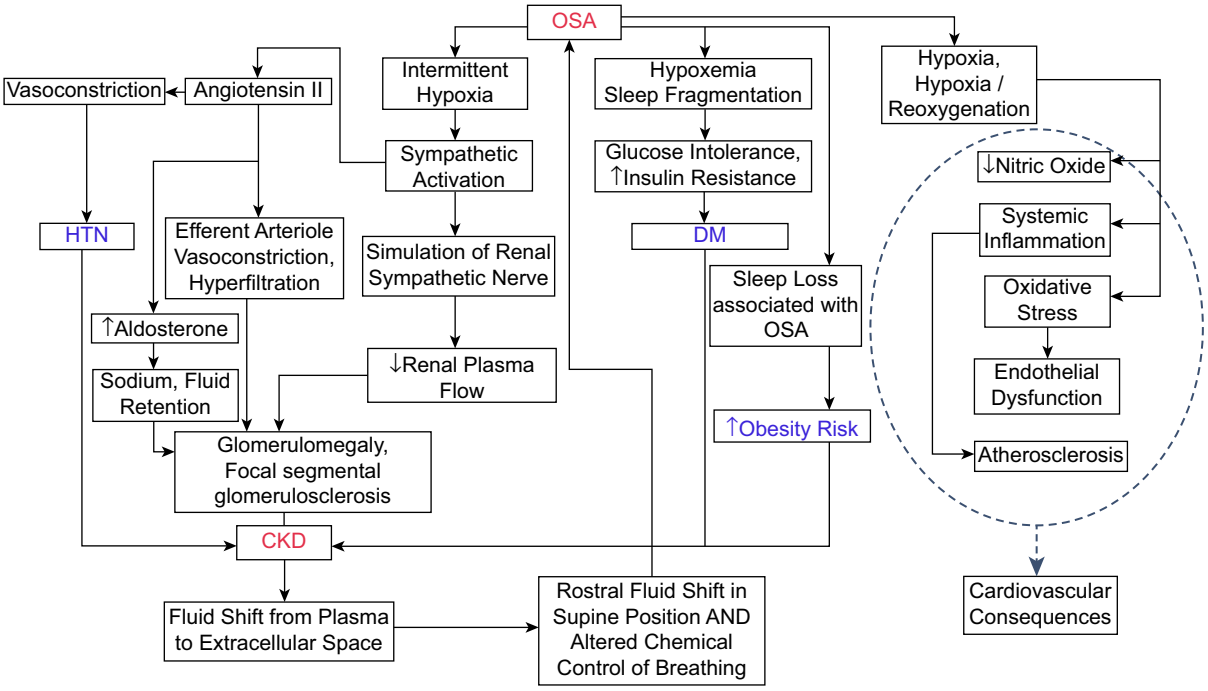
Although the severity of proteinuria is a key predictor of CKD outcomes, the relationship between proteinuria and OSA severity remains unclear. Frank proteinuria has been described in a very small study of OSA patients who, after treatment of OSA, showed improvement in proteinuria.[101] A study by Faulx of 496 adults showed that severe OSA is significantly associated with increased urine albumin excretion. This association remained significant after adjustment for confounding factors such as obesity, diabetes, hypertension, GFR, age, sex, and race.[102] Urinary albumin excretion in patients with OSA may result from an influence of OSA-related pathophysiologic changes on glomerular endothelial function. In a cross-sectional study from Greece published in 2008, nondiabetic adults with untreated HTN and OSA were compared with hypertensive patients without OSA. Patients with OSA were found to have a 57% increase in log 10 urinary albumin:creatinine levels (UACR) on average, which correlated with AHI and 24-hour pulse pressure, even after adjustment for confounders.[103] Presumably, the observed association of UACR with 24-hour pulse pressure relates to the mechanisms cited above.[104,105] In a prospective study by Chou et al., UACR showed a linear increase (3.6−16.5 mg/g) with the increase in sleep-disordered breathing severity (ranging from simple snorer to severe OSA).[94] On the other hand, Casserly et al.[106] published a cross-sectional study assessing the prevalence of nephrotic range proteinuria in OSA patients. Although proteinuria was not associated with OSA, microalbuminuria was not measured and the use of angiotensin converting enzyme inhibitors (ACEIs) by their patients may have impaired the ability to assess a potential association. In a study of 679 diabetic patients, more severe OSA was related to higher levels of albuminuria after adjusting for potential confounders.[107]

Pathogenesis

The pathogenesis of OSA in CKD patients (Figure 36.2) may be related to fluid overload leading to upper airway edema, reduced upper airway muscle tone due to putative or known CKD toxins, peripheral neuropathy due to underlying T2DM or CKD itself, aberrations in ventilatory control (perhaps due to enhanced peripheral and central chemoreceptor sensitivity or acidosis) contributing to an increase in respiratory control system "loop gain" and the development of unstable breathing during sleep, or some combination of these factors.[108] Patients with CKD usually have varying degrees of obstructive, mixed, and central sleep apneas.[27,28,84−86] Hypocapnia associated with chronic metabolic acidemia may lower the arterial pCO_2 to below the apneic threshold during sleep, predisposing to periodic breathing. Chronic acidemia in CKD patients may also alter the hydrogen ion set point for respiration.

It is generally accepted that OSA in most patients is the result of anatomic upper airway narrowing (such as from obesity) in combination with the state-dependent reduction in upper airway dilator muscle tone that occurs during sleep. In CKD, these mechanisms may be supplemented or even replaced by the aforementioned factors specific to CKD, such as ventilatory instability and volume overload. Although the lack of typical features may make OSA more difficult to recognize among CKD patients, it can also lead to disease-specific diagnostic and treatment approaches, such as early recognition and aggressive management of OSA in CKD patients. This approach may inhibit, or possibly prevent, the progression of CKD, by reducing the incidence or severity of HTN, type 2 diabetes, and obesity, known risk factors for worsening renal function.

CSA in CKD is exclusively hyperventilatory in nature. The pathogenesis of this variety of CSA/HCSB is a function of ventilatory control during sleep, the most important aspect of which is the presence of an apneic threshold for $PaCO_2$ that occurs only during nonrapid eye movement sleep. The most likely pathogenetic mechanism related to CKD involves fluid overload. Pulmonary capillary engorgement leads to increased



Abbreviations: OSA= obstructive sleep apnea; HTN = hypertension; DM = diabetes; CKD = chronic kidney disease

FIGURE 36.2 Pathophysiologic link between OSA, complications of OSA and CKD.

afferent tone from the juxta-capillary (J) receptors in the lungs, which promotes hyperventilation and drives the $PaCO_2$ to values adjacent to the apneic threshold and destabilizes ventilatory control. Heart failure and CKD are often seen together, and heart failure further promotes hyperventilation due to hypoxemia.

Effects of OSA on Renal Function

Although CKD may lead to OSA by a variety of mechanisms, and the above considerations clearly indicate a bidirectional relationship mediated by HTN, type 2 diabetes, and obesity, there are other mechanisms specific to obstructive respiratory events that arguably could hasten the decline in renal function in and of themselves. Intermittent airway occlusion during apnea or hypopnea leads to intermittent hypoxia, a known upregulator of inflammatory mediators and oxidative stress.[109,110] Strenuous inspiratory efforts against an occluded airway result in repetitive arousals associated with measurable degrees of sympathetic activation, leading to vasoconstriction. Increased sympathetic activity upregulates the production of angiotensin II, a potent vasoconstrictor, by stimulating the production of renin in the kidney. Angiotensin II also stimulates the adrenal cortex to secrete aldosterone, which decreases sodium excretion and causes water retention, key mechanisms for the control of blood volume and blood pressure. The vasoconstrictor response to angiotensin II is increased in patients with OSA and contributes to the secondary HTN[111] seen in 50% of OSA patients. Intermittent hypoxia decreases the bioavailability of nitric oxide, causing ischemia.[110] OSA has been linked to glomerular hyperfiltration and may be related to increased angiotensin II activity. Glomerulomegaly results from renal venous hypertension, and the characteristic histologic findings of glomerular hypertrophy and/or focal segmental glomerulosclerosis have been reported in OSA patients.[112–114]

In a small study, patients with OSA were found to have GFR within the normal range, but renal plasma flow was significantly lower than normal, pathognomonic of a high filtration fraction (FF). The FF before continuous positive airway pressure (CPAP) treatment was instituted was not significantly correlated with blood pressure, age, or body mass index; however, FF did correlate with increased hypoxemia. After treatment with CPAP, FF significantly decreased, suggesting that CPAP might ameliorate hyperfiltration and therefore prevent progressive decline in kidney function in CKD patients with OSA.[115] Biomarkers of inflammation, oxidative stress, and endothelial dysfunction are associated with worsening kidney function.[116,117] OSA, by acutely increasing sympathetic discharge to the kidney and other vascular beds during obstructive events, by raising BP during occlusive episodes and by a sustained increase in BP during wakefulness contributes to

progressive decline in kidney function.[118] Cycles of hypoxia and reoxygenation induce oxidative stress, which leads to endothelial cell injury and dysfunction.[109] Arterial stiffness is increased in patients with OSA.[119] Treatment of OSA with CPAP leads to significant decrease in measures of arterial stiffness. Higher arterial stiffness and lower arterial elasticity are linearly and independently associated with more rapid decline in renal function in persons with GFR $\geq$60 mL/min/1.73 m^2.[120] More recent data demonstrating that OSA bears a causal relationship to worsening renal function are now also available. Animal models of intermittent hypoxia have shed light on possible mechanisms that include oxidative injury in mice and rats,[121,122] and renal hypoperfusion in pigs.[123] One study in humans implicated activation of the renin–angiotensin system by recurrent hypoxemia.[124] Recent individual studies include a longitudinal, prospective study by Lin et al.[125] and a prospective study by Tahrani et al. in patients with diabetic nephropathy, demonstrated that estimated glomerular filtration rate (eGFR) declined more quickly over time in patients with OSA.[126] A systematic review and meta-analysis by Hwu et al. supported this finding.[127] These data suggest that treatment of OSA in CKD patients may attenuate the rate of decline of kidney function.

Impact

OSA may contribute to increased morbidity and mortality in CKD patients, in whom cardiovascular disease is an important risk factor for mortality. Population-based longitudinal studies, such as the Wisconsin Sleep Cohort[128] and the Busselton Health Study,[129] have shown significant increases in mortality in patients with untreated OSA. The former study found an almost fourfold greater risk of all-cause mortality and a fivefold increase in cardiovascular mortality for patients with severe OSA at a mean 13.8 years of follow-up.[128] The latter investigation demonstrated sixfold greater all-cause mortality for moderate to severe OSA after an average of 13.4 years of follow-up.[129] In the large multiethnic Sleep Heart Health Study, moderate to severe OSA was associated with an increased risk of death among men aged 40–70 years.[130] OSA has been independently linked to specific cardiovascular outcomes such as hypertension,[131] especially treatment-resistant hypertension, left ventricular hypertrophy, stroke,[132,133] myocardial ischemia,[134,135] arrhythmias,[136] fatal and nonfatal cardiovascular events,[137,138] and all-cause mortality.[128,129] Although studies searching for pathological lesions in the CNS in OSA patients have thus far been inconsistent, OSA is commonly associated with neurocognitive impairments. Specific deficits are found in intellectual ability, learning and memory, sustained and focused attention, executive function, information processing efficiency, and visual and psychomotor performance.[139–142] OSA has been strongly associated with depressed mood, metabolic disorders, and diminished HRQOL in the general population. OSA, particularly when associated with intermittent hypoxemia, is associated with erectile dysfunction.[143] OSA increases the risk for glucose intolerance, insulin resistance,[144,145] and overt clinical diabetes,[146] which itself is an important etiology of CKD.

Coexistent OSA is likely to be even more relevant in CKD patients because several important factors involved in the pathogenesis of CKD (such as HTN, T2DM, and obesity) are the same factors that result from, or are associated with, OSA in the general population. Sleep-related hypoxia and recurrent arousals due to OSA result in sympathetic activation leading to HTN, which then contributes to the development and progression of CKD.[147,148] Nocturnal hypoxia (Sao2 $<$ 90% for $>$12% of nocturnal monitoring time) is independently associated with increased (three times more likely) risk of accelerated loss of kidney function (GFR decline by $>$4 mL/min/1.73 m^2/year).[149] One study showed a very high prevalence of OSA in obese patients with drug-resistant hypertension (DRH).[150] Greater rostral fluid displacement centrally in patients with DRH has also been associated with more severe apnea compared to patients with HTN alone.[151] Spironolactone has been shown to reduce the severity of OSA in one small study of 12 obese patients with DRH, linking aldosterone-mediated fluid retention to the severity of OSA in these patients.[152] A large-cohort of VA CKD patients with incident OSA documented by administrative claims were demonstrated to have an increased risk of mortality, coronary artery disease, and CKD progression compared to patients without a diagnosis of OSA.[153] In this cohort there was only a slight attenuation in risk for adverse outcomes associated with treatment of OSA. To date, only limited hypothesis-generating studies have appeared concerning the potential bidirectional nature of causality between OSA and CKD.

Surprisingly few data are available concerning the impact of CSA/HCSB alone on patients with CKD. Only one relevant study, is that of Xu et al., who examined a cohort of patients with and without CKD for the presence of either OSA or CSA/HCSB.[154] Patients with an eGFR $<$ 60 mL/min/1.73 m^2 were far more likely to exhibit CSA/HCSB than other forms of sleep-disordered breathing, after adjusting for all potentially relevant confounders. Moreover, CSA constituted more than a fourfold increased risk for all-cause mortality after the data were adjusted for other related covariates. The authors concluded that CSA/HCSB was an independent risk factor for all-cause mortality in a nondialyzed population of patients with CKD.

Diagnosis and Treatment

The failure to recognize OSA and CSA/HCSB among CKD patients may be not only due to a lack of awareness by providers but also due to known variations in the clinical phenotype. Although the typical OSA patient may be readily recognized by providers when an obese individual complains of sleepiness and snoring, neither obesity nor somnolence is required for the diagnosis of OSA. The screening and diagnosis of OSA in patients with CKD remains challenging due to the lack of disease-specific screening tools and, if access to laboratory PSG is limited, the uncertain validity of home sleep testing in patients with complex comorbidities. The nephrologist should have a low clinical threshold for referral of CKD patients to either sleep medicine physicians for expert assessment and laboratory PSG. Certainly, CKD patients should be considered for PSG or referral when complaining of typical sleep-related breathing symptoms such as snoring, awakening with choking or gasping, or if they complain of daytime sleepiness despite allowing sufficient time for sleep. However, patients with less-specific findings such as difficult-to-control HTN, frequent awakenings, restless sleep, fatigue, depression, irritability, general impairment of daily function, impaired social interactions, and sexual dysfunction may also merit screening.[155] These same symptoms may also suggest the possibility of CSA/HCSB, although the diagnostic pathway remains the same as with OSA.

The gold standard for diagnosing OSA or CSA/HCSB is an overnight in-laboratory PSG. The American Academy of Sleep Medicine currently recommends that home sleep apnea testing only be used for diagnosis when the pretest probability for moderate to severe OSA is high and the patient does not have a significant comorbid medical condition. ESRD/CKD stage 2−5 would constitute a contraindication to home testing due to the possibility of CSAs, or if one or more sleep disorders in addition to OSA are suspected. Negative or technically inadequate home sleep testing in patients with a high pretest probability of moderate to severe OSA should prompt in-laboratory PSG.[82] In a descriptive study of 290 patients performing home sleep studies, those with CKD and ESRD were not significantly more likely than the general population to have an inadequate study.[156]

The converse of determining a suspicion for OSA in CKD has also been recently examined. Voulgaris et al. hypothesized that it might be possible to detect incipient CKD in patients with OSA, and examined Cystatin C (Cyst C) and neutrophil gelatinase-associated lipocalin (NGAL) as possible novel biomarkers for the earlier detection of latent kidney disease in individuals without relevant comorbidities.[157] After adjustment for age and BMI, serum NGAL levels were associated with AHI and minimum oxyhemoglobin saturation during sleep, whereas serum Cyst C levels were associated with percentage of time with oxyhemoglobin saturation <90%, average saturation, and minimum saturation during sleep. They concluded that these markers may allow for the early detection of latent CKD in OSA patients and that the strongest predictor of such a relationship appeared to be the degree of sleep-associated hypoxemia.

Although CPAP has demonstrated improved HRQOL and mood among those with moderate to severe OSA, the effect sizes of CPAP on cardiovascular outcomes have been more modest. A meta-analysis of nine trials demonstrated no significant impact of CPAP on any major cardiovascular event with substantial study heterogeneity.[158] Two meta-analyses that reviewed the RCT data on CPAP and blood pressure demonstrated that overall, CPAP therapy may lead to small (1−2 mm Hg), but statistically significant ($p = 0.001$), reduction in 24-hour mean blood pressure.[159] RCTs have repeatedly shown that CPAP therapy significantly improves or resolves subjective symptoms of daytime sleepiness in patients with severe OSA.[160] Most RCTs find inconsistent, if any, improvement in neurobehavioral performance parameters.[161,162] Data regarding the therapeutic effects of CPAP treatment on mood and HRQOL are also somewhat variable and inconsistent, but most trials found benefits of CPAP therapy compared with conservative treatment. In two meta-analyses, CPAP improved physical functioning, energy/vitality, and general well-being as measured by the Short-Form 36[163,164] among patients with sleep apnea. Subsequent clinical studies have demonstrated improvements in the disease-specific Functional Outcomes of Sleep Questionnaire and general HRQOL measures among those with moderate to severe OSA treated with CPAP.[165,166] More recently, the effect of OSA treatment on renal function has been studied in additional, well-performed clinical trials. A substudy of the international SAVE (Sleep Apnea Cardiovascular Endpoints) trial followed 200 of the 2,717 subjects with at least moderately severe OSA and established coronary or cerebrovascular disease who had OSA treated with CPAP.[167] CPAP treatment in these individuals did not alter renal function or the occurrence of renal adverse events. The authors also sought evidence of a dose−response relationship by analyzing changes in renal function vs. CPAP adherence; no such relationship was found. However, Li et al. were able to demonstrate a salutary effect of CPAP treatment of OSA in patients with respect to progression of CKD,[168] as were Koga et al.[169] A one-year randomized, controlled, nonblinded, parallel clinical trial is being conducted to compare conventional medical therapy or medical therapy plus CPAP in patients with OSA and CKD.[170]

We recommend that patients with OSA and CKD receive treatment when the AHI is 15 or higher, or when the AHI is 5–14 and the patient also exhibits excessive daytime sleepiness, impaired neurocognitive function, mood disorders, insomnia, or cardiovascular disease (HTN, ischemic heart disease, or stroke). Koga et al., in a study of 38 OSA patients, found that longer mean apnea duration and advanced age were associated with reduced eGFR, which improved following nightly CPAP use of more than 4 hours for 3 months.[169] Koyama et al., in a small study of congestive heart failure (CHF) patients who also had sleep-disordered breathing and CKD, showed improvement in renal function after using adaptive servo-ventilation (ASV, an advanced positive airway pressure modality), for 1 year.[171] Increases in LVEF positively correlated with improvement in renal function, and levels of CRP were negatively correlated with improvement in eGFR. It is presumed that ASV improved renal function by preventing inflammatory responses associated with sleep-disordered breathing (SDB).[169,171] The use of CPAP to treat OSA in patients with ESRD has a stronger evidence base than alternative approaches that involve oral appliances or upper airway surgery. Lifestyle approaches such as weight loss, and cessation of smoking and alcohol use are also recommended.

OSA, in spite of its high prevalence in the CKD population, remains underdiagnosed and undertreated. OSA likely increases the risk of cardiovascular insults and impairs HRQOL. Because studies have demonstrated markedly impaired HRQOL among patients with CKD and OSA, treatment of OSA should receive increased emphasis. Despite the benefits of treating OSA, there are a paucity of data regarding treatment of OSA in CKD patients. Data regarding adherence to CPAP use in OSA patients who have CKD are lacking. However, because CPAP use in symptomatic CKD patients may increase their daytime alertness, physical functioning, and social interaction, patients should have a significant incentive for using CPAP. Well-designed RCTs to determine the effect of treating OSA with CPAP on CKD progression are clearly needed.

The treatment of CSA/HCSB is more complex. Treatment modalities include oxygen, CPAP, bilevel PAP in spontaneous/timed mode (BPAP-S/T), ASV, phrenic nerve stimulation, acetazolamide or theophylline (which acts by reducing plant gain, a component of loop gain that, if excessive, destabilizes ventilatory control), and hypnotics to modulate respiratory arousal, and methods to increase $PaCO_2$ (exogenous administration of CO_2 or apparatus to increase respiratory dead space) to create more distance from the apneic threshold. Some of these methodologies are detailed in a recent publication.[155] The current state of knowledge suggests that one of the modalities of positive airway pressure or oxygen represent the most viable choices, along with optimizing the fluid status of the CKD patient, perhaps using diuretics. The goal would appear to be ameliorating any symptoms produced by CSA/HCSB because any effect on renal function by treating this form of sleep-disordered breathing is unknown.

RESTLESS LEGS SYNDROME (WILLIS–EKBOM DISEASE)

RLS, also known as Willis–Ekbom Disease (referring to the first description) is a neurological sleep disorder characterized by unpleasant sensations (usually in the lower extremities but sometimes involving the arms and trunk) in the evening that interfere with sleep onset, and which is diagnosed clinically. Although the symptoms present predominantly in the evening, they may occur at any time of day. Symptoms may be exacerbated by a resting position such as when HD patients are receiving dialysis. The symptoms are described by patients as unpleasant sensations in the extremities. The dysesthesia is often poorly characterized by the patient, but may be described as achy, itchy, painful, creepy—crawly sensations, most often in the lower extremities. Given the predilection of RLS symptoms for occurring in the evening, most patients with severe RLS note difficulty initiating sleep. Diagnostic criteria for RLS have been established by the International RLS Study Group (IRLSSG).[172] The revised IRLSSG diagnostic criteria for RLS are listed in Table 36.3.[173]

TABLE 36.3 Revised International Restless Leg Syndrome Study Group Diagnostic Criteria for Restless Legs Syndrome*

1	An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.
2	The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3	The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4	The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
5	The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).

* *Reprinted from reference 173.*

Prevalence

The prevalence of RLS among patients with CKD remains uncertain. Although many studies have suggested a prevalence of RLS as high as 5–15% in the general population,[174] observational studies in Europe and the US determined the prevalence of RLS prominent enough to occur at least twice a week and cause moderate or severe distress is between 1.5% and 3%.[174] RLS in ESRD patients has been reported in the US and internationally at a higher 12–25% prevalence.[175–177] Plantinga estimated the prevalence of RLS in CKD patients using data from the National Health and Nutrition Examination Survey. This ongoing study of multiple aspects of health in US adults incorporates in-home interviews followed by physical examinations and blood and urine collections at a mobile study center. Out of 930 patients, the prevalence of RLS in CKD patients was similar to that in non-CKD patients. The results for CKD patients, however, were considered unreliable because the relative standard error was ≥30%.[22] The diagnosis of RLS generally requires an evaluation by a physician with knowledge of RLS criteria and conditions with which it may be confused such as leg cramps. In another observational study of home PSG, 17.5% of participants with CKD stages 1–3 had RLS symptoms.[178] A study using claims data from the USRDS demonstrated that the ICD9 diagnosis of RLS was present less than 1% of the time, suggesting that RLS remains underdiagnosed in the US.[179] Riar et al. reported on the prevalence of RLS in children with CKD, finding a prevalence of 15% in 124 such individuals.[180] The number of days per week that subjects had symptoms was not given, and there was no significant association between RLS and CKD stage. Children with RLS rated their quality of sleep as poor, frequently used hypnotic medication, and had lower HRQOL by parent report.

Winkelmann et al. followed 11 patients with uremic RLS who underwent successful kidney transplantation. Symptoms of RLS resolved after transplantation, but reappeared in some of them after several years, and in most patients in whom the transplanted kidney was failing.[181] Molnar et al. reported on RLS in patients after renal transplantation, finding a 4.8% prevalence overall and an association with residual CKD. In groups formed on the basis of eGFR, the prevalence of RLS increased with decreases in renal function (2%, 5%, 7%, 24% in patients with eGFR ≥60 mL/min/1.73 m^2; eGFR 30–59 mL/min/1.73 m^2; eGFR 15–29 mL/min/1.73 m^2; and eGFR < 15 mL/min/1.73 m^2, respectively).[182] Similar findings of increasing RLS prevalence with declining kidney function were also reported by Aritake-Okada et al.[183] Quinn et al. reported iron deficiency and CKD stage 4 (eGFR 15–29 mL/min/1.73 m^2) were associated with a significantly higher odds ratio for RLS in a multivariate analysis.[184]

Pathogenesis

The pathophysiology of RLS among patients with CKD remains unknown. RLS is associated with downregulation of dopamine D_2 receptors in the putamen, and the degree of loss of receptors in RLS correlates with severity of the disorder.[185] Levels of tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis, are increased in the substantia nigra in RLS, thought to be a compensatory mechanism to the reduction in dopamine receptors. Reduced putaminal D_2 receptors were seen in iron-deficient rats along with increased tyrosine hydroxylase levels in the brain.[185] These findings suggest a link between intracerebral iron deficiency and RLS. Genome-wide association studies have found predisposing polymorphisms in a variety of genes. Most common is BTBD9 on chromosome 6p with a protein product widely expressed in brain.[186] These observations relating BTBD9 to RLS have been extended to patients with ESRD in a small observational study.[187] Secondary causes of RLS include acquired iron deficiency,[184] CKD,[184] peripheral neuropathy, and a variety of medications. Among patients with CKD, the potential contributors to RLS include iron deficiency (which may be of minimal degree, not presenting as clinically apparent anemia), peripheral neuropathy, and the CKD-associated inflammatory state. All potentially contribute to the pathogenesis of RLS in CKD. In the presence of inflammation, iron deficiency may not be excluded even by high levels of ferritin. Fatigue, social isolation, helplessness, and pain are common symptoms of RLS,[188] and these problems may predispose to patient to depression.

Impact

General

Among the general population and those patients with CKD, RLS has been associated with an increased risk of cardiovascular disease, impaired HRQOL, cognitive dysfunction, daytime sleepiness, and psychiatric morbidity. A potential mechanism whereby RLS may produce CVD is autonomic arousal associated with periodic limb movements of sleep. Most often involving the legs, these repetitive contractions occur in about 80% of RLS patients and may be associated with arousals or awakenings. Just as in OSA, the increase in sympathetic outflow may promote HTN, increased coagulability, or a risk of plaque rupture.[189,190] Using Wisconsin Sleep Cohort data, Winkelman et al. reported that RLS

symptoms (even after adjustment for confounders) were associated with an approximately 2.5-fold risk of prevalent CVD.[191] Emerging evidence from prevalence studies of RLS indicates at least twice the risk of cardiovascular disease in these individuals.[192,193] RLS symptoms have a strong association with DSM-4 major depressive disorder and panic disorder in a community population.[193,194] Individuals with RLS are at least twice as likely to have scores indicating depression or anxiety disorders.[191] These findings have significant clinical implications, as medications commonly employed to treat these disorders may worsen underlying RLS.[194,195] Also, ongoing sleep disturbance is a risk factor both for the onset, as well as persistence of depressive disorders and suicide. QOL impairments are also significant in patients with moderate to severe RLS, comparable to or even more severe than those in patients with CHF or T2DM.[193] Patients with RLS scored lower across all eight subscales of the SF-36, with diminished physical and mental health scores.[174,196] An insomnia complaint is two to four times more likely in RLS patients compared to controls. This may mediate comorbidities commonly seen with RLS, including CVD, impaired perception of HRQOL, cognitive dysfunction, daytime sleepiness, and psychiatric morbidity.[189,197]

CKD

The presence of both RLS and CKD was significantly associated with depression and complaints of a sleep disturbance.[183] RLS symptoms are associated with depression in CKD patients.[198] A prospective study of kidney transplant patients tested the hypothesis that the presence of RLS predicts mortality in 804 transplant recipients. Using a multivariate Cox proportional hazard analysis, the presence of RLS was a significant risk factor for mortality with a hazard ratio of 2.[199] RLS has been associated with HRQOL, mood, and subjective sleep disturbance in CKD patients.

Diagnosis and Treatment

RLS is a clinical diagnosis based on the IRLSSG criteria. Laboratory PSG or other sleep studies are not necessary to establish the diagnosis. Iron should be supplemented orally in case of iron deficiency. Ferritin levels should be checked and iron supplementation should be commenced if the level is below 50 ng/mL. Additional diagnostic workup for blood loss or other causes of iron deficiency should not be neglected. Patients with malabsorption and intolerance to oral iron will require IV iron therapy. As ferritin is an acute phase reactant, the levels of ferritin may be high in the presence of inflammation, but including an iron level and iron saturation will help confirm iron deficiency.

Nonpharmacological measures to manage RLS symptoms include (i) elimination of alcohol, nicotine, (ii) caffeine reduction, (iii) moderate exercise, and (iv) discontinuation of offending medications, when possible. By definition, symptoms will respond to walking, massaging the affected limb, or other mechanical stimuli but will return when these maneuvers cease. A randomized trial of progressive exercise over 6 months reduced symptoms of RLS among HD patients. Examining the impact of exercise on RLS in the nondialysis population is an area of active investigation.[200] Given the circadian rhythmicity and exacerbation of RLS symptoms by rest, studies have suggested that time of day and mode of dialysis may be related to symptom severity. Patients undergoing HD earlier in the day and patients performing short daily home dialysis have reported decreased symptoms.

Pharmacological treatments include dopamine receptor agonists, such as ropinirole 0.25 mg or pramipexole 0.125 mg, taken 2 hours before the usual onset of symptoms. Medications are usually reserved for patients with RLS symptoms that occur at least twice a week. Dosages are increased after a few weeks if the patient is still symptomatic. Maximum approved dose for ropinirole is 4 mg and for pramipexole is 0.75 mg. Pramipexole is primarily excreted in its active form in the urine, which may limit its utility in CKD patients. Ropinirole is also excreted by the kidneys, but only after being extensively metabolized to mostly inactive derivatives. Serious side effects of these drugs include augmentation, impulse control disorders, and daytime sleepiness.[201] Augmentation consists of worsening of symptoms, early occurrence, or involvement of the arms or trunk that was not present prior to treatment. Augmentation is initially treated with additional doses of medication but may require discontinuation of the drug. Another dopamine agonist, rotigotine, is administered once a day as a patch and may be particularly useful in patients with augmentation due to its constant drug levels. Rotigotine is eliminated as inactive conjugates in the urine.

Patients with RLS symptoms occurring less than twice a week often respond to clonazepam 0.25 mg. For patients with RLS symptoms occurring at least twice a week, $\alpha 2\delta$ agents such as gabapentin and pregabalin are also options, particularly when RLS symptoms are characterized as painful or associated with possible neuropathy. Both gabapentin and pregabalin are eliminated by the kidney, and therefore the half-life increases with decrements in kidney function. Dose adjustment for gabapentin and pregabalin is required based on renal function. Gabapentin has been shown to reduce RLS symptoms in two studies among patients with RLS treated with HD. There are no studies evaluating the efficacy of pregabalin in CKD. Augmentation has not been reported with these drugs. Opioids may be considered

for treatment-resistant RLS. This class of drugs requires additional monitoring and has an increased risk of adverse events in the CKD population. Given the association between OSA and CKD detailed above, it is imperative to identify and treat OSA in such patients prior to consideration of opioid therapy.

CKD

There is a paucity of studies examining treatment of RLS among patients with CKD. A systematic review found nine RCTs for the treatment of RLS in HD patients and no studies in the CKD population.[202] Only one very small study reported in the German literature has reported on RLS treatment in CKD patients. In this report, CKD and HD patients treated with clonidine 0.075 mg showed improvement in RLS symptoms.[203] Treatment of anemia with erythropoietin and IV iron alone does not improve RLS symptoms in patients with renal failure.[204] Aerobic exercise training has been shown to improve RLS symptoms and QOL in HD patients.[205] A small study comparing gabapentin with levodopa showed that gabapentin was equally efficacious for RLS treatment in HD patients.[206] Ropinirole was found more effective than sustained release levodopa for RLS in HD patients.[207]

CONCLUSION

The diagnosis and treatment of sleep disorders in CKD may provide the opportunity to improve QOL and cardiovascular outcomes. Sleep disorders have been linked to the development of numerous chronic diseases. The treatment of sleep disorders in patients with chronic disease plays an important role in their management. Optimal sleep duration and sleep quality play a significant role in improving control of T2DM. OSA independently increases the risk for HTN and thus cardiovascular disease, a leading cause of death in CKD patients. Insufficient sleep increases the risk of obesity, and the effect is pronounced in children. Diabetes, hypertension, and obesity are all etiologies of CKD. Addressing sleep disorders could prevent both the development as well as the progression of CKD. Nephrologists should be vigilant in looking for symptoms of sleep disorders in CKD patients and address them as a part of the overall treatment regimen. Future prospective studies are critical to determine causal relationships. Does OSA contribute to the development of CKD and its progression? Does CKD contribute to the pathogenesis of OSA? Does CPAP treatment in OSA patients prevent onset of CKD and its progression? Studies of CPAP therapy in CKD patients may help to clarify the extent to which OSA contributes to the morbidity and mortality in this high-risk population.

References

1. Carskadon MA, Dement WC. Monitoring and staging human sleep. In: Kryger MH, Roth T, Dement WC, editors. *Principles and practice of sleep medicine*. 5th ed. St.Louis: Elsevier Saunders; 2011. p. 16–26.
2. Shokri-Kojori E, Wang GJ, Wiers CE, et al. β-Amyloid accumulation in the human brain after one night of sleep deprivation. *Proc Natl Acad Sci U S A* 2018;**115**(17):4483–8.
3. Stamatakis KA, Punjabi NM. Effects of sleep fragmentation on glucose metabolism in normal subjects. *Chest* 2010;**137**(1):95–101.
4. Calvin AD, Carter RE, Adachi T, et al. Effects of experimental sleep restriction on caloric intake and activity energy expenditure. *Chest* 2013;**144**(1):79–86.
5. Thomas M, Sing H, Belenky G, et al. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *J Sleep Res* 2000;**9**(4):335–52.
6. Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. *J Clin Sleep Med* 2007;**3**(5):519–28.
7. Chang LC, Mahoney 3rd JJ, Raty SR, Ortiz J, Apodaca S, De la Garza 2nd R. Neurocognitive effects following an overnight call shift on faculty anesthesiologists. *Acta Anaesthesiol Scand* 2013; **57**(8):1051–7.
8. American Academy of Sleep Medicine. *International classification of sleep disorders: diagnostic and coding manual, ICSD-3*. 3rd ed. 2014. Darien, IL.
9. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002;**6**(2):97–111.
10. De Santo RM, Cesare CM, Bartiromo M, Cirillo M. High prevalence of sleep disorders at the time of CKD diagnosis. *J Ren Nutr* 2008;**18**(1):104–6.
11. Novak M, Molnar MZ, Ambrus C, et al. Chronic insomnia in kidney transplant recipients. *Am J Kidney Dis* 2006;**47**(4):655–65.
12. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry* 1996;**39**(6):411–8.
13. Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ. Insomnia in young men and subsequent depression. The Johns Hopkins precursors study. *Am J Epidemiol* 1997;**146**(2):105–14.
14. Kumar B, Tilea A, Gillespie BW, et al. Significance of self-reported sleep quality (SQ) in chronic kidney disease (CKD): the Renal Research Institute (RRI)-CKD study. *Clin Nephrol* 2010;**73**(2): 104–14.
15. Iliescu EA, Yeates KE, Holland DC. Quality of sleep in patients with chronic kidney disease. *Nephrol Dial Transplant* 2004;**19**(1): 95–9.
16. Kurella M, Luan J, Lash JP, Chertow GM. Self-assessed sleep quality in chronic kidney disease. *Int Urol Nephrol* 2005;**37**(1):159–65.
17. Cohen SD, Patel SS, Khetpal P, Peterson RA, Kimmel PL. Pain, sleep disturbance, and quality of life in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2007;**2**(5):919–25.
18. Sabbatini M, Pisani A, Crispo A, et al. Sleep quality in patients with chronic renal failure: a 3-year longitudinal study. *Sleep Med* 2008;**9**(3):240–6.
19. Ezzat H, Mohab A. Prevalence of sleep disorders among ESRD patients. *Ren Fail* 2015;**37**(6):1013–9.
20. De Santo RM, Bartiromo M, Cesare CM, Cirillo M. Sleep disorders occur very early in chronic kidney disease. *J Nephrol* 2008; **21**(Suppl. 13):S59–65.

21. De Santo RM, Bilancio G, Santoro D, Vecchi ML, Perna A, De Santo NG, Cirillo M. A longitudinal study of sleep disorders in early-stage chronic kidney disease. *J Ren Nutr* 2010;**20**(5 Suppl.): S59–63.
22. Plantinga L, Lee K, Inker LA, et al. Association of sleep-related problems with CKD in the United States, 2005-2008. *Am J Kidney Dis* 2011;**58**(4):554–64.
23. Burkhalter H, Brunner DP, Wirz-Justice A, et al. Self-reported sleep disturbances in renal transplant recipients. *BMC Nephrol* 2013;**14**:220.
24. Liaveri PG, Dikeos D, Ilias I, et al. Quality of sleep in renal transplant recipients and patients on hemodialysis. *J Psychosom Res* 2017;**93**:96–101.
25. Knezevic MZ, Djordjevic VV, Jankovic SM, Djordjevic VM. Influence of dialysis modality and membrane flux on insomnia severity in haemodialysis patients. *Nephrology* 2013;**18**(11):706–11.
26. Losso RL, Minhoto GR, Riella MC. Sleep disorders in patients with end-stage renal disease undergoing dialysis: comparison between hemodialysis, continuous ambulatory peritoneal dialysis and automated peritoneal dialysis. *Int Urol Nephrol* 2015;**47**(2): 369–75.
27. Parker KP, Bliwise DL, Bailey JL, Rye DB. Polysomnographic measures of nocturnal sleep in patients on chronic, intermittent daytime haemodialysis vs those with chronic kidney disease. *Nephrol Dial Transplant* 2005;**20**(7):1422–8.
28. Roumelioti ME, Buysse DJ, Sanders MH, Strollo P, Newman AB, Unruh ML. Sleep-disordered breathing and excessive daytime sleepiness in chronic kidney disease and hemodialysis. *Clin J Am Soc Nephrol* 2011;**6**(5):986–94.
29. Agarwal R, Light RP. Sleep and activity in chronic kidney disease: a longitudinal study. *Clin J Am Soc Nephrol* 2011;**6**(6):1258–65.
30. Barmar B, Dang Q, Isquith D, Buysse D, Unruh M. Comparison of sleep/wake behavior in CKD stages 4 to 5 and hemodialysis populations using wrist actigraphy. *Am J Kidney Dis* 2009;**53**(4): 665–72.
31. Ramer S, Germain A, Dohar S, Unruh M. Event-related distress in kidney disease patients. *Nephrol Dial Transplant* 2012;**27**(1): 299–303.
32. Perlis M, Smith M, Pigeon W. Etiology and pathophysiology of insomnia. In: Kryger M, Roth T, Dement W, editors. *Principles and practice of sleep medicine*. 4th ed. Elsevier Saunders; 2005. p. 714–25.
33. Riemann D, Spiegelhalder K, Feige B, Voderholzer U, Berger M, Perlis M, Nissen C. The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Med Rev* 2010;**14**(1):19–31.
34. Bonnet MH, Arand DL. Heart rate variability in insomniacs and matched normal sleepers. *Psychosom Med* 1998;**60**(5):610–5.
35. Nofzinger EA, Buysse DJ, Germain A, Price JC, Miewald JM, Kupfer DJ. Functional neuroimaging evidence for hyperarousal in insomnia. *Am J Psychiatry* 2004;**161**(11):2126–8.
36. Leger D, Guilleminault C, Bader G, Levy E, Paillard M. Medical and socio-professional impact of insomnia. *Sleep* 2002;**25**(6): 625–9.
37. Ozminkowski RJ, Wang S, Walsh JK. The direct and indirect costs of untreated insomnia in adults in the United States. *Sleep* 2007; **30**(3):263–73.
38. Kessler RC, Berglund PA, Coulouvrat C, et al. Insomnia and the performance of US workers: results from the America insomnia survey. *Sleep* 2011;**34**(9):1161–71.
39. Simon GE, VonKorff M. Prevalence, burden, and treatment of insomnia in primary care. *Am J Psychiatry* 1997;**154**(10):1417–23.
40. Buysse DJ, Thompson W, Scott J, et al. Daytime symptoms in primary insomnia: a prospective analysis using ecological momentary assessment. *Sleep Med* 2007;**8**(3):198–208.
41. Edinger JD, Means MK, Carney CE, Krystal AD. Psychomotor performance deficits and their relation to prior nights' sleep among individuals with primary insomnia. *Sleep* 2008;**31**(5): 599–607.
42. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord* 2011;**135**(1–3):10–9.
43. Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the risk of acute myocardial infarction: a population study. *Circulation* 2011;**124**(19):2073–81.
44. Meisinger C, Heier M, Lowel H, Schneider A, Doring A. Sleep duration and sleep complaints and risk of myocardial infarction in middle-aged men and women from the general population: the MONICA/KORA Augsburg cohort study. *Sleep* 2007;**30**(9): 1121–7.
45. Spiegelhalder K, Scholtes C, Riemann D. The association between insomnia and cardiovascular diseases. *Nat Sci Sleep* 2010;**2**:71–8.
46. Nakazaki C, Noda A, Koike Y, Yamada S, Murohara T, Ozaki N. Association of insomnia and short sleep duration with atherosclerosis risk in the elderly. *Am J Hypertens* 2012;**25**(11):1149–55.
47. Palmer SC, Vecchio M, Craig JC, et al. Association between depression and death in people with CKD: a meta-analysis of cohort studies. *Am J Kidney Dis* 2013;**62**(3):493–505.
48. Ricardo AC, Knutson K, Chen J, et al. The association of sleep duration and quality with CKD progression. *J Am Soc Nephrol* 2017;**28**(12):3708–15.
49. Yamamoto R, Shinzawa M, Isaka Y, , et al Investigators CKD-JAC. Sleep quality and sleep duration with CKD are associated with progression to ESKD. *Clin J Am Soc Nephrol* 2018;**13**(12):1825–32.
50. Huang ST, Lin CL, Yu TM, Yang TC, Kao CH. Nonapnea sleep disorders and incident chronic kidney disease: a population-based retrospective cohort study. *Medicine (Baltim)* 2015;**94**(4):e429.
51. Lin HY, Hung CC, Chang YH, et al. Nonapnea sleep disorders in patients younger than 65 years are significantly associated with CKD: a nationwide population-based study. *PLoS One* 2015; **10**(10):e0140401.
52. Li J, Huang Z, Hou J, et al. Sleep and CKD in Chinese adults: a cross-sectional study. *Clin J Am Soc Nephrol* 2017;**12**(6):885–92.
53. Lu JL, Freire AX, Molnar MZ, Kalantar-Zadeh K, Kovesdy CP. Association of chronic insomnia with mortality and adverse renal outcomes. *Mayo Clin Proc* 2018;**93**(11):1563–70.
54. Sasaki S, Yoshioka E, Saijo Y, et al. A prospective cohort study of insomnia and chronic kidney disease in Japanese workers. *Sleep Breath* 2018;**22**(1):257–65.
55. Hauri PJ. Insomnia. *Clin Chest Med* 1998;**19**(1):157–68.
56. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med* 2008;**4**(5):487–504.
57. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med* 2017;**13**(2):307–49.
58. Morin CM, Culbert JP, Schwartz SM. Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. *Am J Psychiatry* 1994;**151**(8):1172–80.
59. Murtagh DR, Greenwood KM. Identifying effective psychological treatments for insomnia: a meta-analysis. *J Consult Clin Psychol* 1995;**63**(1):79–89.
60. Morin CM, Blais F, Savard J. Are changes in beliefs and attitudes about sleep related to sleep improvements in the treatment of insomnia? *Behav Res Ther* 2002;**40**(7):741–52.
61. Sivertsen B, Omvik S, Pallesen S, et al. Cognitive behavioral therapy vs zopiclone for treatment of chronic primary insomnia in older adults: a randomized controlled trial. *J Am Med Assoc* 2006;**295**(24):2851–8.
62. Espie CA, Fleming L, Cassidy J, et al. Randomized controlled clinical effectiveness trial of cognitive behavior therapy compared

with treatment as usual for persistent insomnia in patients with cancer. *J Clin Oncol* 2008;**26**(28):4651–8.
63. Espie CA, Kyle SD, Williams C, Ong JC, Douglas NJ, Hames P, Brown JS. A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. *Sleep* 2012;**35**(6): 769–81.
64. Ho FY, Chung KF, Yeung WF, et al. Self-help cognitive-behavioral therapy for insomnia: a meta-analysis of randomized controlled trials. *Sleep Med Rev* 2015;**19**:17–28.
65. Espie CA, Emsley R, Kyle SD, et al. Effect of digital cognitive behavioral therapy for insomnia on health, psychological well-being, and sleep-related quality of life: a randomized clinical trial. *JAMA Psychiatry* 2019;**76**(1):21–30.
66. Chan R, Dear BF, Titov N, Chow J, Suranyi M. Examining internet-delivered cognitive behaviour therapy for patients with chronic kidney disease on haemodialysis: a feasibility open trial. *J Psychosom Res* 2016;**89**:78–84.
67. Hudson JL, Moss-Morris R, Game D, et al. Improving distress in dialysis (iDiD): a feasibility two-arm parallel randomised controlled trial of an online cognitive behavioural therapy intervention with and without therapist-led telephone support for psychological distress in patients undergoing haemodialysis. *BMJ Open* 2016;**6**(4):e011286.
68. Hudson JL, Moss-Morris R, Game D, Carroll A, Chilcot J. Improving Distress in Dialysis (iDiD): a tailored CBT self-management treatment for patients undergoing dialysis. *J Ren Care* 2016;**42**(4):223–38.
69. Valsaraj BP, Bhat SM, Latha KS. Cognitive behaviour therapy for anxiety and depression among people undergoing haemodialysis: a randomized control trial. *J Clin Diagn Res* 2016;**10**(8): VC06–10.
70. Lerma A, Perez-Grovas H, Bermudez L, Peralta-Pedrero ML, Robles-García R, Lerma C. Brief cognitive behavioural intervention for depression and anxiety symptoms improves quality of life in chronic haemodialysis patients. *Psychol Psychother* 2017; **90**(1):105–23.
71. Hedayati SS, Daniel DM, Cohen S, et al. Rationale and design of a trial of sertraline vs. cognitive behavioral therapy for end-stage renal disease patients with depression (ASCEND). *Contemp Clin Trials* 2016;**47**:1–11.
72. Mehrotra R, Cukor D, Unruh M, Rue T, Heagerty P, Cohen SD, et al. Comparative efficacy of therapies for treatment of depression for patients undergoing maintenance hemodiualysis. *Ann Intern Med* 2019;**170**(6):369–79.
73. Dashti-Khavidaki S, Chamani N, Khalili H, et al. Comparing effects of clonazepam and zolpidem on sleep quality of patients on maintenance hemodialysis. *Iran J Kidney Dis* 2011;**5**(6):404–9.
74. Fillastre JP, Geffroy-Josse S, Etienne I, et al. Pharmacokinetics and pharmacodynamics of zolpidem following repeated doses in hemodialyzed uraemic patients. *Fundam Clin Pharmacol* 1993; **7**(1):1–9.
75. Krystal AD, Walsh JK, Laska E, Caron J, Amato DA, Wessel TC, Roth T. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep* 2003; **26**(7):793–9.
76. McCall WV, Blocker JN, D'Agostino Jr R, et al. Treatment of insomnia in depressed insomniacs: effects on health-related quality of life, objective and self-reported sleep, and depression. *J Clin Sleep Med* 2010;**6**(4):322–9.
77. Chen HY, Chiang CK, Wang HH, et al. Cognitive-behavioral therapy for sleep disturbance in patients undergoing peritoneal dialysis: a pilot randomized controlled trial. *Am J Kidney Dis* 2008; **52**(2):314–23.
78. Cui D, Cabalu T, Yee KL, et al. In vitro and in vivo characterisation of the metabolism and disposition of suvorexant in humans. *Xenobiotica* 2016;**46**(10):882–95.
79. Duarte PS, Miyazaki MC, Blay SL, Sesso R. Cognitive-behavioral group therapy is an effective treatment for major depression in hemodialysis patients. *Kidney Int* 2009;**76**(4):414–21.
80. American Academy of Sleep Medicine. *The international classification of sleep disorders: diagnostic and coding manual, ICSD-2*. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.
81. Meoli AL, Casey KR, Clark RW, et al. Hypopnea in sleep-disordered breathing in adults. *Sleep* 2001;**24**(4):469–70.
82. Collop NA, Anderson WM, Boehlecke B, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2007;**3**(7):737–47.
83. Nicholl DD, Ahmed SB, Loewen AH, et al. Diagnostic value of screening instruments for identifying obstructive sleep apnea in kidney failure. *J Clin Sleep Med* 2013;**9**(1):31–8.
84. Kimmel PL, Miller G, Mendelson WB. Sleep apnea syndrome in chronic renal disease. *Am J Med* 1989;**86**(3):308–14.
85. Markou N, Kanakaki M, Myrianthefs P, et al. Sleep-disordered breathing in nondialyzed patients with chronic renal failure. *Lung* 2006;**184**(1):43–9.
86. Fleischmann G, Fillafer G, Matterer H, Skrabal F, Kotanko P. Prevalence of chronic kidney disease in patients with suspected sleep apnoea. *Nephrol Dial Transplant* 2010;**25**(1):181–6.
87. Canales MT, Taylor BC, Ishani A, et al. Reduced renal function and sleep-disordered breathing in community-dwelling elderly men. *Sleep Med* 2008;**9**(6):637–45.
88. Sim JJ, Rasgon SA, Kujubu DA, et al. Sleep apnea in early and advanced chronic kidney disease: Kaiser Permanente Southern California cohort. *Chest* 2009;**135**(3):710–6.
89. Sakaguchi Y, Shoji T, Kawabata H, et al. High prevalence of obstructive sleep apnea and its association with renal function among nondialysis chronic kidney disease patients in Japan: a cross-sectional study. *Clin J Am Soc Nephrol* 2011;**6**(5):995–1000.
90. Nicholl DD, Ahmed SB, Loewen AH, et al. Clinical presentation of obstructive sleep apnea in patients with chronic kidney disease. *J Clin Sleep Med* 2012;**8**(4):381–7.
91. Nicholl DD, Ahmed SB, Loewen AH, et al. Declining kidney function increases the prevalence of sleep apnea and nocturnal hypoxia. *Chest* 2012;**141**(6):1422–30.
92. Canales MT, Lui LY, Taylor BC, et al. Renal function and sleep-disordered breathing in older men. *Nephrol Dial Transplant* 2008; **23**(12):3908–14.
93. Iseki K, Tohyama K, Matsumoto T, Nakamura H. High prevalence of chronic kidney disease among patients with sleep related breathing disorder (SRBD). *Hypertens Res* 2008;**31**(2):249–55.
94. Chou YT, Lee PH, Yang CT, et al. Obstructive sleep apnea: a stand-alone risk factor for chronic kidney disease. *Nephrol Dial Transplant* 2011;**26**(7):2244–50.
95. Yayan J, Rasche K, Vlachou A. Obstructive sleep apnea and chronic kidney disease. *Adv Exp Med Biol* 2017;**1022**:11–8.
96. Marrone O, Battaglia S, Steiropoulos P, et al. ESADA study group. Chronic kidney disease in European patients with obstructive sleep apnea: the ESADA cohort study. *J Sleep Res* 2016;**25**(6): 739–45.
97. Young T, Shahar E, Nieto FJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults: the sleep heart health study. *Arch Intern Med* 2002;**162**(8):893–900.
98. Fernandes JFR, Barreto Silva MI, Loivos CP, et al. Obstructive sleep apnea in non-dialyzed chronic kidney disease patients: association with body adiposity and sarcopenia. *Nutrition* 2019;**57**: 282–9.

99. Huang ST, Lin CL, Yu TM, Kao CH, Liang WM, Chou TC. Risk, severity, and predictors of obstructive sleep apnea in hemodialysis and peritoneal dialysis patients. *Int J Environ Res Public Health* 2018;**15**(11):2377.
100. Nigam G, Pathak C, Riaz M. A systematic review of central sleep apnea in adult patients with chronic kidney disease. *Sleep Breath* 2016;**20**(3):957–64.
101. Chaudhary BA, Sklar AH, Chaudhary TK, Kolbeck RC, Speir Jr WA. Sleep apnea, proteinuria, and nephrotic syndrome. *Sleep* 1988;**11**(1):69–74.
102. Faulx MD, Storfer-Isser A, Kirchner HL, Jenny NS, Tracy RP, Redline S. Obstructive sleep apnea is associated with increased urinary albumin excretion. *Sleep* 2007;**30**(7):923–9.
103. Tsioufis C, Thomopoulos C, Dimitriadis K, et al. Association of obstructive sleep apnea with urinary albumin excretion in essential hypertension: a cross-sectional study. *Am J Kidney Dis* 2008; **52**(2):285–93.
104. Furtner M, Kiechl S, Mair A, et al. Urinary albumin excretion is independently associated with carotid and femoral artery atherosclerosis in the general population. *Eur Heart J* 2005; **26**(3):279–87.
105. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B, et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation* 2004;**110**(1):32–5.
106. Casserly LF, Chow N, Ali S, Gottlieb DJ, Epstein LJ, Kaufman JS. Proteinuria in obstructive sleep apnea. *Kidney Int* 2001;**60**(4): 1484–9.
107. Stadler S, Zimmermann T, Franke F, et al. Association of sleep-disordered breathing with diabetes-associated kidney disease. *Ann Med* 2017;**49**(6):487–95.
108. Jordan AS, Wellman A, Edwards JK, et al. Respiratory control stability and upper airway collapsibility in men and women with obstructive sleep apnea. *J Appl Physiol* 2005;**99**(5):2020–7.
109. Lavie L. Oxidative stress–a unifying paradigm in obstructive sleep apnea and comorbidities. *Prog Cardiovasc Dis* 2009;**51**(4): 303–12.
110. Foster GE, Poulin MJ, Hanly PJ. Intermittent hypoxia and vascular function: implications for obstructive sleep apnoea. *Exp Physiol* 2007;**92**(1):51–65.
111. Fletcher EC, Orolinova N, Bader M. Blood pressure response to chronic episodic hypoxia: the renin-angiotensin system. *J Appl Physiol* 2002;**92**(2):627–33.
112. Bailey RR, Lynn KL, Burry AF, Drennan C. Proteinuria, glomerulomegaly and focal glomerulosclerosis in a grossly obese man with obstructive sleep apnea syndrome. *Aust N Z J Med* 1989; **19**(5):473–4.
113. Jennette JC, Charles L, Grubb W. Glomerulomegaly and focal segmental glomerulosclerosis associated with obesity and sleep-apnea syndrome. *Am J Kidney Dis* 1987;**10**(6):470–2.
114. Sklar AH, Chaudhary BA. Reversible proteinuria in obstructive sleep apnea syndrome. *Arch Intern Med* 1988;**148**(1):87–9.
115. Kinebuchi S, Kazama JJ, Satoh M, et al. Short-term use of continuous positive airway pressure ameliorates glomerular hyperfiltration in patients with obstructive sleep apnoea syndrome. *Clin Sci (Lond)* 2004;**107**(3):317–22.
116. Fassett RG, Venuthurupalli SK, Gobe GC, Coombes JS, Cooper MA, Hoy WE. Biomarkers in chronic kidney disease: a review. *Kidney Int* 2011;**80**(8):806–21.
117. Kovesdy CP, Kalantar-Zadeh K. Review article: biomarkers of clinical outcomes in advanced chronic kidney disease. *Nephrology* 2009;**14**(4):408–15.
118. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation* 2008;**118**(10):1080–111.
119. Doonan RJ, Scheffler P, Lalli M, Kimoff RJ, Petridou ET, Daskalopoulos ME, Daskalopoulou SS. Increased arterial stiffness in obstructive sleep apnea: a systematic review. *Hypertens Res* 2011;**34**(1):23–32.
120. Peralta CA, Jacobs Jr DR, Katz R, et al. Association of pulse pressure, arterial elasticity, and endothelial function with kidney function decline among adults with estimated GFR >60 mL/min/1.73 m(2): the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Kidney Dis* 2012;**59**(1):41–9.
121. Abuyassin B, Badran M, Ayas NT, Laher I. The antioxidant alpha lipoic acid attenuates intermittent hypoxia-related renal injury in a mouse model of sleep apnea. *Sleep* 2019;**42**(6):zsz066.
122. Wu X, Gu W, Lu H, Liu C, et al. Soluble receptor for advanced glycation end product ameliorates chronic intermittent hypoxia induced renal injury, inflammation, and apoptosis via P38/JNK signaling pathways. *Oxid Med Cell Longev* 2016;**2016**:1015390.
123. Linz D, Mahfoud F, Linz B, et al. Effect of obstructive respiratory events on blood pressure and renal perfusion in a pig model for sleep apnea. *Am J Hypertens* 2014;**27**(10):1293–300.
124. Zalucky AA, Nicholl DD, Hanly PJ, et al. Nocturnal hypoxemia severity and renin-angiotensin system activity in obstructive sleep apnea. *Am J Respir Crit Care Med* 2015;**192**(7):873–80.
125. Lin YS, Liu PH, Lin SW, et al. Simple obstructive sleep apnea patients without hypertension or diabetes accelerate kidney dysfunction: a population follow-up cohort study from Taiwan. *Sleep Breath* 2017;**21**(1):85–91.
126. Tahrani AA, Ali A, Raymond NT, et al. Obstructive sleep apnea and diabetic nephropathy: a cohort study. *Diabetes Care* 2013; **36**(11):3718–25.
127. Hwu DW, Lin KD, Lin KC, Lee YJ, Chang YH. The association of obstructive sleep apnea and renal outcomes-a systematic review and meta-analysis. *BMC Nephrol* 2017;**18**(1):313.
128. Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep* 2008;**31**(8):1071–8.
129. Marshall NS, Wong KK, Liu PY, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. *Sleep* 2008;**31**(8): 1079–85.
130. Punjabi NM, Caffo BS, Goodwin JL, et al. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009;**6**(8):e1000132.
131. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;**342**(19):1378–84.
132. Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of sleep-disordered breathing and the occurrence of stroke. *Am J Respir Crit Care Med* 2005;**172**(11):1447–51.
133. Munoz R, Duran-Cantolla J, Martinez-Vila E, Gallego J, Rubio R, Aizpuru F, De La Torre G. Severe sleep apnea and risk of ischemic stroke in the elderly. *Stroke* 2006;**37**(9):2317–21.
134. Mooe T, Rabben T, Wiklund U, Franklin KA, Eriksson P. Sleep-disordered breathing in women: occurrence and association with coronary artery disease. *Am J Med* 1996;**101**(3):251–6.
135. Peled N, Abinader EG, Pillar G, Sharif D, Lavie P. Nocturnal ischemic events in patients with obstructive sleep apnea syndrome and ischemic heart disease: effects of continuous positive air pressure treatment. *J Am Coll Cardiol* 1999;**34**(6):1744–9.
136. Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: the sleep heart health study. *Am J Respir Crit Care Med* 2006;**173**(8):910–6.

137. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. *N Engl J Med* 2005; **352**(12):1206–14.
138. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2001;**163**(1):19–25.
139. Bedard MA, Montplaisir J, Richer F, Malo J. Nocturnal hypoxemia as a determinant of vigilance impairment in sleep apnea syndrome. *Chest* 1991;**100**(2):367–70.
140. Bedard MA, Montplaisir J, Richer F, Rouleau I, Malo J. Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. *J Clin Exp Neuropsychol* 1991;**13**(6):950–64.
141. Naegele B, Thouvard V, Pepin JL, et al. Deficits of cognitive executive functions in patients with sleep apnea syndrome. *Sleep* 1995; **18**(1):43–52.
142. Berry DT, Webb WB, Block AJ, Bauer RM, Switzer DA. Nocturnal hypoxia and neuropsychological variables. *J Clin Exp Neuropsychol* 1986;**8**(3):229–38.
143. Budweiser S, Enderlein S, Jorres RA, Hitzl AP, Wieland WF, Pfeifer M, Arzt M. Sleep apnea is an independent correlate of erectile and sexual dysfunction. *J Sex Med* 2009;**6**(11):3147–57.
144. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med* 2002;**165**(5):677–82.
145. Broussard JL, Ehrmann DA, Van Cauter E, Tasali E, Brady MJ. Impaired insulin signaling in human adipocytes after experimental sleep restriction; a randomized, crossover study. *Ann Intern Med* 2012;**157**(8):549–57.
146. Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: a population-based study. *Am J Respir Crit Care Med* 2005;**172**(12):1590–5.
147. Nangaku M. Mechanisms of tubulointerstitial injury in the kidney: final common pathways to end-stage renal failure. *Intern Med* 2004;**43**(1):9–17.
148. Nangaku M. Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. *J Am Soc Nephrol* 2006;**17**(1):17–25.
149. Ahmed SB, Ronksley PE, Hemmelgarn BR, et al. Nocturnal hypoxia and loss of kidney function. *PLoS One* 2011;**6**(4):e19029.
150. Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *J Hypertens* 2001;**19**(12):2271–7.
151. Friedman O, Bradley TD, Chan CT, Parkes R, Logan AG. Relationship between overnight rostral fluid shift and obstructive sleep apnea in drug-resistant hypertension. *Hypertension* 2010;**56**(6):1077–82.
152. Gaddam K, Pimenta E, Thomas SJ, Cofield SS, Oparil S, Harding SM, Calhoun DA. Spironolactone reduces severity of obstructive sleep apnoea in patients with resistant hypertension: a preliminary report. *J Hum Hypertens* 2010;**24**(8):532–7.
153. Molnar MZ, Mucsi I, Novak M, et al. Association of incident obstructive sleep apnoea with outcomes in a large cohort of US veterans. *Thorax* 2015;**70**(9):888–95.
154. Xu J, Yoon IY, Chin HJ. The effect of sleep apnea on all-cause mortality in nondialyzed chronic kidney disease patients. *Sleep Med* 2016;**27**–**28**:32–8.
155. Dharia SM, Brown LK, Unruh ML. Recognition and treatment of obstructive sleep apnea. *Semin Dial* 2013;**26**(3):273–7.
156. Lee J, Turin TC, Nicholl DD, et al. Predictors of successful completion of diagnostic home sleep testing in patients with chronic kidney disease. *Sleep Breath* 2015;**19**(2):669–75.
157. Voulgaris A, Archontogeorgis K, Nena E, et al. Serum levels of NGAL and cystatin C as markers of early kidney dysfunction in patients with obstructive sleep apnea syndrome. *Sleep Breath* 2019;**23**(1):161–9. 120.
158. da Silva Paulitsch F, Zhang L. Continuous positive airway pressure for adults with obstructive sleep apnea and cardiovascular disease: a meta analysis of randomized trials. *Sleep Med* 2019;**54**: 28–34.
159. Bazzano LA, Khan Z, Reynolds K, He J. Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. *Hypertension* 2007;**50**(2):417–23.
160. Ballester E, Badia JR, Hernandez L, et al. Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 1999;**159**(2):495–501.
161. Gay P, Weaver T, Loube D, Iber C, Positive Airway Pressure Task Force, Standards of Practice Committee, American Academy of Sleep Medicine. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. *Sleep* 2006;**29**(3): 381–401.
162. Zimmerman ME, Arnedt JT, Stanchina M, Millman RP, Aloia MS. Normalization of memory performance and positive airway pressure adherence in memory-impaired patients with obstructive sleep apnea. *Chest* 2006;**130**(6):1772–8.
163. Jing J, Huang T, Cui W, Shen H. Effect on quality of life of continuous positive airway pressure in patients with obstructive sleep apnea syndrome: a meta-analysis. *Lung* 2008;**186**(3):131–44.
164. Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev* 2006;**3**(3): CD001106.
165. Weaver TE, Maislin G, Dinges DF, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep* 2007;**30**(6):711–9.
166. Antic NA, Catcheside P, Buchan C, et al. The effect of CPAP in normalizing daytime sleepiness, quality of life, and neurocognitive function in patients with moderate to severe OSA. *Sleep* 2011;**34**(1):111–9.
167. Loffler KA, Heeley E, Freed R, et al. SAVE (Sleep Apnea Cardiovascular Endpoints) Investigators. Effect of obstructive sleep apnea treatment on renal function in patients with cardiovascular disease. *Am J Respir Crit Care Med* 2017;**196**(11):1456–62.
168. Li X, Liu C, Zhang H, Zhang J, et al. Effect of 12-month nasal continuous positive airway pressure therapy for obstructive sleep apnea on progression of chronic kidney disease. *Medicine (Baltim)* 2019;**98**(8):e14545.
169. Koga S, Ikeda S, Yasunaga T, Nakata T, Maemura K. Effects of nasal continuous positive airway pressure on the glomerular filtration rate in patients with obstructive sleep apnea syndrome. *Intern Med* 2013;**52**(3):345–9.
170. Rimke AN, Ahmed SB, Turin TC, et al. Effect of CPAP therapy on kidney function in patients with obstructive sleep apnoea and chronic kidney disease: a protocol for a randomised controlled clinical trial. *BMJ Open* 2019;**9**(3):e024632.
171. Koyama T, Watanabe H, Terada S, Makabe S, Igarashi G, Nobori K, Ito H. Adaptive servo-ventilation improves renal function in patients with heart failure. *Respir Med* 2011;**105**(12): 1946–53.
172. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003;**4**(2):101–19.
173. *2011 revised IRLSSG diagnostic criteria for RLS*. International Restless Legs Syndrome Study Group; 2011.
174. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med* 2005;**165**(11): 1286–92.

175. Takaki J, Nishi T, Nangaku M, et al. Clinical and psychological aspects of restless legs syndrome in uremic patients on hemodialysis. *Am J Kidney Dis* 2003;**41**(4):833–9.
176. Unruh ML, Levey AS, D'Ambrosio C, Fink NE, Powe NR, Meyer KB. Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. Restless legs symptoms among incident dialysis patients: association with lower quality of life and shorter survival. *Am J Kidney Dis* 2004;**43**(5):900–9.
177. Gigli GL, Adorati M, Dolso P, Piani A, Valente M, Brotini S, Budai R. Restless legs syndrome in end-stage renal disease. *Sleep Med* 2004;**5**(3):309–15.
178. Ogna A, Forni Ogna V, Haba Rubio J, et al. Sleep characteristics in early stages of chronic kidney disease in the HypnoLaus cohort. *Sleep* 2016;**39**(4):945–53.
179. Kutner NG, Zhang R, Bliwise DL. Restless legs syndrome is underdiagnosed in the US Renal Data System. *QJM* 2013;**106**(5): 487.
180. Riar SK, Leu RM, Turner-Green TC, et al. Restless legs syndrome in children with chronic kidney disease. *Pediatr Nephrol* 2013; **28**(5):773–95.
181. Winkelmann J, Stautner A, Samtleben W, Trenkwalder C. Long-term course of restless legs syndrome in dialysis patients after kidney transplantation. *Mov Disord* 2002;**17**(5):1072–6.
182. Molnar MZ, Novak M, Ambrus C, et al. Restless Legs Syndrome in patients after renal transplantation. *Am J Kidney Dis* 2005;**45**(2): 388–96.
183. Aritake-Okada S, Nakao T, Komada Y, et al. Prevalence and clinical characteristics of restless legs syndrome in chronic kidney disease patients. *Sleep Med* 2011;**12**(10):1031–3.
184. Quinn C, Uzbeck M, Saleem I, et al. Iron status and chronic kidney disease predict restless legs syndrome in an older hospital population. *Sleep Med* 2011;**12**(3):295–301.
185. Connor JR, Wang XS, Allen RP, Beard JL, Wiesinger JA, Felt BT, Earley CJ. Altered dopaminergic profile in the putamen and substantia nigra in restless leg syndrome. *Brain* 2009;**132**(Pt 9): 2403–12.
186. Trenkwalder C, Hogl B, Winkelmann J. Recent advances in the diagnosis, genetics and treatment of restless legs syndrome. *J Neurol* 2009;**256**(4):539–53.
187. Schormair B, Plag J, Kaffe M, et al. MEIS1 and BTBD9: genetic association with restless leg syndrome in end stage renal disease. *J Med Genet* 2011;**48**(7):462–6.
188. Kushida C, Martin M, Nikam P, Blaisdell B, Wallenstein G, Ferini-Strambi L, Ware Jr JE. Burden of restless legs syndrome on health-related quality of life. *Qual Life Res* 2007;**16**(4):617–24.
189. Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. *Neurology* 2008;**70**(1):35–42.
190. Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. *Sleep* 2009;**32**(5):589–97.
191. Winkelman JW, Finn L, Young T. Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. *Sleep Med* 2006;**7**(7):545–52.
192. Picchietti DL, Picchietti MA. Restless legs syndrome: what have we learned from prevalence studies and how will incidence studies further clinical knowledge? *J Clin Sleep Med* 2012;**8**(2): 125–6.
193. Earley CJ, Silber MH. Restless legs syndrome: understanding its consequences and the need for better treatment. *Sleep Med* 2010; **11**(9):807–15.
194. Lee HB, Hening WA, Allen RP, Kalaydjian AE, Earley CJ, Eaton WW, Lyketsos CG. Restless legs syndrome is associated with DSM-IV major depressive disorder and panic disorder in the community. *J Neuropsychiatry Clin Neurosci* 2008;**20**(1):101–5.
195. Hornyak M. Depressive disorders in restless legs syndrome: epidemiology, pathophysiology and management. *CNS Drugs* 2010;**24**(2):89–98.
196. Winkelman JW, Redline S, Baldwin CM, Resnick HE, Newman AB, Gottlieb DJ. Polysomnographic and health-related quality of life correlates of restless legs syndrome in the Sleep Heart Health Study. *Sleep* 2009;**32**(6):772–8.
197. Pearson VE, Allen RP, Dean T, Gamaldo CE, Lesage SR, Earley CJ. Cognitive deficits associated with restless legs syndrome (RLS). *Sleep Med* 2006;**7**(1):25–30.
198. Szentkiralyi A, Molnar MZ, Czira ME, et al. Association between restless legs syndrome and depression in patients with chronic kidney disease. *J Psychosom Res* 2009;**67**(2):173–80.
199. Molnar MZ, Szentkiralyi A, Lindner A, et al. Restless legs syndrome and mortality in kidney transplant recipients. *Am J Kidney Dis* 2007;**50**(5):813–20.
200. Giannaki CD, Hadjigeorgiou GM, Karatzaferi C, et al. A single-blind randomized control trial to evaluate the effect of 6 months of progressive aerobic exercise training in patients with uraemic restless legs syndrome. *Nephrol Dial Transplant* 2013;**28**(11): 2834–40.
201. Lipford MC, Silber MH. Long-term use of pramipexole in the management of restless legs syndrome. *Sleep Med* 2012;**13**(10): 1280–5.
202. Gopaluni S, Sherif M, Ahmadouk NA. Interventions for chronic kidney disease-associated restless legs syndrome. *Cochrane Database Syst Rev* 2016;**11**:CD010690.
203. Ausserwinkler M, Schmidt P. Successful clonidine treatment of restless leg syndrome in chronic kidney insufficiency. *Schweiz Med Wochenschr* 1989;**119**(6):184–6.
204. Zilberman M, Silverberg DS, Schwartz D, Oksenberg A. Restless legs syndrome (RLS) in anemic patients with congestive heart failure and chronic renal failure: lack of effect of anemia treatment. *Int J Cardiol* 2010;**143**(2):205–7.
205. Sakkas GK, Hadjigeorgiou GM, Karatzaferi C, et al. Intradialytic aerobic exercise training ameliorates symptoms of restless legs syndrome and improves functional capacity in patients on hemodialysis: a pilot study. *Am Soc Artif Intern Organs J* 2008;**54**(2): 185–90.
206. Micozkadioglu H, Ozdemir FN, Kut A, Sezer S, Saatci U, Haberal M. Gabapentin versus levodopa for the treatment of Restless Legs Syndrome in hemodialysis patients: an open-label study. *Ren Fail* 2004;**26**(4):393–7.
207. Pellecchia MT, Vitale C, Sabatini M, Longo K, Amboni M, Bonavita V, Barone P. Ropinirole as a treatment of restless legs syndrome in patients on chronic hemodialysis: an open randomized crossover trial versus levodopa sustained release. *Clin Neuropharmacol* 2004;**27**(4):178–81.
208. Molnar MZ, Novak M, Szeifert L, et al. Restless legs syndrome, insomnia, and quality of life after renal transplantation. *J Psychosom Res* 2007;**63**(6):591–7.

QUESTIONS AND ANSWERS

Question 1

During an office visit, a 60-year-old woman with CKD complains about difficulty falling asleep until very late in the night and feeling tired during the day. She describes a crawly, achy feeling in her legs when she is trying to fall asleep, which gets better after walking or massaging her legs but returns when she stops. She has been trying to keep her mind occupied by reading and watching television but complains that the symptoms recur during the periods of inactivity. She occasionally experiences this in the evening while reading, but not earlier in the day. She lives alone and is not aware about whether she snores. Based on the history, which one of the following is the most appropriate next step in her evaluation?

A. Diagnostic sleep study
B. Actigraphy
C. Obtain serum ferritin level
D. Prescribe hypnotic agent
E. All of the above

Answer: C

This patient has symptoms of unpleasant sensations in her legs during periods of inactivity, particularly when she is trying to fall asleep. The dysesthesias are relieved by activity but recur during inactivity and are associated with sleep onset insomnia. The circadian variation in symptoms described by the patient is one of the key criteria for the diagnosis of RLS, and her description fulfills International Restless Legs Syndrome Study Group criteria for the diagnosis. Intra-cerebral iron deficiency is linked to RLS, and a serum ferritin level should be obtained to commence iron supplementation if lower than 50 pg/mL. The etiology of iron deficiency, if found, should be determined.

Question 2

A 60-year-old man has poorly controlled hypertension and CKD. The patient is being treated with amlodipine, lisinopril, and hydrochlorothiazide. He denies any symptoms of daytime sleepiness. However, his wife complains that she is unable to sleep because of his very loud snoring. She has been particularly worried over observing him gasping in his sleep when on his back. The patient has not been able to exercise as he is tired and gets out of breath easily. Physical examination reveals his height is 5 feet 8 inches, weight 240 pounds, blood pressure 180/95 mm Hg. Head Eyes Ears Nose and Throat: edematous soft palate, uvula is barely seen, teeth indention marks are seen along the tongue, neck circumference is 16.5 inches. Chest: clear. Cardiac: S4 gallop. Extremities: 1−2+ edema. An echocardiogram done the previous week showed left ventricular hypertrophy and mild pulmonary hypertension. S[Cr] is 1.5 mg/dL.

What is the most appropriate next step in the evaluation?

A. Cardiac catheterization
B. Renal angiography
C. Prescribe furosemide
D. Nocturnal polysomnogram
E. None of the above

Answer: D

Even though the patient does not endorse sleepiness, his clinical presentation is very suggestive of obstructive sleep apnea. Although he has risk factors for coronary artery disease, he more urgently requires evaluation for obstructive sleep apnea, because treatment for this would be expected to improve his blood pressure control, reduce the risk for cardiovascular sequelae, and may potentially prevent progression of CKD. Additional antihypertensive treatment may not be required once obstructive sleep apnea is controlled. Should treatment of obstructive sleep apnea not allow for satisfactory control of his blood pressure, evaluation for secondary causes of hypertension such as from renovascular disease can be considered; however, at this point it is not warranted.

Question 3

Obstructive sleep apnea increases the risk of which of the following?

A. Hypertension
B. Type 2 diabetes mellitus
C. Coronary ischemia
D. Worsening obesity
E. All of the above

Answer: E

Studies of obstructive sleep apnea in the general population have shown an increased risk of all these comorbidities. Furthermore, all these comorbidities are implicated in the progression of CKD. Strategies for minimizing these risk factors would improve the overall prognosis of CKD patients.

Question 4

A 70-year-old woman comes for routine follow-up of hypertension and CKD. The patient is concerned about her inability to sleep well for over a year or so,

perceiving her sleep to be not as restful as before. She denies daytime sleepiness but says she feels miserable during the day. She has not been able to enjoy the things she previously did, and she is not as active as before. She denies feeling depressed. Recently she began drinking 2 cups of coffee with her lunch to complete her afternoon chores. Her physical examination and laboratory blood tests, including her kidney function, appear unchanged from last visit. The most correct next step would be:

A. Prescribe zolpidem
B. Ignore her complaints, just order chemistries for the next visit
C. Ask her to cut down caffeine intake
D. Refer to a sleep specialist
E. None of the above

Answer: D

Even though the patient's hypertension and CKD appear to be optimally treated, her QOL is affected because of her insomnia complaint: sleep that she perceives as not restful along with impaired daytime function. Cutting down caffeine might help but her insomnia has preceded the increased caffeine intake and, given the impact of her sleep complaint including probable depression, she would certainly benefit from proper evaluation and not just a hypnotic agent. Evaluation for a sleep disorder may uncover SDB or periodic limb movement disorder that can be treated effectively. In the long term, she might benefit from cognitive behavioral therapy for insomnia as she may have thoughts and behaviors that could worsen her symptoms further that would be elicited during a sleep medicine consultation. If for a short time she requires hypnotics as well, the newer nonbenzodiazepine hypnotics such as zolpidem would be preferable given their efficacy and side effect profile, but this is best considered after the possibility of an intrinsic sleep disorder is eliminated.

Question 5

RLS has been shown to increase the risk of depression, insomnia complaints, and mortality among patients with CKD.

A. Yes
B. No

Answer: A

RLS is associated with increased mortality in patients with a renal transplant with CKD.[208] CKD patients with RLS have an increased risk of depression. Both CKD and RLS could additively increase their risk of insomnia.[183]

Question 6

In CKD patients, which of the following is correct?

A. Insomnia is independently associated with comorbidities, depression, RLS, and increased risk of obstructive sleep apnea
B. Depression is independently associated with increased mortality
C. RLS and CKD together increase the risk of depression and insomnia
D. All of the above
E. None of the above

Answer: D

Insomnia in CKD patients is independently associated with comorbidities including depression, RLS, and increased risk of obstructive sleep apnea.[11] RLS and insomnia both worsen heath-related QOL in CKD patients.[208] Emerging evidence links both insomnia and RLS to an increased risk of cardiovascular disease, which is the most important cause of mortality in CKD patients. Thus, it is critical to look for and address insomnia and RLS in CKD patients to improve overall prognosis.

CHAPTER

37

Sexual Dysfunction in Chronic Kidney Disease

Kirsten Johansen

Division of Nephrology, Hennepin County Medical Center, Minneapolis, MN, United States

Abstract

Sexual dysfunction is common among men and women with chronic kidney disease (CKD) and is associated with depression and worse perception of quality of life. The pathophysiology is complex and may be related to hormonal disturbances related to CKD, comorbid conditions, medications, or psychosocial factors. We describe the prevalence, pathophysiology, diagnosis, and management separately for men and women. Because there are relatively few data directly addressing these issues among patients with nondialysis-dependent CKD, we have leaned heavily on the literature among patients with end-stage renal disease and on guidelines for treatment for the general population, emphasizing treatment differences related to CKD. Because sexual dysfunction is common, affects quality of life, and can be treated, it deserves more attention in the management of patients with CKD.

SEXUAL DYSFUNCTION AMONG MEN WITH CKD

Scope of the Problem

In men with CKD, sexual dysfunction often refers to erectile dysfunction (ED) alone but can also include decreased libido, difficulty with arousal, difficulty achieving orgasm, and ejaculatory abnormalities.[1] Sexual dysfunction is much more common in patients with chronic kidney disease (CKD) than in the general population, and the prevalence of ED increases with decreasing glomerular filtration rate (GFR).[2] Navaneethan et al. performed a meta-analysis and reported that 70% of men with CKD or end-stage renal disease (ESRD)[3] reported sexual dysfunction.[3] Because there were so few data on the prevalence and affects of sexual dysfunction in men with nondialysis-dependent CKD, it may be useful to examine the available data in patients with ESRD.[3] Seventy-five percent of patients treated with dialysis reported sexual dysfunction, but substantial heterogeneity in prevalence among studies was noted. Subsequently, a multinational cross-sectional study of 1611 men treated with hemodialysis demonstrated an 83% prevalence of ED.[4] Another study of men with stages 3–5 CKD not receiving renal replacement therapy (n = 81) reported an overall prevalence of ED of 76.5%, with a small gradient of prevalence with advancing stages of CKD that was not statistically significant (72.3% in stage 3 CKD, 81.5 in stage 4, and 85.7% in stage 5).[5] Sexual dysfunction often goes unaddressed by medical professionals. In one study of patients treated with hemodialysis, only 24.1% had talked to their doctor about their sexual activity. Only 55.4% were sexually active compared to 79% from the age-matched general population.[6]

Sexual dysfunction in patients with ESRD has been associated with impaired health-related quality of life (HRQOL), anxiety, and depression.[7–11] Patients with ED reported poorer social interactions, decreased emotional well-being, more role limitations due to emotional problems, and poorer social function than patients with ESRD who did not report ED.[11] Both the composite scores of the physical and mental components of quality of life of the SF-12 were lower among patients with ED, but after adjusting for age, diabetes, and comorbid conditions, ED remained associated only with lower mental composite score. Depression and anxiety are also associated with sexual dysfunction in hemodialysis patients.[1,7,9,12,13] The association is probably bidirectional, with depression causing or exacerbating ED, and ED leading to or worsening depression.[14,15] Overall, the strong association between sexual dysfunction and HRQOL raises the possibility that treatment of sexual dysfunction could improve HRQOL in the CKD population.[12] Given that poor HRQOL has been associated with adverse outcomes including death[16] and hospitalization,[17] alleviation of sexual dysfunction could have a major impact.

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00037-1

Pathophysiology

Sexual dysfunction is a multifaceted problem that can be related to hormonal, vascular, neural, or psychosocial causes (Figure 37.1).[1] In CKD, available data indicate that libido and potency decline with progression of kidney disease, remain low during dialysis,[18] and improve after transplantation,[19] suggesting a direct role of uremia or uremic toxins, possibly acting to cause testicular damage and/or perturbations in hormone production and metabolism. In addition, medications, psychosocial issues, vascular disease, and neurologic disease are common causes of or contributors to sexual dysfunction.[20]

Testicular function is abnormal in the setting of uremia. Testicular damage and impaired spermatogenesis have been well documented in patients with nondialysis-dependent CKD and ESRD.[19–21] In addition, testosterone levels are low in men with CKD.[19,22–24] In a cohort study of 260 men treated with dialysis with a median age of 59 years, only 23% had normal testosterone levels.[22] Free testosterone levels are also low among men with nondialysis-dependent CKD,[19] although patients with nephrotic syndrome may have low sex hormone binding globulin (SHBG).[25]

Whether testicular dysfunction is the primary cause of low testosterone or whether there is a contribution of hypothalamic and/or pituitary dysfunction has been the subject of considerable study and debate. Gonadotropins are elevated in most studies of men with ESRD, but it has been difficult to ascertain whether the elevation of gonadotropins is high enough to suggest normal hypothalamic–pituitary function, or lower than expected, which would indicate a contribution of hypothalamic–pituitary dysfunction in addition to the testicular abnormalities.[19] Hyperprolactinemia is also common among patients with CKD, likely as a result of disturbed hypothalamic regulation of pituitary prolactin secretion, although use of some medications can exacerbate the problem. Both low testosterone and high prolactin have in turn been associated with sexual dysfunction among men, including decreased libido and ED.

Opioid-induced androgen deficiency has been described for decades,[26] but its importance may be increasing given the high frequency of chronic opioid use among patients with CKD. For example, a recent study reported that 64% of patients treated with dialysis received opioids over an 11-month period.[27] The incidence of hypogonadotropic hypogonadism among chronic opioid users ranges from 21% to 86%.[26] Its onset is rapid, occurring within hours to weeks of treatment initiation. It is dose-dependent. A recent meta-analysis found that testosterone was 165 ng/dL lower on average among those using opioids compared to those not

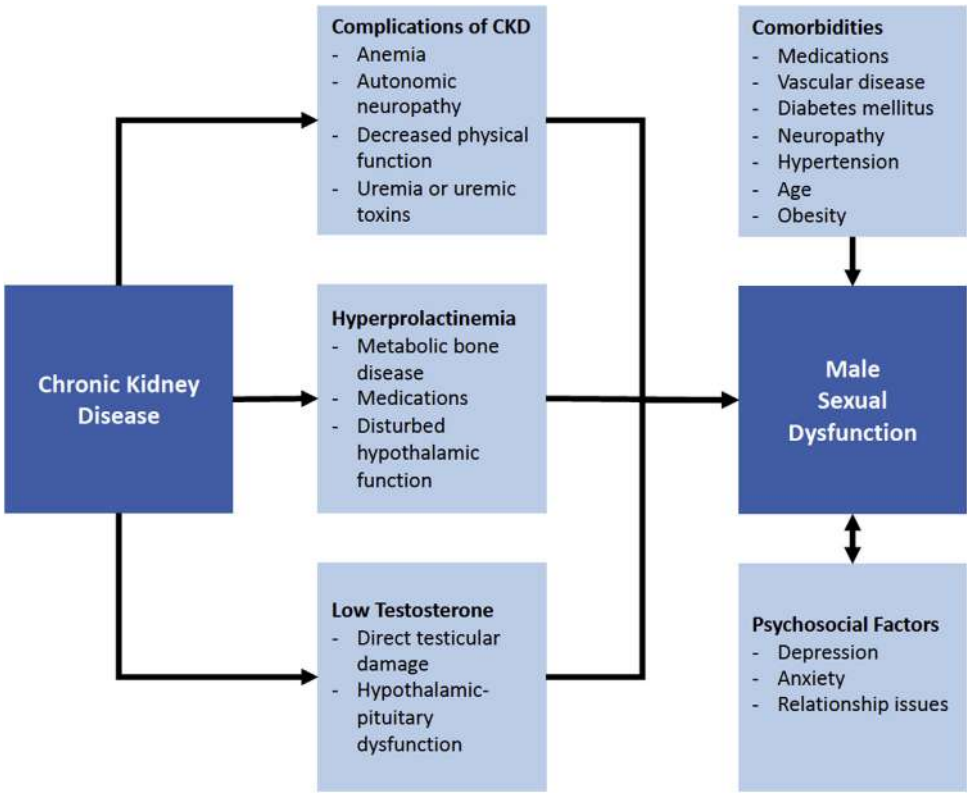


FIGURE 37.1 Factors contributing to male sexual dysfunction.

receiving opioids (95% CI 84−245 ng/dL lower) regardless of opioid type or indication for use.[28] Testosterone suppression is reversible on discontinuation of opioid treatment, within 24−72 hours in some cases, but it can persist for months or years after long-term use.[26]

Patients with CKD have several other risk factors for ED that may contribute to the high prevalence or worsen the severity of symptoms, but may be less likely to cause decreased libido, including older age, diabetes, hypertension, and neuropathy.[10] Erection involves responses to external stimuli through parasympathetic activity, release of nitric oxide, and smooth muscle relaxation resulting in blood flow into the penis.[29] Thus, any process that affects nervous system input, endothelial function, or systemic blood pressure has the potential to interfere with erectile function. Diabetes and hypertension, the most common causes of CKD, are both associated with vascular disease that can contribute to ED by limiting blood flow to the penis.[10,30] Furthermore, the treatment of hypertension can also cause or exacerbate ED, with centrally acting agents and beta blockers most commonly implicated.[20] One study among patients treated with dialysis found a higher prevalence of sexual dysfunction among patients not treated with angiotensin-converting enzyme inhibitor.[10] Anemia and autonomic neuropathy may also contribute to ED among patients with CKD. Finally, depression, anxiety, and difficulties with interpersonal relationships are potential causes of sexual dysfunction.[1]

Diagnosis

Diagnosis of male sexual dysfunction begins with a detailed medical and psychosocial history and physical examination (Table 37.1). The history should first define the problem, distinguishing ED and decreased libido from problems with ejaculation or orgasm, and establishing the time course and severity of symptoms.[31] It is also important to obtain a history of potential risk factors for ED, including the presence of vascular disease, diabetes mellitus, neuropathy or other neurological disorders, dyslipidemia, and hypertension, which are common among patients with CKD. Other clinical risk factors include obesity, smoking, endocrine disorders including gonadal dysfunction, as well as trauma, surgery or radiation to the pelvic organs.[31] Psychosocial factors such as depression, anxiety, alcohol or other substance abuse, and relationship issues involving a partner may also be important contributors to ED.[1] A thorough medication history should focus on antihypertensive medications, selective serotonin reuptake inhibitor (SSRI) antidepressants and venlafaxine, opioids, and antitestosterone agents. Antidepressants are the most common psychotropic drugs associated with ED, but antipsychotics such as risperidone and olanzapine have the highest likelihood of all psychotropic drugs of causing ED.[32] Physical examination should exclude anatomic abnormalities of the pelvis and genitalia and assess vascular and neurologic function. Specifically, resting and orthostatic vital signs should be obtained and lower extremity pulses examined.

The European Male Aging Study found that decreased frequency of morning erection, decreased frequency of sexual thoughts, and ED were related to free or total testosterone level, with a higher probability of symptoms among men with lower testosterone.[33] These authors proposed a syndrome of late-onset hypogonadism, requiring the presence of at least three sexual symptoms with a total testosterone level of less than

TABLE 37.1 History and Physical Examination for Male Sexual Dysfunction

Hypogonadal Symptoms	Medical & Surgical History Risk Factors	Psychosocial History Risk Factors	Potential ED-Causing Medication Review	Focused Physical Exam
- Decreased libido - Depressed mood - Fatigue - Muscle wasting	- Vascular disease - Diabetes mellitus - Hypertension - Dyslipidemia - Obesity - Endocrine disorders - Neuropathy - Other neurological disorders - Pelvic surgery or trauma - Pelvic radiation	- Smoking - Alcohol abuse - Other substance abuse - Depression - Anxiety - Relationship issues with partner	- Antihypertensives (beta-blockers, thiazides, calcium channel blockers) - SSRIs - Opioids - Antiandrogens (5-alpha-reductase inhibitors, spironolactone, ketoconazole, GnRH agonists)	- Resting and orthostatic vitals - Femoral pulses/ bruits and distal extremity pulses - Anatomic abnormalities of pelvis and genitalia (e.g. atrophic testicles, penile plaques in Peyronie's disease) - Neurologic exam (e.g. cremasteric reflex)

ED, erectile dysfunction; *SSRI*, selective serotonin reuptake inhibitor.

11 nmol/L (~320 ng/dL), which appears to be very similar to the disturbances reported by many men with CKD.

The American Urological Association,[31] the International Society for the Study of the Aging Male,[34] and the Endocrine Society[25] have released recently updated guidelines on ED and hypogonadism. ED guidelines recommend that clinicians measure testosterone level in patients presenting with ED with or without reduced sexual desire (libido).[31,34] The specific recommendation is that the initial diagnostic test for hypogonadism should be measurement of morning total testosterone level by a reliable assay, followed by confirmation of the diagnosis by repeating the measurement of total testosterone.[25] Because testosterone levels may decrease transiently in the setting of acute or subacute illness, evaluation should be avoided during such events. Determination of free testosterone level is recommended among patients whose total testosterone level is near the lower limit of the normal range, and among certain groups likely to have altered SHBG concentrations, including older patients who may have increased SHBG, as well as patients with obesity, diabetes mellitus, nephrotic syndrome, and those taking corticosteroids, in whom SHBG may be low.[25] Free testosterone can either be measured directly from equilibrium dialysis assays or calculated using total testosterone, SHBG, and albumin concentrations. Among patients with low testosterone, evaluation of LH, FSH, and prolactin may also be helpful. Overall, the much higher prevalence of sexual dysfunction and androgen deficiency among men with CKD suggests that a substantial proportion of men with symptoms are likely to have low testosterone. Formal vascular or neurological assessment and monitoring of nocturnal erections may be indicated in select patients in whom the organic nature of the problem is in doubt.[31,35]

Treatment

Lifestyle Modifications and Cardiovascular Risk Reduction

There is some evidence that lifestyle modification can improve ED. In obese men with ED, weight loss and increased physical activity were associated with an improvement in erectile function in about one-third of patients.[36] Lifestyle modifications such as Mediterranean diet, weight loss, and exercise improved ED in studies of men with hypertension, diabetes, or the metabolic syndrome.[37–39] Additionally, a meta-analysis looking at the aforementioned trials as well as two other trials of atorvastatin use found that statins and lifestyle modification were effective at improving ED in men.[40]

There has been considerable emphasis in recent years on the overlap between ED and cardiovascular (CV) diseases, and on the importance of lifestyle modification and CV risk management in men with ED. Not only does ED share common risk factors with cardiovascular disease (CVD), but ED is itself a marker of significantly higher risk of CVD.[41] These issues have been addressed in several multidisciplinary Princeton Consensus conferences dedicated to optimizing sexual function and preserving CV health, attended by urologists, cardiologists, and endocrinologists.[41] Recommendations from these conferences have been incorporated into ED practice guidelines.[31] Because incident ED has a similar or greater predictive value for CV events as traditional risk factors and may be the presenting symptom of CVD among men with silent coronary artery disease (particularly younger men), organic ED should alert the clinician to the possibility of increased CVD risk, even in the absence of symptoms or history. Consensus recommendations, which have been incorporated into recent guidelines,[31] are that CVD risk assessment should be performed and the results incorporated into the treatment plan for ED in affected patients (Figure 37.2).[41]

Assessment should include a history and physical examination to uncover other risk factors as well as a resting electrocardiogram, fasting lipids, and glucose. Lifestyle modifications and aggressive management of CV risk factors (e.g. hypertension, hyperlipidemia, hyperglycemia) is recommended. Additional noninvasive or invasive testing for CVD may be indicated at the discretion of the clinician or cardiologist. Given that sexual activity is comparable to mild to moderate intensity physical activity in the range of 3–5 metabolic equivalents (METs) or to climbing two flights of stairs or walking briskly,[42] CV risk stratification is recommended before treatment of ED and resumption of sexual activity (Figure 37.2).[31,41] The first steps are a careful history for CV events and symptoms and exercise tolerance. Individuals who have not had recent CV events and can perform routine moderate activities (3–5 METs) without symptoms are at low risk and can be treated for ED. Those who are unstable (e.g. NYHA class IV heart failure, uncontrolled hypertension, recent myocardial infarction without intervention) should be stabilized before resumption of sexual activity. Exercise stress testing is recommended for those at intermediate or indeterminate risk.

PDE5 Inhibitors

Phosphodiesterase-5 (PDE5) inhibitors (PDE5i) can be effective regardless of the underlying etiology or severity of ED (Figure 37.3). PDE5i act by inhibiting degradation of cyclic guanosine monophosphate (GMP) by PDE5, an enzyme present in the corpus cavernosum of the penis. During erection, cyclic GMP causes vascular smooth muscle relaxation leading to increased blood flow into the corpus cavernosum. In a meta-analysis of 27 trials enrolling 6659 men, sildenafil was more likely than

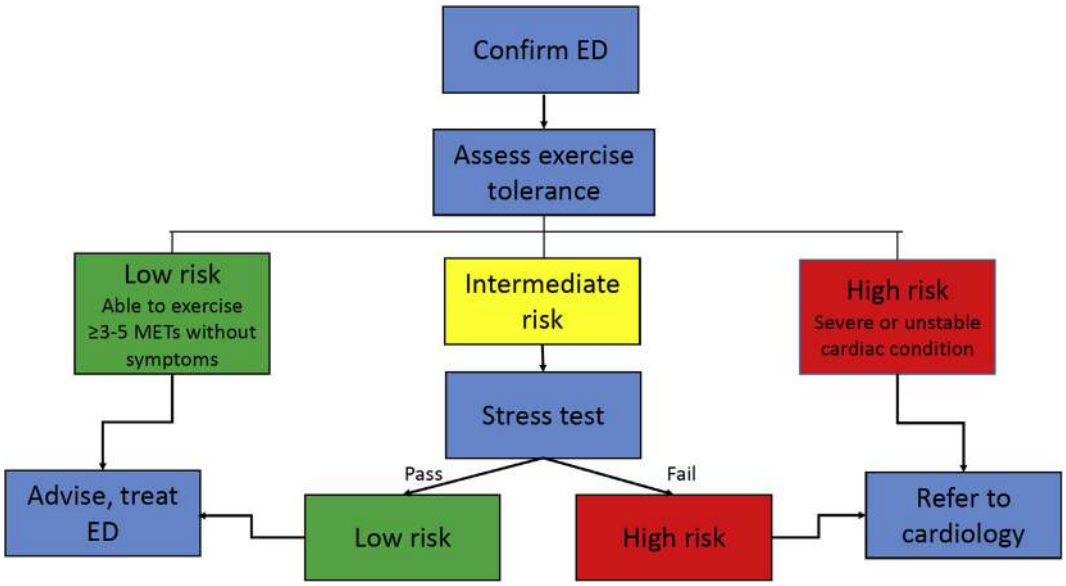


FIGURE 37.2 Cardiovascular risk stratification among men presenting with erectile dysfunction (ED).

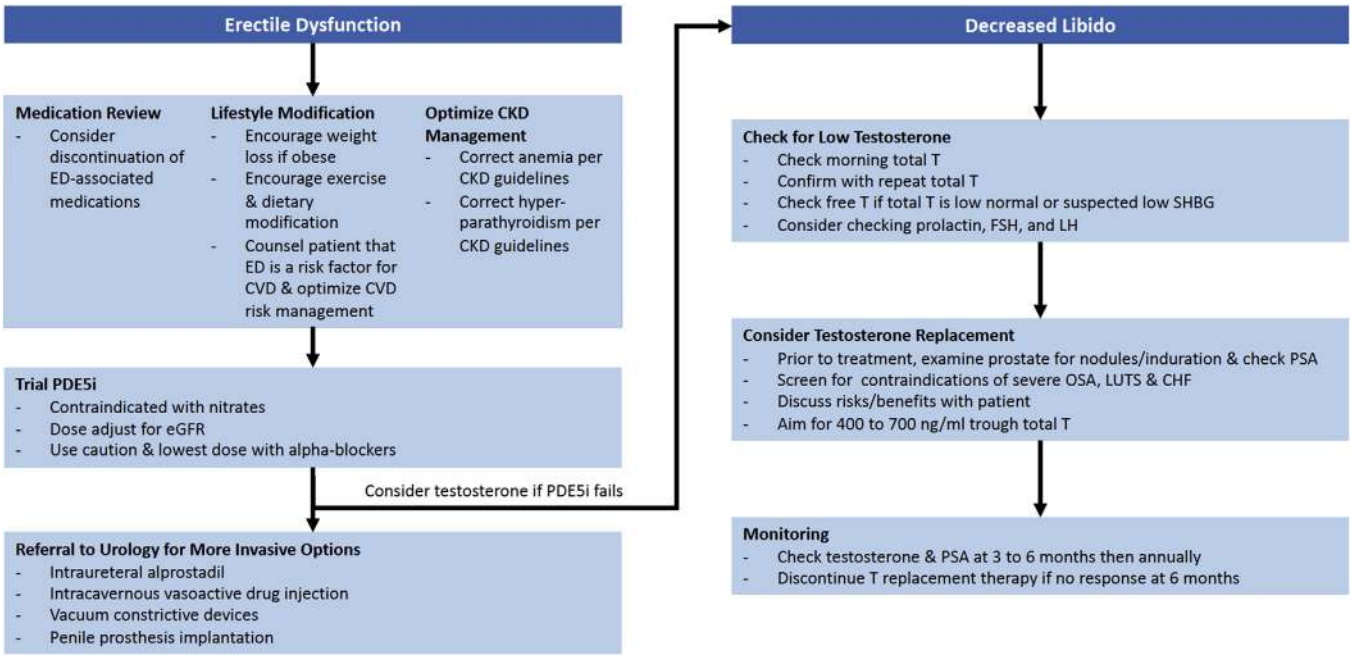


FIGURE 37.3 Evaluation and management of male sexual dysfunction. *CHF*, congestive heart failure; *CVD*, cardiovascular disease; *ED*, erectile dysfunction; *eGFR*, estimated glomerular filtration rate; *FSH*, follicle stimulating hormone; *LH*, luteinizing hormone; *LUTS*, lower urinary tract symptoms; *OSA*, obstructive sleep apnea; *PDE5i*, phosphodiesterase-5 inhibitor; *PSA*, prostate-specific antigen; *T*, testosterone.

placebo to lead to successful intercourse. Fifty-seven percent of intercourse attempts were successful among sildenafil-treated participants vs. 21% receiving placebo, and 83% of those assigned to sildenafil vs. 45% of men receiving placebo achieved at least one success.[43] Although there have been few direct comparisons of different PDE5i, the AUA notes that they appear to have similar efficacy in the general ED population.[31]

Inhibition of degradation of cyclic GMP can cause vasodilation and lead to hypotension, which may be of particular concern among patients with CKD. However, in a pharmacokinetic study of sildenafil among patients treated with hemodialysis, there was no increase in intradialytic hypotension when sildenafil was given immediately before a hemodialysis session.[44] Concomitant use of nitrates and PDE5i is contraindicated because

the combination can lead to severe hypotension. In addition, in patients taking alpha-blockers, commonly used for benign prostatic hypertrophy, using a PDE5i can also lead to symptomatic hypotension. It is recommended that patients treated with alpha-blockers should be on a stable dose before starting a PDE5i at the lowest dose. Alternatively, if the patient is already on a PDE5i, initiation of an alpha-blocker should be at the lowest possible dose. Other common side effects of PDE5i are headache, flushing, dizziness, nasal congestion, rhinitis, and dyspepsia. In the small studies of patients on dialysis or after kidney transplantion, headache was the most commonly reported side effect, and no reported severe adverse events related to PDE5i.[45–50]

The AUA strongly recommends that men who are prescribed a PDE5i be instructed carefully in their appropriate use. In particular, it should be explained that sexual stimulation is needed and that more than one trial with the medication may be needed to establish efficacy.[31] Guideline authors further noted that dose–response effects of PDE5i are relatively small and nonlinear, whereas stronger dose–response patterns have been observed for many adverse effects. Therefore, men should use the lowest dose that produces acceptable effects.

Although studies have examined the safety and efficacy of sildenafil among patients with ESRD,[45,51] there are no studies focusing specifically on patients with nondialysis-dependent CKD. A recent systematic review included six studies of PDE5i among patients treated with dialysis and after a kidney transplant.[45–50] These studies were all of modest size (13–60 participants) and short duration (1–2 months). Generally, there were marked improvements in sexual function, on the order of 75–85% among patients receiving PDE5i compared to 0–28% among patients receiving placebo. Of note, although there was consistent and substantial improvement in symptoms of ED and overall sexual function, libido and desire were not improved.

In the US, there are four PDE5i currently available: sildenafil, vardenafil, tadalafil, and avanafil. Although sildenafil is primarily eliminated by hepatic metabolism and excretion, its clearance is reduced in patients with CrCl <30 mL/min.[44,52] A lower starting dose of 25 mg daily as needed, approximately 1 hour before sexual activity and no more than once per day is recommended in these patients (https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/20895s039s042lbl.pdf).

The pharmacokinetics of sildenafil among dialysis patients appears to be similar to that of healthy individuals without CKD, suggesting that the reduced clearance observed in the setting of advanced CKD is the result of inhibition of hepatic sildenafil metabolism by a uremic toxin that is removed by dialysis.[44] Vardenafil and avanafil do not require dose adjustment in CKD (https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021400s010lbl.pdf). Vardenafil has not been evaluated in patients treated with dialysis and therefore is not recommended in this population. Avanafil is not recommended for patients with CrCl <30 mL/min because of a lack of detailed pharmacokinetic data (https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021400s010lbl.pdf). Recommended dosing of tadalafil is 5 mg daily as needed among patients with CrCl 30–50 mL/min, with a maximum of 10 mg in 48 hours. For patients with CrCl <30 mL/min or ESRD treated with hemodialysis, the maximum dose is 5 mg every 72 hours (http://pi.lilly.com/us/cialis-pi.pdf).

A small retrospective study reported good efficacy among men on HD treated with low dose tadalafil for three months.[53] Among kidney transplant recipients, sildenafil and vardenafil do not appear to alter the pharmokinetics of tacrolimus, cyclosporine, or mycophenolate mofetil in a clinically significant manner.[46,50,54]

Testosterone

Testosterone replacement therapy is a reasonable option among men with low testosterone and sexual dysfunction, particularly if decreased libido is a prominent symptom, if PDE5i therapy has not been successful, or if other potential symptoms or sequelae of hypogonadism are present, such as muscle wasting or osteoporosis (Figure 37.3). A recent meta-analysis of four trials (1779 patients) of testosterone therapy for hypogonadism defined strictly on the basis of low testosterone plus at least one relevant sign or symptom, found that testosterone therapy was associated with small but significant increases in libido, erectile function, and sexual satisfaction compared to placebo.[55] Although some participants in these trials likely had CKD, there have been no CKD-specific studies. Lawrence et al. described their experience treating 27 dialysis patients with injected testosterone in a renal impotence clinic.[56] Sexual function was fully restored in only 3 patients (11%), but another 19 (70%) had partial responses. Five patients (18.5%) did not respond.[56]

A new Endocrine Society guideline published in 2018 recommends testosterone therapy in hypogonadal men to correct symptoms of testosterone deficiency, which can include decreased libido and ED.[25] The guideline stresses that diagnosis of hypogonadism be based on "unequivocally and consistently" low total and/or free testosterone concentrations, measured on two separate mornings when the patient is fasting, accompanied by symptoms and signs of testosterone deficiency. The authors recommend against testosterone therapy in patients with breast or prostate cancer, a palpable prostate nodule, prostate-specific antigen (PSA) greater than 4 ng/mL or PSA greater than 3 ng/mL in men at

high risk for prostate cancer. In hypogonadal men 55–69 years old who are being considered for testosterone therapy and have a life expectancy greater than 10 years, the guideline suggests discussing the potential benefits and risks of evaluating prostate cancer risk and prostate monitoring and engaging the patient in shared decision-making regarding prostate cancer monitoring. For patients who choose monitoring, clinicians should assess risk (by performing digital prostate examination and evaluation of PSA levels) before starting testosterone therapy and again after 3–12 months. Urological evaluation is recommended if PSA increases by >1.4 ng/mL above baseline, or to a concentration >4.0 mg/mL, or if a prostatic abnormality is detected on examination. These recommendations represent a distinct change from prior guidelines, which stated that PSA should be measured before considering testosterone therapy.[57] The shift appears to be a result of heightened awareness that it is not possible to distinguish prostate cancers that will remain indolent from those destined to be lethal. In addition, testosterone therapy increases the risk of detecting subclinical prostate cancer because of increased surveillance and testosterone-induced increase in PSA, leading to concern that many men are being subjected to harms of treatment of prostate cancer that might never become symptomatic.[25] In addition to known breast or prostate cancer, other potential contraindications to testosterone therapy include hematocrit greater than 50%, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within the last 6 months, or thrombophilia.[25]

There are many types of testosterone preparations available, including injections, transdermal patches, gels, and solutions, nasal gel, buccal bioadhesive tablets and subcutaneous pellets. There are insufficient data to suggest important differences in efficacy among these. Thus, cost and patient preferences should dictate choice of therapy. There is no need for dose adjustment in CKD.[58] The primary goal of treatment is to alleviate symptoms. Available evidence from studies of healthy or hyopgonadal men suggests that the threshold testosterone level below which symptoms of sexual dysfunction occur varies among individuals but corresponds on average to the lower limit of the normal range for young men.[33,59–61] A recent study commissioned by the Endocrine Society in its guideline development process established harmonized testosterone reference ranges for total testosterone that can be applied across laboratories by cross-calibrating assays.[62] This process reduced intercohort variation in testosterone concentration substantially and resulted in a normal range of 264–916 ng/dL. The Endocrine Society guideline recommends using this range in defining testosterone deficiency and in targeting treatment.[25] They recommend monitoring testosterone level 3–6 months after initiation of treatment, and then annually thereafter, targeting testosterone levels in the mid-normal range. In men receiving injections of testosterone enanthate or cypionate, the recommendation is to aim for normal levels (400–700 ng/dL) one week after the injection. Unlike PDE5i, the effects of testosterone are not immediate. A recent review assessed the time course of testosterone effects on symptoms and found that the effects on libido and sexual satisfaction begin after approximately 3 weeks and peak at 6 weeks after initiation of testosterone therapy.[63] However, maximal effect on ED appears to take longer—usually by 3–6 months but sometimes up to 1 year.

The biggest safety concerns related to testosterone therapy are related to prostate cancer and CVD, but increase in hematocrit, acne, oiliness of skin, and breast tenderness are also common drug-related adverse events. Increased hematocrit is less likely to be a concern among patients with CKD although hematocrit should still be monitored with testosterone therapy.[25] There is little evidence that endogenous androgens are related to the development or progression of prostate cancer,[64] or that testosterone therapy increases the risk of prostate cancer or BPH.[55,64,65] However, testosterone can stimulate growth and aggravate symptoms in men with locally advanced and metastatic prostate cancer and increases the risk of prostate biopsy if patients choose to undergo surveillance for prostate cancer.[64–66]

Reliance on observational data and short-term studies has made it difficult to assess the CV effects of testosterone. There are no long-term data on testosterone therapy in CKD populations, and a relative paucity of long-term data in older men with late-onset hypogonadism from which clinicians could generalize to men with CKD. Observational studies show that men with CVD have lower testosterone levels.[67–69] Cross-sectional studies of risk factors for CVD have shown inverse correlations between testosterone levels and triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, and body mass index. Short-term testosterone administration has been linked to many positive effects on CV risk factors, including reduction in total and LDL cholesterol, improvement in insulin sensitivity, and decrease in visceral fat mass and markers of inflammation. Furthermore, short-term testosterone administration has been shown to have positive effects on vascular function, alleviating angina, and enhancing vasoreactivity in patients with CAD.[68] Low testosterone is associated with higher overall and CV mortality among men in the general population[69] and among ESRD patients.[23,24] Thus, with the exception of HDL cholesterol, which is generally unchanged or reduced after testosterone administration, observational data and outcome data based on surrogate markers suggest a

potential favorable risk profile of replacement testosterone therapy.

Indeed, early indications from prospective studies did not report an increase in CV risk with testosterone, including a meta-analysis of 51 studies of testosterone replacement therapy, which found that there was no significant effect on mortality, myocardial infarction, need for coronary revascularization, or arrhythmias.[7] However, there has been considerable controversy about how to interpret the conflicting results of more recent observational and randomized studies, some of which suggested that testosterone might increase risk of major adverse cardiovascular events (MACE), whereas others did not. Publication of a randomized controlled trial among older men with low testosterone and mobility limitations that was halted because of a higher rate of CV events among the participants receiving testosterone[70] and two large retrospective cohorts of patients treated in the Veterans Affairs system[71] and another large healthcare system[72] that found a higher risk of MACE among those treated with testosterone led the US Food and Drug Administration (FDA) to issue a black box warning (https://www.fda.gov/Drugs/DrugSafety/ucm436259.htm) about these risks. However, the methodology of these studies has come under considerable criticism.[73,74] Subsequent randomized trials have not found testosterone to be associated with higher risk.[75–77] Therefore, the review panel for the Endocrine Society guideline[25] and other experts[74] have concluded that the randomized trials of testosterone therapy have been neither large enough nor long enough to evaluate the effects on MACE, and that there is no clear evidence that testosterone increases the risk of MACE.

CKD-Related Factors

Anemia has been associated with reduced libido and ED, and treatment with erythropoetin has been associated with improvements in ED, sexual performance, and sexual desire in some ESRD patients.[1,78–81] Some investigators have suggested that favorable changes in hormone levels with correction of anemia could underlie this improvement.[79,82] These data were all among patients with ESRD and severe anemia at baseline who experienced very large increases in hematocrit in response to erythropoietin. It is unclear if there are any data to address whether smaller changes in hemoglobin within currently recommended target ranges have any relation to sexual function, but it is reasonable to treat anemia according to current guideline recommendations among men with CKD and sexual dysfunction.

Parathyroid hormone may contribute to sexual dysfunction in CKD by an unknown mechanism. A study of 20 dialysis patients with CKD and secondary hyperparathyroidism undergoing parathyroidectomy showed improvements in sexual function after surgery and concomitant reductions in prolactin levels.[83] Similar caveats apply to this study as to the studies of erythropoietin—that it does not address effects of more modern therapies for hyperparathyroidism.

Zinc deficiency is a known cause of hypogonadism. Zinc levels have been found to be low in some hemodialysis patients. Studies have examined oral zinc supplementation as well as zinc in the dialysate as a treatment for ED.[45] Among dialysis patients treated with oral zinc, testosterone was increased as was potency and frequency of intercourse. However, zinc in the dialysate did not improve testosterone, FSH, or LH levels. A study with oral zinc led to increased serum LH and testosterone without any effect on serum FSH and prolactin levels, but did not address changes in sexual function among patients treated with hemodialysis.[84]

Bromocriptine, a dopamine D2 agonist used in the treatment of hyperprolactinemia, was studied in the past in hemodialysis patients with sexual dysfunction. Although there was an improvement in sexual function, hypotension was a common and limiting side effect,[85] and this agent has been abandoned as a therapy for ED and hyperprolactinemia.

Conclusions

Sexual dysfunction is common among men with CKD and is associated with lower HRQOL. Causes of sexual dysfunction include vascular, hormonal, neurologic, and psychosocial factor. The presence of more than one factor is common, particularly among older patients with CKD. Guidelines for the treatment of male sexual dysfunction do not present a uniform treatment algorithm. Men should be counseled about lifestyle modifications and should have CKD-related complications of anemia and hyperparathyroidism treated in accordance with CKD-related guidelines. If additional treatment of sexual dysfunction is needed, PDE5i should be the first-line treatment for most patients. For patients with low serum testosterone levels who fail PDE5i, or in whom decreased libido is a particularly important symptom, testosterone therapy can be considered as long as the patient is aware of potential risks. In addition, low testosterone levels should be confirmed after PDE5i therapy because PDE5i use can increase testosterone levels.[64] Because PDE5i and testosterone operate by different mechanisms and have different side effect profiles, they can be combined to address ED and decreased libido.[64] Other options for patients who fail PDE5i and/or testosterone therapy include intraurethral alprostadil, intracavernous vasoactive drug injection, vacuum constrictive devices, and penile prosthesis

implantation.[86] Patients should be referred to a urology specialist for consideration and implementation of these strategies.

SEXUAL DYSFUNCTION AMONG WOMEN WITH CKD

Scope of the Problem

Female sexual dysfunction (FSD) is common among patients with CKD, yet it remains understudied and probably undertreated. FSD can be categorized as sexual desire disorders, sexual arousal disorder, orgasmic disorder, and sexual pain disorders.[87] Each of these is diagnosed based on the presence of the relevant symptoms causing marked distress or interpersonal difficulty.[88] Estimates of the prevalence of FSD, among women with and without CKD, vary depending on whether the presence of personal distress is considered in the definition.[89] A recent large survey of women in the US found that 44% reported at least one problem with sexual function, with low desire being the most common complaint. Sexually related personal distress was reported by 23%.[89]

Up to 30–80% of women with advanced CKD suffer from FSD.[90–92] It has been suggested that as renal function declines, the frequency of sexual dysfunction increases.[1,3,45,93] In a small study by Basok et al. that included patients with various stages of CKD and healthy controls, half of the participants in the control and postkidney transplantion groups met the criteria for FSD. The proportions of women with FSD were much higher in the other groups: 81% among women with nondialysis-dependent CKD, 66.7% among women on peritoneal dialysis, and 75% among women treated with hemodialysis.[94] A larger study among women treated with hemodialysis found a similarly high proportion (84%) experienced sexual dysfunction.[95] These studies suggest that symptoms become more common with more advanced CKD and return to approximately the level of sexual dysfunction experienced by women in the general population after transplantation. Mor et al. examined sexual function and satisfaction among older women on dialysis,[96] and an accompanying editorial[97] called into question whether sexual inactivity and lack of sexual desire should be classified as dysfunction in older women treated with dialysis. Among 125 women who completed repeated administrations of the Female Sexual Function Index, 89% of the scores were consistent with sexual dysfunction, consistent with prior reports. However, sexual inactivity was the most common reason for identifying sexual dysfunction (82%), which in turn was frequently due to lack of interest in sex (43%) or lack of a partner (39%) but rarely due to sexual difficulty (2%). Sixty-four percent of surveys indicated that participants were moderately to very satisfied with their sexual life, and few were interested in learning about treatment options. Thus, it is important to consider patients' age and degree of concern when evaluating sexual function.

Pathophysiology

The etiology of sexual dysfunction among women with CKD is complex (Figure 37.4). Sexual dysfunction in women with CKD has been attributed to both hormonal disturbances and psychosocial factors and may also be complicated or exacerbated by the use of multiple medications and the presence of comorbidities.[51] The majority of women with CKD are postmenopausal, which may be due in part to premature menopause, which occurs approximately 4.5 years earlier (at age 47 years) among women with CKD than among women with normal kidney function.[98,99] There are few studies evaluating ovarian failure in women with less-advanced CKD, but by the time women reach ESRD, the frequency of menstruation among women of childbearing age is approximately 8–10%, with anovulatory cycles occurring commonly.[98] The effects of hypogonadism can include FSD. The hormonal disturbances that lead to ovarian failure in women with CKD include abnormalities in the hypothalamic–pituitary–ovarian axis and elevated prolactin levels. Ovarian failure is characterized by low estradiol levels, which cause decreased blood flow to the vagina and the vulva. Decreased estrogen levels may also increase tissue fragility, dryness, irritation, and susceptibility to vaginal tissue trauma.[87] Ovarian failure among women with CKD can ultimately lead to decreased vaginal lubrication and atrophy, pain during intercourse, and FSD.[1,98,99] Elevated prolactin levels may also play a role in ovulatory dysfunction, and ultimately in symptoms of FSD in women with CKD.[1] Serum prolactin levels appear to rise with declining GFR.[100] Elevated prolactin levels are thought to contribute to symptoms of decreased libido.[1,101]

Psychosocial factors, including depression and poverty, may also be associated with FSD in women with CKD (Figure 37.4). In the general population, a deterioration in economic position is associated with an increase in risk for FSD, and higher education levels are inversely associated with the prevalence of FSD.[102] The association between depression and FSD is complex. Among patients with ESRD, depression is the most commonly encountered psychological problem and has been associated with sexual dysfunction and lower quality of life.[1,92,103,104] Similar to men, depression can interfere with libido and lead to decreased sexual activity.[1] On the other hand, FSD may lead to depression

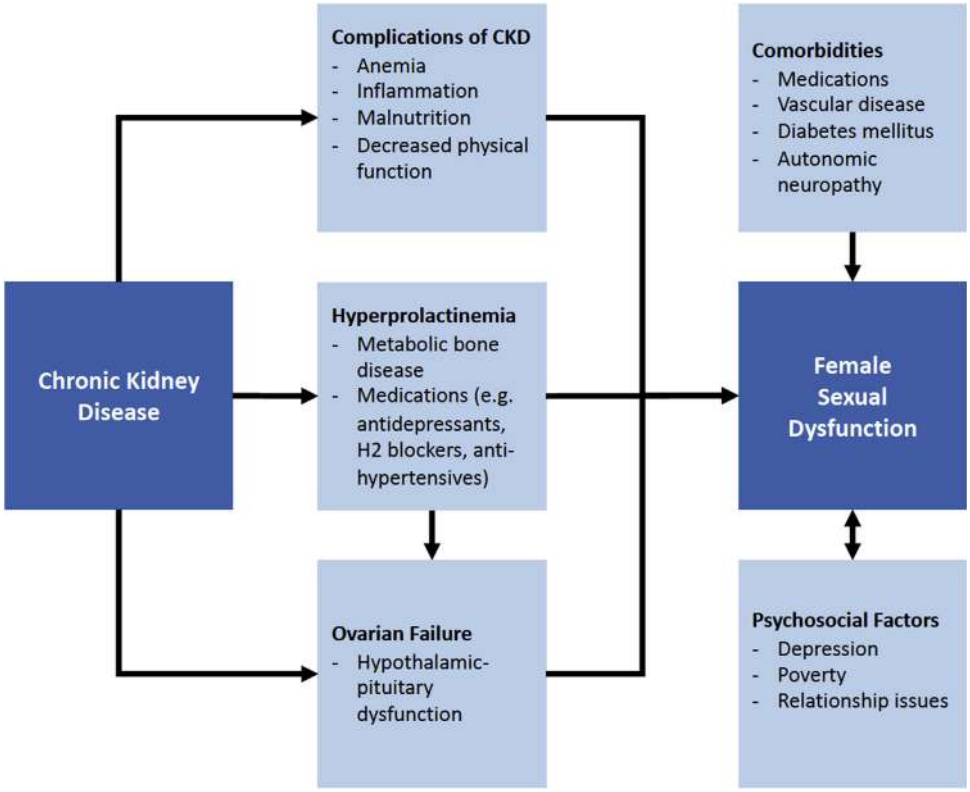


FIGURE 37.4 Factors contributing to female sexual dysfunction. *H2*, histamine 2.

or exacerbate preexisting depression, given the strong correlation between all categories of FSD and low feelings of happiness.[102] In addition, treatment of depression may contribute to the problem, as sexual dysfunction is a side effect of SSRIs in up to 30–70% of women.[105]

The presence of other comorbid illnesses including vascular disease, diabetes, and autonomic neuropathy also correlates with FSD in patients with CKD.[3,51] As vaginal sexual arousal is both a neuromuscular and vasocongestive event that relies on intact parasympathetic and inhibitory sympathetic input, women with CKD and autonomic neuropathy can be afflicted with sexual dysfunction.[106] Finally, commonly used medications in the CKD population, including antihypertensives, antidepressants, and histamine receptor blockers may also contribute to the frequent occurrence of sexual dysfunction.[51]

Diagnosis

The first step in diagnosing FSD begins with obtaining a detailed sexual history, which can be done with the aid of a questionnaire.[1,107,108] Although previously available assessments for FSD were one-dimensional, more recently, the normal female sexual response cycle is being recognized as a composite of a variety of domains, making a multidimensional instrument more appropriate.[108] Currently, FSD is defined using six separate domains, which include hypoactive sexual desire disorder, sexual aversion disorder, sexual arousal disorders, orgasmic disorders, sexual pain disorders, and noncoital sexual pain disorders.[108]

The next step in evaluating sexual function is to carefully review all medications, as patients with CKD are often prescribed multiple medications that may lead to sexual dysfunction (Figure 37.5). Consideration should also be given to obtaining hormone levels including FSH and LH among premenopausal women, and TSH and prolactin for all women. Although androgen levels continue to decrease in premenopausal women until they reach menopause, there is no proven clinical utility in monitoring androgen levels.[87] Further, parathyroid hormone and hemoglobin concentrations should be evaluated, as these are commonly abnormal and are associated with FSD. Finally, it is essential to screen for depression because of the high frequency of depression in the CKD and ESRD population, and the close associations between FSD and depression.[108,109]

Treatment

Given the high prevalence of FSD in the CKD population and its correlations with depression and perception

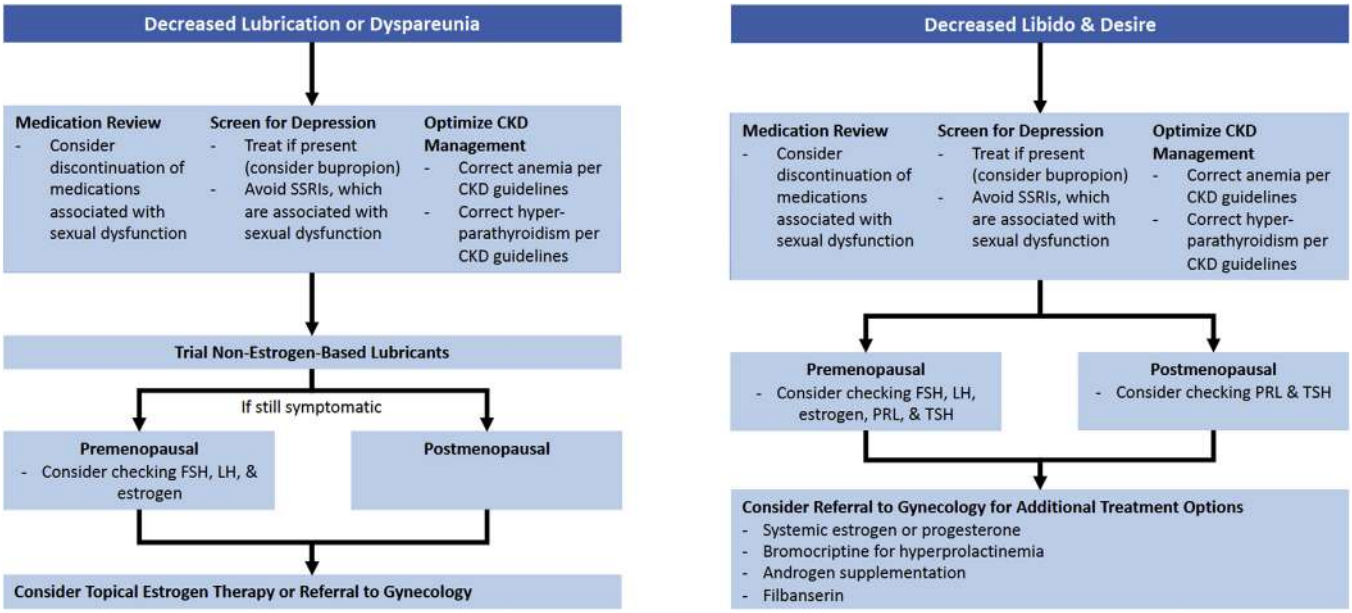


FIGURE 37.5 Evaluation and management of female sexual dysfunction. *FSH*, follicle stimulating hormone; *LH*, luteinizing hormone; *PRL*, prolactin; *SSRIs*, selective serotonin reuptake inhibitors; *TSH*, thyroid stimulating hormone.

of quality of life,[3] effective treatment of this problem is important as it may lead to improvements in these outcomes. Unfortunately, there are no randomized trials evaluating interventions for sexual dysfunction among women with CKD.[45] Treatment of FSD should take a systematic approach based on the findings of the evaluation and should follow guidelines established for women in the general population (Figure 37.5).[1,87] After initial evaluation, treatment can be initiated (Figure 37.5) or, depending on the comfort level and training of the physician, a referral can be made to a trained specialist, such as a gynecologist, marriage counselor, or sex therapist.[87]

Many patients with CKD are prescribed medications that may affect sexual function. After a thorough review of medications, unnecessary medications should be discontinued. Certain antihypertensive medications, histamine receptor blockers, and SSRI antidepressants are commonly used in the CKD population and are especially likely to be associated with FSD.[51,87] Consideration should be given to switching such medications to alternative drugs as a first-line approach for the treatment of FSD. Studies have shown that hypertensive women have worse sexual function than normotensive controls.[110,111] One study found approximately twice the prevalence of FSD among women with hypertension (42%) compared with women without hypertension (19%) in a group of relatively young participants.[110] Although this study did not report a difference based on type of therapy, a larger study by Doumas et al. reported that β-blocker administration was associated with a higher prevalence of FSD among 216 women with hypertension. However, no associations were found between FSD and the use of diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium antagonists.[111] Smoking[110] and acute nicotine administration[112] have also been shown to be associated with sexual dysfunction among women.

If the evaluation reveals untreated depression, treatment of depression may ameliorate sexual dysfunction. However, because SSRIs may themselves cause decreased arousal, decreased sexual desire, and orgasmic dysfunction among women, they are not the treatment of choice. Alternatives, such as bupropion or nonpharmacologic treatments including cognitive behavioral therapy,[113] are preferred.[87] Among women with depression treated with SSRIs, decreasing the dosage of the SSRI may help to alleviate symptoms. However, if symptoms do not improve with this strategy or if depression worsens, the SSRI may need to be switched to an alternative medication class, and consultation with a mental health provider should be considered. Bupropion inhibits both dopamine and norepinephrine reuptake, has a very low incidence of drug-induced sexual dysfunction, and has even been shown to improve sexual function.[114] In a randomized, double-blind, placebo-controlled trial, 66 premenopausal women with hypoactive sexual desire disorder were studied. Women assigned to receive bupropion reported significant improvement, measured by an increase in the overall score on the Changes in Sexual Function Questionnaire, as well as on the arousal and orgasm subscales.[114] Although scores on the desire

subscale increased more in the bupropion group, this change did not reach statistical significance. Limited pharmacokinetic data suggest that elimination of bupropion or its active metabolites may be reduced in the setting of moderate to severe CKD, so it should be used with caution and the dose interval may need to be increased (i.e. dose frequency reduced).

The next step in the treatment of FSD is the alleviation of targeted symptoms including decreased vaginal lubrication and dyspareunia (Figure 37.5). The use of topical vaginal estrogen can aid lubrication and improve postmenopausal atrophy and lead to decreased dyspareunia. The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on FSD notes that treatment using tablets, gels, creams, and vaginal rings is equally effective.[87] Systemic absorption of topical estrogen is limited following intravaginal application, but the lowest effective dose should be used for the least amount of time to alleviate symptoms. The ACOG recommends beginning with daily treatment for a few weeks and then tapering down based on symptoms.[87] For women who cannot or choose not to use estrogen, nonestrogen water-based or silicone-based lubricants can also aid with lubrication and decrease dyspareunia.[87] Ospemifene, a nonhormonal selective estrogen receptor modulator, was approved by the FDA for once-daily administration for the treatment of moderate to severe dyspareunia due to menopause subsequent to the publication of the ACOG guidelines.[115] It carries a warning about risk of endometrial cancer, deep vein thrombosis, and stroke (https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203505s000lbl.pdf) and is contraindicated in women with breast cancer. Because it is hepatically metabolized (and therefore contraindicated in patients with severe hepatic failure), no dose adjustment is required in women with CKD. However, the CV risks noted in the FDA warning should lead to particular caution in the CKD population.

Among women with orgasmic disorders, vasoactive medications such as sildenafil are thought to increase pelvic blood flow to the clitoris and vagina in a manner similar to their effects among men.[87] However, the results of randomized clinical trials evaluating the efficacy of sildenafil for the treatment of sexual arousal disorder have been contradictory.[87,116–119] A recent review concluded that although data suggest a possible role of sildenafil for the treatment of FSD, the information should be interpreted cautiously because many of the studies were small and used nonvalidated assessment tools.[120] The safety and efficacy of sildenafil has not been established among women with CKD, and therefore it should be used cautiously in this population. The ACOG notes that more research is needed before a recommendation can be made.[87]

Although levels of circulating androgens among women correlate weakly if at all with sexual function,[121,122] many studies have evaluated the use of testosterone supplementation among women in the general population with hypoactive sexual desire disorder.[123–125] Several formulations have been tested, and there is evidence for a beneficial effect on sexual function with a dose–response effect, particularly for transdermal testosterone.[87,123,124] However, testosterone is not approved by the FDA for the treatment of hypoactive sexual desire disorder among women. The most studied formulation, transdermal testosterone in the form of a matrix patch, is not available in the US.[87] Furthermore, because of lack of long-term safety data, neither the Endocrine Society[124] nor the ACOG recommend long-term use (longer than 6 months) of testosterone.[87] If androgens are used in the short-term treatment of FSD, there is no role for monitoring androgen levels.[87] Rather, monitoring should focus on assessment for potential side effects, including acne and hirsutism, and adverse changes in lipid profiles. The use of androgen supplementation to treat sexual dysfunction has not been studied among women with CKD, and there are currently no recommendations advocating for or against such supplementation in the CKD population. Since the publication of the ACOG guidelines, flibanserin has been approved by the FDA for the treatment of premenopausal women with generalized hypoactive sexual desire disorder that causes marked distress (https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022526lbl.pdf) based on three randomized controlled trials reporting an increase in the number of satisfying sexual events, and in one study, an improvement in desire was reported. However, severe hypotension is a concern, particularly when flibanserin is combined with alcohol or moderate or strong cytochrome P450 3A4 inhibitors or in the setting of hepatic impairment. Therefore, flibanserin is available only through a restricted program in which prescribers must be certified by enrolling and completing training.

Treatment of hormonal abnormalities, including elevated prolactin levels and low estradiol and progesterone levels, may also improve sexual dysfunction in women with CKD. Hyperprolactinemia has been associated with decreased libido and is thought to contribute to ovulatory dysfunction, and ultimately to sexual dysfunction. Bromocriptine may reduce the prolactin level to a normal range, but gonadotropin concentrations are not always normalized and the drug is poorly tolerated.[1,98] Correction of secondary hyperparathyroidism may also lower prolactin levels, and use of 1,25-dihydroxy vitamin D_3 appears to reduce prolactin secretion in patients with CKD.[98,101]

There is also some evidence that recombinant human erythropoietin (rHuEPO) therapy may improve the function of the pituitary gonadal axis and reverse the hormonal alterations seen in women with CKD by lowering FSH, LH, and prolactin levels.[98] Given the associations of anemia with decreased sexual dysfunction, it is important to correct anemia to guideline-recommended target hemoglobin levels.[101] Consideration should be given to hormone replacement with estrogen with or without progesterone, but this decision should be made following a careful evaluation of the patient, and on a case-by-case basis.[1] Finally, referral for kidney transplantation is important because improvement in sexual function has been reported by 85–90% of female kidney transplant recipients.[98] Improvement in sexual function characterized by improved libido and increased frequency of intercourse has been linked to the normalization of the hormonal profiles following kidney transplantion.[98]

Conclusions

Sexual dysfunction is a common problem in women with CKD. As renal function declines its prevalence increases. Multiple factors including comorbid diseases, hormonal disturbances, psychosocial factors, mineral and bone disorders, medications, anemia, and autonomic neuropathy may contribute to the occurrence or severity of sexual dysfunction in women with CKD.[51] Sexual dysfunction adversely affects quality of life in many women due to its associations with decreased self-esteem, poor self-image, anxiety, and marital discord.[3] However, some women may be less bothered by sexual inactivity.[96] Providers should be sensitive to this issue, balancing the importance of treatment when symptoms cause distress and avoiding overtreatment if sexual satisfaction is not low.[97] Accurate diagnosis and appropriate treatment of this common problem are very important, and more studies are urgently needed to identify beneficial treatment options in this population.

Acknowledgements

The author would like to acknowledge the contributions of Tavis Dancik and Gloria No.

References

1. Finkelstein FO, Shirani S, Wuerth D, Finkelstein SH. Therapy Insight: sexual dysfunction in patients with chronic kidney disease. *Nat Clin Pract Nephrol* 2007;**3**(4):200–7.
2. Bellinghieri G, Santoro D, Mallamace A, Savica V. Sexual dysfunction in chronic renal failure. *J Nephrol* 2008;**21**(Suppl. 13):S113–7.
3. Navaneethan SD, Vecchio M, Johnson DW, Saglimbene V, Graziano G, Pellegrini F, et al. Prevalence and correlates of self-reported sexual dysfunction in CKD: a meta-analysis of observational studies. *Am J Kidney Dis* 2010;**56**(4):670–85.
4. Collaborative, Depression Sexual Dysfunction in Hemodialysis Working Group, Vecchio M, Palmer S, De Berardis G, Craig J, Johnson D, et al. Prevalence and correlates of erectile dysfunction in men on chronic haemodialysis: a multinational cross-sectional study. *Nephrol Dial Transplant* 2012;**27**(6):2479–88.
5. Mesquita JF, Ramos TF, Mesquita FP, Bastos Netto JM, Bastos MG, Figueiredo AA. Prevalence of erectile dysfunction in chronic renal disease patients on conservative treatment. *Clinics* 2012;**67**(2): 181–3.
6. Lew-Starowicz M, Gellert R. The sexuality and quality of life of hemodialyzed patients–ASED multicenter study. *J Sex Med* 2009; **6**(4):1062–71.
7. Fernandes GV, dos Santos RR, Soares W, de Lima LG, de Macedo BS, da Fonte JE, et al. The impact of erectile dysfunction on the quality of life of men undergoing hemodialysis and its association with depression. *J Sex Med* 2010;**7**(12):4003–10.
8. Turk S, Guney I, Altintepe L, Tonbul Z, Yildiz A, Yeksan M. Quality of life in male hemodialysis patients. Role of erectile dysfunction. *Nephron Clin Pract* 2004;**96**(1):c21–7.
9. Peng YS, Chiang CK, Hung KY, Chiang SS, Lu CS, Yang CS, et al. The association of higher depressive symptoms and sexual dysfunction in male haemodialysis patients. *Nephrol Dial Transplant* 2007;**22**(3):857–61.
10. Rosas SE, Joffe M, Franklin E, Strom BL, Kotzker W, Brensinger C, et al. Prevalence and determinants of erectile dysfunction in hemodialysis patients. *Kidney Int* 2001;**59**(6):2259–66.
11. Rosas SE, Joffe M, Franklin E, Strom BL, Kotzker W, Brensinger C, et al. Association of decreased quality of life and erectile dysfunction in hemodialysis patients. *Kidney Int* 2003;**64**(1):232–8.
12. Weisbord SD. Sexual dysfunction and quality of life in patients on maintenance dialysis. *Semin Dial* 2013;**26**(3):273–80.
13. Vecchio M, Palmer SC, Tonelli M, Johnson DW, Strippoli GF. Depression and sexual dysfunction in chronic kidney disease: a narrative review of the evidence in areas of significant unmet need. *Nephrol Dial Transplant* 2012;**27**(9):3420–8.
14. Seidman S. Exploring the relationship between depression and erectile dysfunction in aging men. *J Clin Psychiatry* 2002; **63**(Suppl. 5):5–12.
15. Seidman S, Roose S, Menza M, Shabsign R, Rosen RC. Treatment of erectile dysfunction in men with depressive symptoms: results of a placebo-controlled trial with sildenafil citrate. *Am J Psychiatry* 2001;**158**(10):1623–30.
16. Mapes DL, Lopes AA, Satayathum S, McCullough KP, Goodkin DA, Locatelli F, et al. Health-related quality of life as a predictor of mortality and hospitalization: the dialysis outcomes and practice patterns study (DOPPS). *Kidney Int* 2003;**64**(1): 339–49.
17. Lopes AA, Bragg J, Young E, Goodkin D, Mapes D, Combe C, et al. Depression as a predictor of mortality and hospitalization among hemodialysis patients in the United States and Europe. *Kidney Int* 2002;**62**(1):199–207.
18. Procci W, Goldstein D, Adelstein J, Massry S. Sexual dysfunction in the male patient with uremia: a reappraisal. *Kidney Int* 1981; **19**(2):317–23.
19. Handelsman D. Hypothalamic-pituitary gonadal dysfunction in renal failure, dialysis and renal transplantation. *Endocr Rev* 1985; **6**(2):151–82.
20. Palmer BF. Sexual dysfunction in uremia. *J Am Soc Nephrol* 1999; **10**(6):1381–8.
21. Holdsworth S, Atkins RC, de Kretser DM. The pituitary-testicular axis in men with chronic renal failure. *N Engl J Med* 1977;**296**(22): 1245–9.

22. Rosen RC, Riley A, Wagner G, Osterloh I, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; **49**(6):822–30.
23. Carrero JJ, Qureshi A, Parini P, Arver S, Lindholm B, Barany P, et al. Low serum testosterone increases mortality risk among male dialysis patients. *J Am Soc Nephrol* 2009;**20**(3):613–20.
24. Kyriazis J, Tzanakis I, Stylianou K, Katsipi I, Moisiadis D, Papadaki A, et al. Low serum testosterone, arterial stiffness and mortality in male haemodialysis patients. *Nephrol Dial Transplant* 2011;**26**(9):2971–7.
25. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2018;**103**(5):1715–44.
26. O'Rourke Jr TK, Wosnitzer MS. Opioid-induced androgen deficiency (OPIAD): diagnosis, management, and literature review. *Curr Urol Rep* 2016;**17**(10):76.
27. Ishida JH, McCulloch CE, Steinman MA, Grimes BA, Johansen KL. Opioid analgesics and adverse outcomes among hemodialysis patients. *Clin J Am Soc Nephrol* 2018;**13**(5):746–53.
28. Bawor M, Bami H, Dennis BB, Plater C, Worster A, Varenbut M, et al. Testosterone suppression in opioid users: a systematic review and meta-analysis. *Drug Alcohol Depend* 2015;**149**:1–9.
29. Tsertsvadze A, Yazdi F, Fink H, MacDonald R, Wilt T, Soares-Weiser K, et al. *Diagnosis and treatment of erectile dysfunction. Evidence Report/Technology Assessment No. 171*. Rockville, MD: Agency for Healthcare Research and Quality; 2009. Contract No.: AHRQ Publication No. 08(09)-E016.
30. Simonsen U, Garcia-Ascristan A, Prieto D. Penile arteries and erection. *J Vasc Res* 2002;**39**(4):283–303.
31. Burnett AL, Nehra A, Breau RH, Culkin DJ, Faraday MM, Hakim LS, et al. *Erectile dysfunction: AUA guideline*. American Urological Association; 2018. Available from: https://www.auanet.org/guidelines/male-sexual-dysfunction-erectile-dysfunction-(2018).
32. Shamloul R, Ghanem H. Erectile dysfunction. *Lancet* 2013; **381**(9861):153–65.
33. Wu F, Tajar A, Beynon J, Pye S, Silman A, Finn J, et al. Identification of late-onset male hypogonadism in middle-aged and elderly men. *N Engl J Med* 2010;**363**(2):123–35.
34. Lunenfeld B, Mskhalaya G, Zitzmann M, Arver S, Kalinchenko S, Tishova Y, et al. Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. *Aging Male* 2015; **18**(1):5–15.
35. American Urological Association. *The management of erectile dysfunction*. 2005. Available from: www.auanet.org/education/guidelines/erectile-dysfunction.cfm.
36. Esposito K, Giugliano F, Di Palo C, Giugliano G, Marfella R, D'Andrea F, et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. *J Am Med Assoc* 2004;**291**(24):2978–84.
37. Esposito K, Ciotola M, Giugliano F, De Sio M, Giugliano G, D'Armiento M, et al. Mediterranean diet improves erectile function in subjects with the metabolic syndrome. *Int J Impot Res* 2006;**18**(4):405–10.
38. Lamina S, Okoye CG, Dagogo TT. Therapeutic effect of an interval exercise training program in the management of erectile dysfunction in hypertensive patients. *J Clin Hypertens* 2009;**11**(3):125–9.
39. Wing RR, Rosen RC, Fava JL, Bahnson J, Brancati F, Gendrano III IN, et al. Effects of weight loss intervention on erectile function in older men with type 2 diabetes in the Look AHEAD trial. *J Sex Med* 2010;**7**(1 Pt 1):156–65.
40. Gupta BP, Murad MH, Clifton MM, Prokop L, Nehra A, Kopecky SL. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. *Arch Intern Med* 2011;**171**(20):1797–803.
41. Nehra A, Jackson G, Miner M, Billups KL, Burnett AL, Buvat J, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. *Mayo Clin Proc* 2012;**87**(8):766–78.
42. Levine GN, Steinke EE, Bakaeen FG, Bozkurt B, Cheitlin MD, Conti JB, et al. Sexual activity and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2012;**125**(8):1058–72.
43. Fink HA, Mac Donald R, Rutks IR, Nelson DB, Wilt TJ. Sildenafil for male erectile dysfunction: a systematic review and meta-analysis. *Arch Intern Med* 2002;**162**(12):1349–60.
44. Grossman EB, Swan SK, Muirhead GJ, Gaffney M, Chung M, DeRiesthal H, et al. The pharmacokinetics and hemodynamics of sildenafil citrate in male hemodialysis patients. *Kidney Int* 2004;**66**(1):367–74.
45. Vecchio M, Navaneethan SD, Johnson DW, Lucisano G, Graziano G, Querques M, et al. Treatment options for sexual dysfunction in patients with chronic kidney disease: a systematic review of randomized controlled trials. *Clin J Am Soc Nephrol* 2010; **5**(6):985–95.
46. Demir E, Balal M, Paydas S, Sertdemir Y, Erken U. Efficacy and safety of vardenafil in renal transplant recipients with erectile dysfunction. *Transplant Proc* 2006;**38**(5):1379–81.
47. Seibel I, Poli De Figueiredo C, Teloken C, Moraes J. Efficacy of oral sildenafil in hemodialysis patients with erectile dysfunction. *J Am Soc Nephrol* 2002;**13**(11):2770–5.
48. Yang J, Ju W, Zeng F, Xiao Y, Zhang X, Xiao C. Efficacy and safety of vardenafil for kidney transplant recipients with erectile dysfunction. *Zhonghua Nan Ke Xue* 2008;**14**(10):911–3.
49. Mahon A, Sidhu P, Muir G, Macdougall I. The efficacy of sildenafil for the treatment of erectile dysfunction in male peritoneal dialysis patients. *Am J Kidney Dis* 2005;**45**(2):381–7.
50. Sharma R, Prasad N, Gupta A, Kapoor R. Treatment of erectile dysfunction with sildenafil citrate in renal allograft recipients: a randomized, double-blind, placebo-controlled, crossover trial. *Am J Kidney Dis* 2006;**48**(1):128–33.
51. Vecchio M, Navaneethan SD, Johnson DW, Lucisano G, Graziano G, Saglimbene V, et al. Interventions for treating sexual dysfunction in patients with chronic kidney disease. *Cochrane Database Syst Rev* 2010;**12**:CD007747.
52. Muirhead GJ, Wilner K, Colburn W, Haug-Pihale G, Rouviex B. The effects of age and renal and hepatic impairment on the pharmacokinetics of sildenafil. *Br J Clin Pharmacol* 2002;**53**(Suppl. 1): 21S–30S.
53. Bolat MS, Ozer I, Cinar O, Akdeniz E, Asci R. The efficacy of low-dose tadalafil in patients undergoing hemodialysis with end-stage renal disease. *Ren Fail* 2017;**39**(1):582–7.
54. Lasaponara F, Sedigh O, Pasquale G, Bosio A, Rolle L, Ceruti C, et al. Phosphodiesterase type 5 inhibitor treatment for erectile dysfunction in patients with end-stage renal disease receiving dialysis or after renal transplantation. *J Sex Med* 2013;**10**(11): 2798–814.
55. Ponce OJ, Spencer-Bonilla G, Alvarez-Villalobos N, Serrano V, Singh-Ospina N, Rodriguez-Gutierrez R, et al. The efficacy and adverse events of testosterone replacement therapy in hypogonadal men: a systematic review and meta-analysis of randomized, placebo-controlled trials. *J Clin Endocrinol Metab* 2018. https://doi.org/10.1210/jc.2018-00404.
56. Lawrence I, Price D, Howlett T, Harris K, Feehally J, Walls J. Correcting impotence in the male dialysis patient: experience with testosterone replacement and vacuum tumescence therapy. *Am J Kidney Dis* 1998;**31**(2):313–9.

57. Bhasin S, Cunningham G, Hayes F, Matsumoto A, Snyder P, Swerdloff R, et al. Testosterone therapy in adults with androgen deficiency syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;**95**(6):2536–59.
58. Johansen KL. Treatment of hypogonadism in men with chronic kidney disease. *Adv Chron Kidney Dis* 2004;**11**(4):348–56.
59. Kelleher S, Conway A, Handelsman D. Blood testosterone threshold for androgen deficiency symptoms. *J Clin Endocrinol Metab* 2004;**89**(8):3813–7.
60. Bhasin S, Woodhouse L, Casaburi R, Singh A, Bhasin D, Berman N, et al. Testosterone dose-response relationships in healthy young men. *Am J Physiol Endocrinol Metab* 2001;**281**(6): E1172–81.
61. Finkelstein J, Lee H, Burnett-Bowie S, Pallais J, Yu E, Borges L, et al. Gonadal steroids and body composition, strength, and sexual function in men. *N Engl J Med* 2013;**369**(11):1011–22.
62. Travison TG, Vesper HW, Orwoll E, Wu F, Kaufman JM, Wang Y, et al. Harmonized reference ranges for circulating testosterone levels in men of four cohort studies in the United States and Europe. *J Clin Endocrinol Metab* 2017;**102**(4):1161–73.
63. Saad F, Aversa A, Isidori AM, Zafalon L, Zitzmann M, Gooren L. Onset of effects of testosterone treatment and time span until maximum effects are achieved. *Eur J Endocrinol* 2011;**165**(5): 675–85.
64. Isidori AM, Buvat J, Corona G, Goldstein I, Jannini EA, Lenzi A, et al. A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment - a systematic review. *Eur Urol* 2013;**65**(1):99–112.
65. Wang C, Nieschlag E, Swerdloff R, Behre H, Hellstrom W, Gooren L, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. *Eur J Endocrinol* 2008;**159**(5):507–14.
66. Fowler J, Whitmore W. Considerations for hte use of testosterone with systemic chemotherapy in prostatic cancer. *Cancer* 1982; **49**(7):1373–7.
67. Yeksan M, Polat M, Turk S, Kazanci H, Akhan G, Erdogan Y, et al. Effect of vitamin E therapy on sexual functions of uremic patients in hemodialysis. *Int J Artif Organs* 1992;**15**(11):648–52.
68. Jones T, Saad F. The effects of testosterone on risk factors for, and the mediators of, the atherosclerotic process. *Atherosclerosis* 2009; **207**(2):318–27.
69. Corona G, Rastrelli G, Monami M, Guay A, Buvat J, Sforza A, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. *Eur J Endocrinol* 2011;**165**(5): 687–701.
70. Basaria S, Coviello A, Travison T, Storer T, Farwell W, Jette A, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010;**363**(2):109–22.
71. Vigen R, O'Donnell C, Baron A, Grunwald G, Maddox T, Bradley S, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *J Am Med Assoc* 2013;**310**(17):1829–36.
72. Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One* 2014;**9**(1):e85805.
73. Morgentaler A, Lunenfeld B. Testosterone and cardiovascular risk: world's experts take unprecedented action to correct misinformation. *Aging Male* 2014;**17**(2):63–5.
74. Goodman N, Guay A, Dandona P, Dhindsa S, Faiman C, Cunningham GR. American association of clinical endocrinologists and American College of Endocrinology position statement on the association of testosterone and cardiovascular risk. *Endocr Pract* 2015;**21**(9):1066–73.
75. Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, et al. Effects of testosterone treatment in older men. *N Engl J Med* 2016;**374**(7):611–24.
76. Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. *J Clin Endocrinol Metab* 2012;**97**(6): 2050–8.
77. Cheetham TC, An J, Jacobsen SJ, Niu F, Sidney S, Quesenberry CP, et al. Association of testosterone replacement with cardiovascular outcomes among men with androgen deficiency. *JAMA Intern Med* 2017;**177**(4):491–9.
78. Bommer J, Kugel M, Schwobel B, Ritz E, Barth H, Seelig R. Improved sexual function during recombinant erythropoietin therapy. *Nephrol Dial Transplant* 1990;**5**(3):204–7.
79. Schaefer R, Kokot F, Wernze H, Geiger H, Heidland A. Improved sexual function in hemodialysis patients on recombinant erythropoietin: a possible role for prolactin. *Clin Nephrol* 1989;**31**(1):1–5.
80. Evans R, Rader B, Manninen D. The quality of life of hemodialysis recipients treated with recombinant human erythropoietin. Cooperative Multicenter EPO Clincial Trial Group. *J Am Med Assoc* 1990;**263**(6):825–30.
81. Beusterien K, Nissenson A, Port F, Kelly M, Steinwald B, Ware J. The effects of recombinant erythropoietin on functional health and well-being in chronic dialysis patients. *J Am Soc Nephrol* 1996;**7**(5):763–73.
82. Schaefer F, van Kaick B, Veldhuis J, Stein G, Scharer K, Robertson W, et al. Changes in the kinetics and biopotency of luteinizing hormone in hemodialyzed men during treatment with recombinant human erythropoietin. *J Am Soc Nephrol* 1994; **5**(5):1208–15.
83. Chou F, Lee C, Shu K, Yu T, Hsu K, Sheen-Chen S. Improvement in sexual function in male patients after parathyroidectomy for secondary hyperparathyroidism. *J Am Coll Surg* 2001;**193**(5):486–92.
84. Jalali GR, Roozbeh J, Mohammadzadeh A, Sharifian M, Sagheb MM, Hamidian Jahromi A, et al. Impact of oral zinc therapy on the level of sex hormones in male patients on hemodialysis. *Ren Fail* 2010;**32**(4):417–9.
85. Muir J, Besser G, Edwards C, Rees L, Cattell W, Ackrill P, et al. Bromocriptine improves reduced libido and potency in men receiving maintenance hemofialysis. *Clin Nephrol* 1983;**20**(6):308.
86. Montague DK, Jarow JP, Broderick GA, Dmochowski RR, Heaton JP, Lue TF, et al. Chapter 1: the management of erectile dysfunction: an AUA update. *J Urol* 2005;**174**(1):230–9.
87. American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Gynecology. ACOG practice Bulletin No. 119: female sexual dysfunction. *Obstet Gynecol* 2011;**117**(4): 996–1007.
88. American Psychological Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington, D.C.: APA; 2000.
89. Shifren J, MOnz B, Russo P, Segreti A, Johannes C. Sexual problems and distress in United States women: prevaluence and correlates. *Obstet Gynecol* 2010;**112**(5):970–8.
90. Toorians AW, Janssen E, Laan E, Gooren LJ, Giltay EJ, Oe PL, et al. Chronic renal failure and sexual functioning: clinical status versus objectively assessed sexual response. *Nephrol Dial Transplant* 1997; **12**(12):2654–63.
91. Altunoglu A, Yavuz D, Canoz MB, Yavuz R, Karakas LA, Bayraktar N, et al. Relationship between inflammation and sex hormone profile in female patients receiving different types of renal replacement therapy. *Transplant Proc* 2014;**46**(5):1585–90.
92. Saglimbene V, Natale P, Palmer S, Scardapane M, Craig JC, Ruospo M, et al. The prevalence and correlates of low sexual functioning in women on hemodialysis: a multinational, cross-sectional study. *PLoS One* 2017;**12**(6):e0179511.

93. Holley JL, Schmidt RJ. Sexual dysfunction in CKD. *Am J Kidney Dis* 2010;**56**(4):612–4.
94. Basok EK, Atsu N, Rifaioglu MM, Kantarci G, Yildirim A, Tokuc R. Assessment of female sexual function and quality of life in predialysis, peritoneal dialysis, hemodialysis, and renal transplant patients. *Int Urol Nephrol* 2009;**41**(3):473–81.
95. Strippoli GF, Collaborative D, Sexual Dysfunction in Hemodialysis Working G, Vecchio M, Palmer S, De Berardis G, et al. Sexual dysfunction in women with ESRD requiring hemodialysis. *Clin J Am Soc Nephrol* 2012;**7**(6):974–81.
96. Mor MK, Sevick MA, Shields AM, Green JA, Palevsky PM, Arnold RM, et al. Sexual function, activity, and satisfaction among women receiving maintenance hemodialysis. *Clin J Am Soc Nephrol* 2014;**9**(1):128–34.
97. Finkelstein FO, Finkelstein SH. Sexual Inactivity among hemodialysis patients: the patients' perspective. *Clin J Am Soc Nephrol* 2014;**9**(1):6–7.
98. Anantharaman P, Schmidt RJ. Sexual function in chronic kidney disease. *Adv Chron Kidney Dis* 2007;**14**(2):119–25.
99. Weisinger JR, Bellorin-Font E. Outcomes associated with hypogonadism in women with chronic kidney disease. *Adv Chron Kidney Dis* 2004;**11**(4):361–70.
100. Cowden EA, Ratcliffe WA, Ratcliffe JG, Dobbie JW, Kennedy AC. Hyperprolactinaemia in renal disease. *Clin Endocrinol* 1978;**9**(3): 241–8.
101. Rathi M, Ramachandran R. Sexual and gonadal dysfunction in chronic kidney disease: pathophysiology. *Indian J Endocrinol Metab* 2012;**16**(2):214–9.
102. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *J Am Med Assoc* 1999;**281**(6): 537–44.
103. Yazici R, Altintepe L, Guney I, Yeksan M, Atalay H, Turk S, et al. Female sexual dysfunction in peritoneal dialysis and hemodialysis patients. *Ren Fail* 2009;**31**(5):360–4.
104. Seethala S, Hess R, Bossola M, Unruh ML, Weisbord SD. Sexual function in women receiving maintenance dialysis. *Hemodial Int* 2010;**14**(1):55–60.
105. Nurnberg HG, Hensley PL, Heiman JR, Croft HA, Debattista C, Paine S. Sildenafil treatment of women with antidepressant-associated sexual dysfunction: a randomized controlled trial. *J Am Med Assoc* 2008;**300**(4):395–404.
106. Giuliano F, Rampin O, Allard J. Neurophysiology and pharmacology of female genital sexual response. *J Sex Marital Ther* 2002; **28**(Suppl. 1):101–21.
107. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000;**26**(2):191–208.
108. Jones LR. The use of validated questionnaires to assess female sexual dysfunction. *World J Urol* 2002;**20**(2):89–92.
109. Guven S, Sari F, Inci A, Cetinkaya R. Sexual dysfunction is associated with depression and anxiety in patients with predialytic chronic kidney disease. *Eurasian J Med* 2018;**50**(2):75–80.
110. Duncan L, Lewis C, Jenkins P, Pearson T. Does hypertension and its pharmacotherapy affect the quality of sexual function in women? *Am J Hypertens* 2000;**13**(6 Pt 1):640–7.
111. Doumas M, Tsiodras S, Tsakiris A, Douma S, Chounta A, Papadopoulos A, et al. Female sexual dysfunction in essential hypertension: a common problem being uncovered. *J Hypertens* 2006; **24**(12):2387–92.
112. Harte C, Meston C. The inhibitory effects of nictoine on physiological sexual arousal in nonsmoking women: results from a randomized, double-blind, placebo-controlled, cross-over trial. *J Sex Med* 2008;**5**(5):1184–97.
113. Xu L, Freeman G, Cowling B, Schooling C. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med* 2013;**11**:108. https://doi.org/10.1186/1741-7015-11-108.
114. Segraves RT, Clayton A, Croft H, Wolf A, Warnock J. Bupropion sustained release for the treatment of hypoactive sexual desire disorder in premenopausal women. *J Clin Psychopharmacol* 2004; **24**(3):339–42.
115. DeGregorio MW, Zerbe RL, Wurz GT. Ospemifene: a first-in-class, non-hormonal selective estrogen receptor modulator approved for the treatment of dyspareunia associated with vulvar and vaginal atrophy. *Steroids* 2014;**90**:82–93.
116. Basson R, McInnes R, Smith M, Hodgson G, Koppiker N. Efficacy and safety of sildenafil citrate in women with sexual dysfunction associated with female sexual arousal disorder. *J Womens Health Gend Based Med* 2002;**11**(4):367–77.
117. Caruso S, Intelisano G, Lupo L, Angnello C. Premenopausal women affected by sexual arousal disorder treated with sildenafil: a double-blind, cross-over, placebo-controlled study. *BJOG* 2001; **108**(6):623–8.
118. Basson R, Brotto L. Sexual psychophysiology and effects of sildenafil citrate in oestrogenised women with acquired genital arousal disorder and impaired orgasm: a randomised controlled trial. *BJOG* 2003;**110**(11):1014–24.
119. Berman J, Berman L, Toler S, Gill J, Haughie S, Group SS. Safety and efficacy of sildenafil citrate for the treatment of female sexual arousal disorder: a double-blind, placebo controlled study. *J Urol* 2003;**170**(6 Pt 1):2333–8.
120. Brown DA, Kyle JA, Ferrill MJ. Assessing the clinical efficacy of sildenafil for the treatment of female sexual dysfunction. *Ann Pharmacother* 2009;**43**(7):1275–85.
121. Davis S, Davison S, Donath S, Bell R. Circulating androgen levels and self-reported sexual function in women. *J Am Med Assoc* 2005; **294**(1):91–6.
122. Santoro N, Torrens J, Crawford S, Allsworth J, Finkelstein J, Gold E, et al. Correlates of circulating androgens in mid-life women: the study of women's health across the nation. *J Clin Endocrinol Metab* 2005;**90**(8):4836–45.
123. Somboonporn W, Davis S, Seif M, Bell R. Testosterone for peri- and postmenopausal women. *Cochrane Database Syst Rev* 2005;**4**: CD004509.
124. Wierman M, Basson R, Davis S, Khosla S, Miller K, Rosner W, et al. Androgen therapy in women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2006;**91**(10):3697–710.
125. North American Menopause Society. The role of testosterone therapy in postmenopausal women: position statement of the North American Menopause Society. *Menopause* 2005;**12**(5): 496–511.

QUESTIONS AND ANSWERS

Question 1

A 40-year-old woman with obesity, chronic kidney disease (CKD) stage 3, hypertension, and recently diagnosed depressive disorder returns for follow-up. She was started on citalopram for depression 3 months ago. Since then, her symptoms of anhedonia, depressed mood, fatigue, and decreased sleep have improved. She has no suicidal ideation. Despite these improvements, she notes new onset anorgasmia. On physical exam, her blood pressure is 120/70 mm Hg. Other vital signs are normal. BMI is 32 kg/m^2. Her physical exam is otherwise unremarkable. You discontinue her citalopram and start her on bupropion.

Which **one** of the following is **false** regarding depression and sexual dysfunction in CKD?

A. Reducing the dose of her citalopram may alleviate her sexual dysfunction
B. Bupropion increases measures of orgasm completion and sexual satisfaction in women
C. Selective serotonin reuptake inhibitors are the treatment of choice in the presence of depression and sexual dysfunction
D. Sexual dysfunction is associated with lower quality of life in both men and women with ESRD

Answer: C

Reducing SSRI dose can alleviate symptoms of sexual dysfunction, thus Choice **A** is true. Choice **B** is true, as bupropion increases measures of orgasm completion, sexual satisfaction, and sexual arousal in women. SSRIs may not be the treatment of choice in the presence of depression and sexual dysfunction because they can worsen sexual dysfunction. Therefore, Choice **C** is false. Bupropion would be a more reasonable choice given its aforementioned positive effects on sexual functioning. Choice **D** is true as lower quality of life in both men and women with ESRD is associated with sexual dysfunction.

Question 2

A 60-year-old man with hypertension, coronary artery disease, hyperlipidemia, anemia of chronic disease, and CKD stage 4 is evaluated for sudden onset ED. He notes that he still has nocturnal erections. He is on stable doses of carvedilol, furosemide, and benazepril for his hypertension for the past year. On physical exam, his blood pressure is 145/85 mm Hg. Other vital signs are normal. His BMI is 28 kg/m^2. Genital exam reveals no penile or testicular abnormalities. Femoral pulses are 2+ bilaterally without bruits and distal pulses are normal. Neurologic exam is unremarkable. Laboratory studies reveal a hemoglobin of 8.5 g/dL and a serum creatinine (S[Cr]) of 3.8 mg/dL.

Which **one** of the following is the **most likely** primary cause of his ED?

A. Medication side effect
B. Anemia
C. CKD
D. Psychogenic

Answer: D

The rapidity of the onset of his ED and presence of nocturnal erections are important historical clues in this question. The correct answer is Choice **D** as rapid onset ED with preserved nocturnal erections is indicative of psychogenic ED. If there is suspicion for psychogenic ED that is not evident from the history, nocturnal penile tumescence is a reasonable test to assess to rule out organic causes. Despite the likely primary psychogenic cause of ED in this patient, it is important to recognize that ED is usually multifactorial. All of the other answers are potentially contributory in this case. Medication side effect, Choice **A**, is a common cause of ED and should be reviewed carefully in patients with ED. Blood pressure medications, such as beta blockers, could be contributory in this case, but the stable doses and lack of hypotension make them a less likely primary cause. Anemia, Choice **B**, has been associated with reduced libido and ED and could be a contributing factor for this patient. Correcting anemia according to current guidelines for CKD may help with ED, although there are no specific data on whether small changes in hemoglobin improve sexual function in men. Worsening glomerular filtration rate is associated with an increased prevalence of ED. Thus, CKD, Choice **C**, could be contributing to his ED.

Question 3

A 30-year-old woman with CKD stage 4 due to IgA nephropathy returns to clinic for treatment of her CKD. She notes that she has not had a menstrual period for over 2 years and that her interest in sex has diminished lately. She is having intercourse less frequently, which is affecting her self-esteem and causing some discord with her partner. Her blood pressure is well controlled and other vital signs are normal. Her BMI is 22 kg/m^2. Her physical examination is unremarkable. Laboratory studies reveal a hemoglobin of 12.0 g/dL, a prolactin level of 700 mU/L (normal reference range <500 mU/L) and intact parathyroid hormone of 240 pg/mL.

Which **one** of the following is **false** regarding sexual dysfunction and amenorrhea in CKD?

A. Correcting hyperparathyroidism may lower her elevated prolactin

B. Kidney transplantation restores normal menstrual function in the majority of premenopausal women
C. Creatinine clearance (CrCl) has no correlation with prolactin level
D. Worsening anemia has been associated with decreased frequency of sexual intercourse

Answer: C

Correcting of hyperparathyroidism may lower elevated prolactin in women, thus Choice **A** is true. Treating hyperparathyroidism to CKD guideline-recommended targets may improve sexual dysfunction. Choice **B** is true since kidney transplantation has been shown to restore menstrual function in the majority of pre-menopausal women. Levels of sexual dysfunction return to approximately those of the general population after kidney transplantation in women. Choice **C** is false as there is a strong correlation between worsening CrCl and higher prolactin levels in women with CKD. Levels of prolactin are even higher in maintenance dialysis but improve after kidney transplantation. Choice **D** is true as worsening anemia has been associated with decreased frequency of sexual intercourse in women with CKD as well as worsened physical and sexual function.

Question 4

A 50-year-old man with type 2 diabetes mellitus, hypertension, hyperlipidemia, benign prostatic hypertrophy, and CKD stage 4 with an estimated glomerular filtration rate of 25 mL/min/1.73 m^2 complains of sexual difficulties. His sex drive and desire are intact, but he cannot achieve an erection. He is on a stable medication regimen that includes insulin glargine, lisinopril, furosemide, simvastatin, sevelamer, sodium bicarbonate, darbepoetin, aspirin, and doxazosin. His blood pressure is 115/65 mm Hg. Other vital signs are normal. His BMI is 32 kg/m^2. His physical examination, including vascular, neurologic, and genital exam, is unremarkable. You decide to treat him with a PDE5i.

Which **one** of the following is **correct** regarding the dosing of the PDE5i vardenafil in this patient?

A. Start vardenafil at 10 mg daily, twice the starting dose, since the patient is on doxazosin
B. Start vardenafil at 5 mg daily, the usual starting dose, as it does not need to be adjusted for reduced GFR
C. Start vardenafil at 2.5 mg daily, the smallest possible dose, because the patient is on doxazosin
D. Do not start vardenafil as it has not been studied in patients with CrCl <30 mL/min.

Answer: C

The dosing of PDE5i and the choice of which specific PDE5i to use are affected by CKD. Additionally, alpha-blockers, commonly used in males with benign prostatic hypertrophy, can interact with PDE5i. Choice **A** is incorrect as the dose of PDE5 inhibitors should be started at the lowest recommended dose when a patient is on a stable alpha-blocker dose due to potential symptomatic hypotension with this combination of medications. Vardenafil does not need to be adjusted for reduced CrCl, but Choice **B** is incorrect because the dose of vardenafil should be reduced to the lowest possible dose in the presence of doxazosin. Choice **C**, starting at the lowest possible dose, is correct. Choice **D** is incorrect, because vardenafil has been studied in patients with CrCl <30 mL/min. Avanafil, however, has not been studied in patients with a CrCl <30 mL/min and should be avoided in this population until more data become available. The starting doses of sildenafil and tadalafil should be reduced in patients with CrCl <30 mL/min, to 25 mg daily for sildenafil and to a maximum dose of 5 mg every 72 hours for tadalafil.

Question 5

A 65-year-old man with hypertension, hyperlipidemia, focal segmental glomerulosclerosis with chronic kidney disease stage 3 with an estimated glomerular filtration rate of 40 mL/min/1.73 m^2 is evaluated for decreased libido for the past year. He denies any difficulty with erectile function but reports increased fatigue and less physical activity. On physical exam, his blood pressure is 125/55 mm Hg. Other vital signs are normal. His BMI is 26 kg/m^2. Genital exam reveals no penile or testicular abnormalities. Digital rectal exam reveals a slightly enlarged prostate without induration or nodules. The remainder of his exam is unremarkable. Laboratory studies reveal a hemoglobin of 12.0 g/dL, a S[Cr] of 1.8 mg/dL, urine protein:creatinine ratio of 1.1 g/g, morning serum total testosterone of 50 ng/dL (reference range 264 ng/dL to 916 ng/dL), and PSA of 1.0 ng/mL (reference range <4.0 ng/mL). Serum testosterone is confirmed to be low on repeat measurement.

Which **one** of the following is **correct** regarding appropriate testosterone replacement after discussion with the patient, who desires testosterone replacement therapy?

A. Start intramuscular injections of testosterone ethanate every two weeks
B. Start testosterone subcutaneously implanted pellets
C. Start transdermal testosterone patches applied daily
D. Start testosterone topical gel applied daily
E. Start bioadhesive, buccal testosterone tablets applied to buccal mucosa twice per day
F. All of the above are reasonable regimens for testosterone replacement

Answer: F

Insufficient evidence is available to suggest significant differences in efficacy between different testosterone replacement preparations. Thus, Choice **F**, all of the above, is correct, and cost and patient preference should dictate the choice of therapy. The Endocrine Society Guidelines recommend the following regimens: Intramuscular injections, Choice **A**, of either testosterone ethanate or cypionate of 75−100 mg weekly or 150−200 mg every two weeks; Choice **B,** subcutaneously implanted pellets (dose and regimen vary based on formulation); One to two 5 mg transdermal testosterone patches, Choice **C,** applied daily to nonpressure areas of the skin; Choice **D,** 5−10 g of 1% testosterone gel applied to a covered area of skin daily; or 30 mg twice daily of bioadhesive, buccal testosterone tablets, Choice **E**.

Question 6

A 55-year-old man with obesity, hypertension, congestive heart failure, chronic atrial fibrillation, hyperlipidemia, and chronic kidney disease stage 3 with an estimated glomerular filtration rate of 40 mL/min/1.73 m^2 presents with complaints of ED, decreased libido, and fatigue. His heart failure has been well controlled. He is on stable doses of warfarin, atorvastatin, metoprolol, isosorbide dinitrate, hydralazine, and furosemide. On physical examination, his blood pressure is 120/65 mm Hg and heart rate is 60 beats per minute. His BMI is 35 kg/m^2. His lungs are clear, heart has an irregular rhythm without a gallop, jugular veins are nondistended, and he has no peripheral edema. Genital exam reveals no penile or testicular abnormalities. Digital rectal exam reveals a nonenlarged prostate without induration or nodules. Laboratory studies reveal a low total testosterone of 150 ng/dL (reference range of 300−800 ng/dL) and PSA of 0.5 ng/mL (reference range <4.0 ng/mL). Serum testosterone is confirmed to be low on repeat measurement.

Which **one** of the following is **false** regarding this patient with decreased libido and ED?

A. A PDE5i could be used in addition to testosterone to treat his erectile dysfunction.
B. Testosterone replacement therapy may enhance the anticoagulation effect of his warfarin.
C. Trials have been neither long enough nor large enough to provide clear data on the cardiovascular risks and benefits among patients with heart failure.
D. Low testosterone may be a marker of poor general health rather than a risk factor for CVD.

Answer: A

Although a PDE5 inhibitor can be effective for treating ED in a patient with low testosterone, Choice **A** is false in the case of this patient because he is currently on a nitrate, isosorbide dinitrate. The combination of PDE5i and nitrates is contraindicated because it can cause severe hypotension. Severe, uncontrolled heart failure is a contraindication to testosterone use. However, this patient has controlled heart failure. Choice **B** is true as testosterone can enhance the anticoagulation effect of his warfarin. Choice **C** is true and reflects experts' current conclusions regarding mixed and in many cases low-quality data about the potential cardiovascular risks of testosterone therapy among men at high risk of cardiovascular events. The risks and benefits of testosterone should be weighed carefully before deciding to treat patients with low testosterone. Choice **D** is true as low testosterone may be a marker of poor general health rather than a risk factor for CVD.

CHAPTER

38

Water Homeostasis in Chronic Kidney Disease

Richard H. Sterns

University of Rochester School of Medicine and Dentistry and Rochester General Hospital, Rochester, NY, United States

Abstract

Normally the tonicity of the extracellular fluid is maintained within a narrow range, favorable to cellular well-being, by the osmoregulatory system. The kidney plays a central role in water homeostasis, guided by the antidiuretic hormone, arginine vasopressin, which is secreted by the posterior pituitary in response to changes in plasma tonicity. The kidney preserves water when it is scarce by concentrating the urine and eliminates excess water by urinary dilution. Chronic kidney disease impairs the ability to concentrate and dilute the urine maximally, restricting the responses to altered water intake and losses, making patients with kidney disease susceptible to hyponatremia and hypernatremia. Impaired concentrating ability also leads to increased vasopressin levels, which increase glomerular filtration rate. Vasopressin-induced hyperfiltration may be maladaptive, leading to kidney hypertrophy and accelerating the loss of renal function. Elevated vasopressin levels are particularly harmful in autosomal dominant polycystic kidney disease (ADPKD) because vasopressin promotes cyst formation. Vasopressin antagonists have been shown to retard progression of this condition. Many studies are currently underway testing the impact of increased water intake on the progression of ADPKD and other kidney diseases.

Water is the stuff of life and health requires precise control of water balance. Normally the salinity (also known as tonicity) of the extracellular fluid is maintained within a narrow range, favorable to cellular well-being, by the osmoregulatory system. The kidney plays a central role in water homeostasis, guided by the antidiuretic hormone (ADH), arginine vasopressin (AVP), which is secreted by the posterior pituitary in response to changes in plasma tonicity. The kidney preserves water when it is scarce by concentrating the urine and eliminates excess water by urinary dilution. The effect of kidney disease on water homeostasis has long been understood. Recently we have come to learn that water balance also has profound effects on the progression of kidney disease.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF WATER HOMEOSTASIS

The tonicity of body fluids is reflected by the serum sodium concentration, which is a function of the body's content of sodium and potassium (more precisely, the portion that is free in solution and not bound to proteoglycans in bone, cartilage, and connective tissue) divided by its content of water:

$$\text{Serum sodium concentration} \approx \text{Total body } (\text{Na} + \text{K})/\text{Total body water}$$

Changes in the serum sodium concentration are determined by the net balance of sodium and potassium (which alters the numerator of the equation) and the net balance of water (which alters the denominator).[1] The osmoregulatory system maintains the serum sodium concentration within a narrow normal range through changes in thirst, which controls water intake, and AVP, which controls water excretion.[2,3]

AVP, also known as ADH or vasopressin, is a nine amino acid peptide that is synthesized in hypothalamic neurons and stored in their axons that end in the posterior pituitary. Vasopressin release from the pituitary is stimulated by hypertonicity (usually associated with hypernatremia) and is inhibited by hypotonicity (associated with hyponatremia). In addition, hypotension and hypovolemia stimulate release of the hormone mediated by signals relayed to vasopressin secreting neurons through ascending neural pathways and by angiotensin II.

Deficiency of vasopressin causes neurogenic diabetes insipidus, a disorder characterized by the excretion of large amounts of dilute urine, and a susceptibility to hypernatremia if water losses are not replaced. The

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00038-3

human disease is mimicked by the Brattleboro rat, a strain in which the gene coding for vasopressin synthesis is defective and the hormone cannot be synthesized. Excess vasopressin causes the syndrome of inappropriate antidiuresis (SIADH), a disorder characterized by water retention and a susceptibility to the development of hyponatremia if water intake is not restricted.

The concentration of vasopressin in the plasma normally falls below detectable levels when excess water intake causes the serum sodium concentration to fall below the threshold level for vasopressin secretion (approximately 135 mEq/L). At low serum sodium concentrations, the sensation of thirst is also suppressed. Above this threshold, as the serum sodium concentration rises because of renal or extrarenal water losses, there is a linear increase in vasopressin levels and thirst. The threshold for vasopressin secretion is set slightly lower than that for thirst so that water conservation by the kidney can make increasing water intake unnecessary unless there are large extrarenal water losses. Low levels of vasopressin result in the excretion of urine that is much more dilute than plasma, and high levels result in urine that is much more concentrated. When the urine osmolality is very low, a small change in plasma vasopressin level will cause large changes in urine flow rate, but when the urine becomes very concentrated, large changes in vasopressin result in much smaller changes in urine output.

Receptors for AVP in the kidney have been classified into two major subtypes—V1a and V2. V2 receptors (V2R) mediate the antidiuretic action of vasopressin.[3] Loss-of-function mutations in V2R cause nephrogenic diabetes insipidus, a disorder characterized by excretion of large volumes of urine because of the inability to respond to vasopressin. Gain of function mutations of V2R result in nephrogenic SIADH, a disorder characterized by water retention despite suppression of vasopressin secretion. Vasopressin is a vasoconstrictor (which is how it got its name), and its vascular effects are mediated by V1a receptors (V1aR), which are expressed on kidney arterioles.

Dilution of the urine is achieved by reabsorbing sodium without water in the ascending limb of the loop of Henle and distal convoluted tubule (which have low permeability to water) and in the collecting duct (which has low permeability to water when vasopressin levels are low). As vasopressin levels fall, aquaporin 2 water channels (AQP2) are removed from the luminal membrane of the collecting duct and relocated to intracellular submembrane vesicles that can be recycled back to the membrane in response to vasopressin when needed.[2] Without AQP2 in its luminal membrane, the collecting duct has a low permeability to water. A water impermeable collecting duct permits dilute luminal fluid formed in upstream diluting sites to be excreted in a dilute final urine.

The antidiuretic effect of vasopressin is mediated by peritubular V2R, through increases in vasopressin's second messenger, intracellular cyclic adenosine monophosphate (c-AMP). Antidiuresis results from three main effects of the hormone on principal cells of the collecting duct: (a) increase in water permeability along the entire collecting duct owing to the insertion of AQP2 water channels in the luminal membrane; (b) an increase in urea permeability in the terminal medullary collecting duct, owing to activation of the urea transporter UT-A1; and (c) stimulation of sodium reabsorption in the cortical and medullary collecting duct.[3] Vasopressin also activates V1aR in the kidney, which tends to limit its antidiuretic activity. Activation of V1aR stimulates formation of prostaglandins, which reduce V2-dependent c-AMP accumulation in principal cells, partially inhibiting all three V2 effects. Because urine is diluted along the nephron before it is concentrated in the medulla, vasopressin is not just required for concentration of the urine, but also for excreting a urine with an osmolality equal to plasma. This process occurs in the renal cortex, and it requires reabsorption of large amounts of water—more than is needed downstream to concentrate the urine.

When vasopressin makes the luminal membranes of the medullary collecting duct permeable to water, water flows out of the lumen, attracted by the hyperosmolar interstitial fluid surrounding the duct. Transport of sodium without water in the ascending limb is required to make the interstitial fluid of the renal medulla more concentrated than plasma. The thick ascending limb expresses V2R and vasopressin increases the number of Na-K 2Cl transporters at this site.[4] Formation of a concentration gradient in the medulla is augmented by accumulation of urea in the interstitium, when urea is transported out of the tubular lumen of the inner medullary collecting duct by its vasopressin-stimulated transporter. Accumulation of urea in the inner medulla is required for the excretion of a maximally concentrated urine (Figure 38.1).[5–7] By activating V1aR that are expressed on the medullary vasculature, vasopressin also reduces renal blood flow to the inner medulla without altering blood flow to the outer medulla, an effect that preserves the high concentrations of solute in the interstitium. Thus, vasopressin plays a role in the formation of the medullary concentration gradient, which provides the osmotic driving force for movement of water out of the collecting duct. Concurrently, by making the tubular membrane permeable to water, the hormone promotes excretion of a concentrated urine.

In addition to its important effects on the concentration of the urine, vasopressin alters the glomerular filtration rate (GFR).[6,8] Low levels of vasopressin result in a

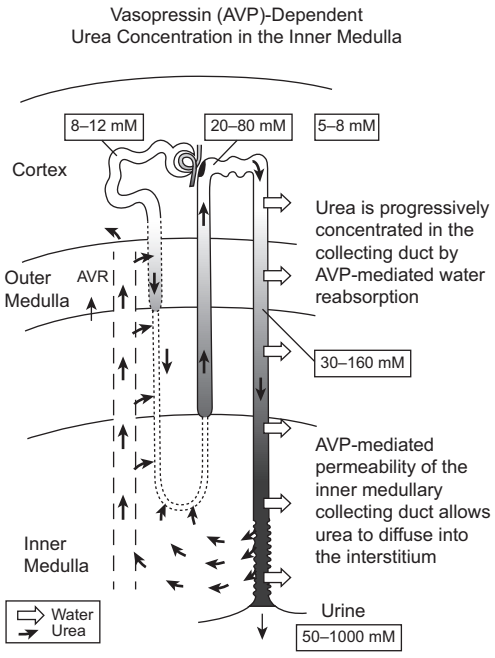


FIGURE 38.1 Vasopressin (AVP)-Dependent Urea Concentration in the Inner Medulla. The figure provides a simplified explanation of the complex mechanisms that result in a urea concentration gradient in the interstitium of the renal medulla (see more comprehensive discussion reviewed in reference 5). The figure depicts one nephron extending from the cortex to the inner medulla and a branch of the ascending vasa recta. In actuality, cortical nephrons differ in their anatomy and transport properties from juxtamedullary nephrons, which have loops of Henle that reach the inner medulla. The anatomy of the vasa recta, which is also complex, allows countercurrent exchange that prevents urea from being washed out of the medulla. Urea recycling and (possibly) pars recta urea secretion presents the inner collecting duct with large amounts of urea to maintain the urea concentration gradient. *Modified with permission from reference 7.*

low GFR and high levels of the hormone increase GFR. These changes, mediated primarily by V2R, are incompletely understood but may involve indirect effects of vasopressin-induced urea recycling on the sodium chloride concentrations achieved at the macula densa, which resets the tubulo-glomerular feedback mechanism controlling GFR (Figure 38.2).[9] Vasopressin-stimulated reabsorption of NaCl in the thick ascending limb of the loop of Henle may also contribute to the lower NaCl concentration at the macula densa. The macula densa expresses mRNA encoding the V1aR. Activation of V1aR in macula densa cells could potentially contribute to the changes in glomerular filtration that occur in response to vasopressin.[4]

Glomerular hyperfiltration due to vasopressin offsets the decreased fractional excretion of urea that occurs when concentrated urine is excreted.[7] Animals deprived of water or infused with the V2-agonist, desmopressin, so as to produce a sustained increase in urine osmolality, develop morphological and functional changes that are similar to those found with a high protein intake. Both conditions increase the plasma urea concentration, but azotemia is minimized by a concurrent increase in GFR. Brattleboro rats (which lack vasopressin, do not recycle urea, and do not accumulate urea in the inner medulla) do not exhibit an increased GFR when fed a high protein diet. Similarly, removing the renal papilla of normal rats, which interrupts urea recycling by ablation of the terminal part of the collecting ducts, where vasopressin initiates the process, results in a marked reduction in GFR despite presumably normal vasopressin levels. A low protein diet decreases the amount of urea that must be excreted. By eliminating urea recycling, low levels of vasopressin or papillectomy increase the fractional excretion of urea, making urea excretion more efficient. All these conditions allow the daily urea load to be excreted without a large increase in plasma urea levels, despite a low GFR. Conversely, a high protein diet increases the amount of urea that must be excreted. High levels of vasopressin decrease the fractional excretion of urea, making urea excretion less efficient. In these conditions a high GFR is required to avoid a large increase in plasma urea levels. When sustained, these adaptations may become maladaptive and accelerate progression of chronic kidney disease (CKD).[10]

URINARY CONCENTRATION IN CHRONIC KIDNEY DISEASE

The kidneys conserve water by excreting concentrated urine. A healthy young person can excrete urine four times more concentrated than plasma, with an osmolality of approximately 1200 mOsm/kg H_2O and a specific gravity of 1.030. Because the electrolyte (sodium plus potassium) concentration of the urine can exceed the plasma sodium concentration, excretion of hypertonic urine can prevent dehydration when extrarenal water losses are large or drinking water is scarce. Excretion of hypertonic urine makes increased water intake unnecessary when salt intake is increased.[11]

Kidney disease impairs the ability to concentrate the urine maximally. Platt noted in 1952, "One of the constant signs of renal failure is the inability of the kidney to produce a concentrated urine, and it is well known that the specific gravity of the urine becomes relatively fixed at 1.010, which is approximately that of blood plasma minus its proteins"—so called isosthenuria.[12] However, although urinary concentrating ability is impaired relatively early in the course of kidney disease, so that urine osmolality cannot be increased to 1200 mOsm/kg H_2O, in most causes of CKD, urine osmolality can still be raised above plasma osmolality until the GFR falls below 25 mL/min/1.73 m^2.[13] In a

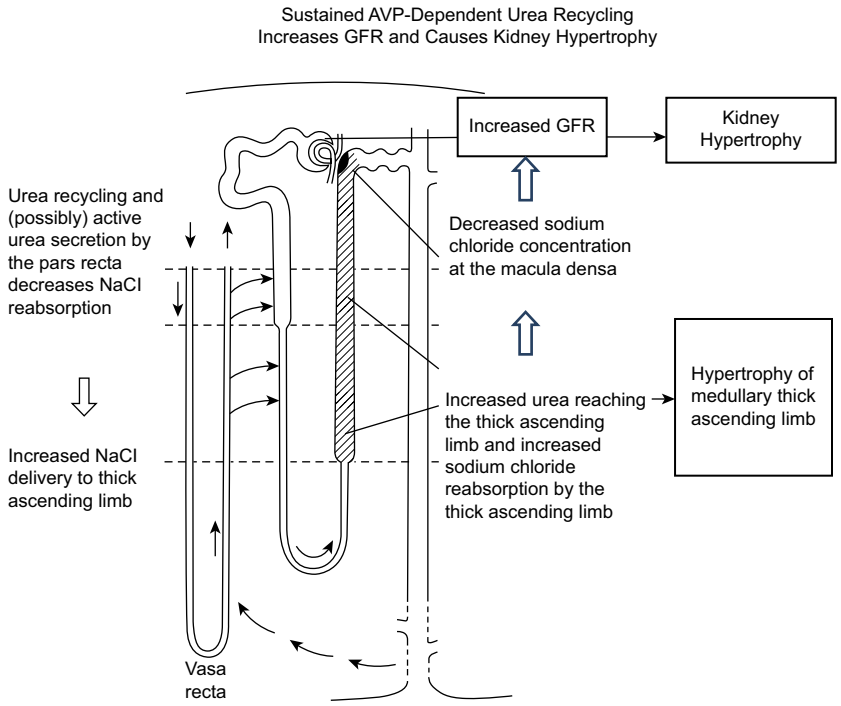


FIGURE 38.2 Theoretical mechanism for hyperfiltration and kidney hypertrophy caused by persistently high vasopressin levels. As in Figure 38.1, the figure depicts one nephron extending from the cortex to inner medulla. In actuality, cortical nephrons and justamedullary nephrons differ in their anatomy and transport processes (see more comprehensive model in reference 5). Urea recycling, enhanced active sodium reabsorption by the thick ascending limb of the loop of Henle, and, possibly, active secretion of urea by the pars recta (see evidence supporting this process in reference 5), result in a decreased sodium chloride concentration in the luminal fluid reaching the macula densa. This alters the set-point of tubulo-glomerular feedback that increases glomerular filtration rate (GFR). *Modified with permission from reference 6.*

study of 27 patients with stable chronic kidney disease (inulin clearances ranging from 6.9 to 38.9 mL/min), Kleeman et al. found urine osmolality after water deprivation and administration of pitressin (a pituitary abstract containing vasopressin) as low as 280 and as high as 392 mOsm/kg H_2O.[14] Similar findings were reported by Baldwin et al.[15]

Urine osmolality indicates how concentrated the urine is, but determination of solute-free water reabsorption (T^cH_2O) provides a better quantitative assessment of the kidney's ability to conserve water.[16] In the process of concentrating the urine, nephrons must reabsorb solute-free water from the initially isotonic glomerular filtrate. T^cH_2O is the difference between the volume of urine that would be required to excrete isosmolar urine (known as "osmolar clearance" or C_{osm}) and the actual urine volume. Osmolar clearance, which is expressed as a volume per unit time, equals the rate of solute excretion divided by the plasma osmolality (P_{osm}). The rate of solute excretion equals Urine osmolality (U_{osm}) multiplied by the urine flow rate (V):

$$C_{osm} = U_{osm} \times V/P_{osm}$$

Because T^cH_2O equals the difference between urine flow rate and osmolar clearance:

$$T^cH_2O = V(1 - U_{osm}/P_{osm})$$

Urine osmolality is altered by the rate of solute excretion ($U_{osm} \times V$). Even in the presence of high concentrations of ADH, when the normal kidney is presented with more solute to excrete, urine osmolality falls as the solute load rises, approaching (but still remaining higher than) plasma osmolality.[17] Although urine osmolality falls as osmolar clearance increases, solute-free water reabsorption increases, reflecting the increasing urine flow rate of an osmotic diuresis.

A limited ability to concentrate the urine in kidney disease could be caused by decreased renal mass (and a decreased number of normally functioning nephrons) or it could be caused by pathological dysfunction of remnant nephrons. According to the intact nephron hypothesis, if dietary intake (and urinary solute excretion) remains constant as disease progresses, each nephron must excrete a larger fraction of the filtered solute load, so that remnant nephrons are subjected to an osmotic diuresis.[18]

Supporting the intact nephron hypothesis, Baldwin et al. studied 25 patients with a variety of kidney diseases and found that water reabsorption (T^cH_2O) corrected for inulin clearance (C_{in}), a measure of GFR, was unimpaired, and, in some cases T^cH_2O/C_{in} was even higher than that in normal controls.[15] Studies in experimental animals with reduced renal function confirmed these observations.

Bricker studied dogs with a unilaterally diseased kidney (induced with pyelonephritis or local infusion of aminoglycoside), allowing comparison between the affected and unaffected kidney in a nonuremic environment.[18] During an osmotic diuresis induced by infusing mannitol, T^cH_2O corrected for glomerular filtration rate (T^cH_2O/GFR) was the same in the experimental and control kidneys, supporting the hypothesis that surviving nephrons reabsorb water normally in kidney disease.

Other investigators found evidence of dysfunctional water reabsorption in patients with kidney disease that are unexplained by an osmotic diuresis. In the study by Kleeman et al., urine osmolality was lower in patients than in controls with normal kidney function across a broad range of solute excretion. Impaired concentrating ability was attributed to additional pathological processes beyond that of a simple osmotic diuresis.[14] Similar conclusions were reached by Dorhout-Mees who measured T^cH_2O in 19 patients with kidney disease undergoing an osmotic diuresis induced with mannitol.[19]

Tannen and colleagues found that 11 of 13 patients with advanced kidney disease (creatinine clearance <15 mL/min) had a urine osmolality lower than plasma osmolality (by a mean of 17 mOsm/kg H_2O) despite administration of maximal doses of vasopressin (Figure 38.3).[20] This finding differs from the response of a normal kidney to an osmotic diuresis in the presence of vasopressin, where the urine osmolality, although reduced, remains higher than plasma osmolality. In response to vasopressin, water channels (aquaporins [AQPs]) are inserted in the luminal membrane of the renal collecting duct, allowing water to equilibrate with the interstitium of the renal medulla, which always has a higher osmolality than plasma. Thus, the finding of vasopressin-resistant fixed hyposthenuria suggests an intrinsic disorder in the function of the renal collecting duct.

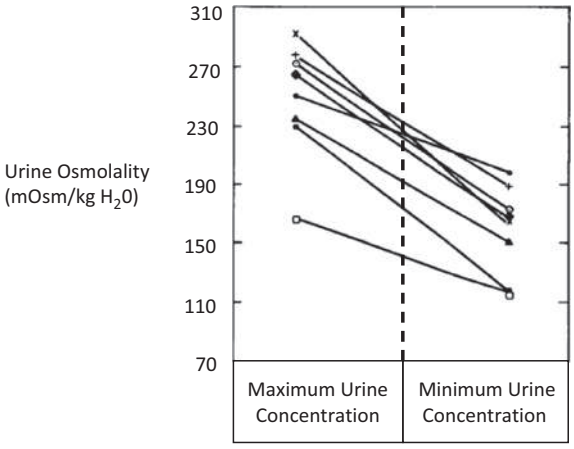


FIGURE 38.3 Maximum and minimum urine osmolality in 13 patients with advanced chronic kidney disease (CKD) (serum creatinine (S[Cr]) >7 mg/dL). Maximum urine osmolality was determined by fluid deprivation followed by administration of exogenous vasopressin. Minimum urine osmolality was determined by a standard water load of 20 mL/kg of body weight. *Modified from Figure 3 in reference 20.*

Loss of the Medullary Concentration Gradient in Chronic Kidney Disease

Concentration of the urine requires generation of a hyperosmolar interstitium in the renal medulla. The medullary concentration gradient is created by active transport of sodium from the lumen to the interstitium by the water-impermeable thick ascending limb of the loop of Henle, and by accumulation of urea in the interstitium owing to vasopressin-responsive urea transporters in the papillary collecting duct (Figure 38.1).[7] Gilbert et al. found that the medullary concentration gradient was lost in rodents with experimental pyelonephritis, but not in uninephrectomized control animals.[21] Micropuncture studies showed that reabsorption of sodium by the thick ascending limb was unimpaired in animals with pyelonephritis, but urea accumulation in the medulla was greatly diminished. Similarly, in rodent models, removal of the renal papilla, where urea transporters are located, markedly impairs renal concentrating ability, whereas it was unimpaired in animals with a comparable decrement in GFR induced with 65% nephrectomy, leaving the papilla intact.[22] Human counterparts of the papillectomy experiments can be found among patients with sickle cell disease, polycystic kidney disease (PKD), and medullary cystic disease.[23–25] Patients with these disorders have disproportionately severe pathology in the inner renal medulla and exhibit severely impaired concentrating ability despite only mildly reduced GFR.

Impaired Collecting Duct Water Permeability in Chronic Kidney Disease

The finding of fixed hyposthenuria in patients with advanced renal failure, unresponsive to vasopressin, suggests abnormal water permeability of the renal collecting duct, where, in response to vasopressin, the luminal fluid

normally achieves osmotic equilibrium with the surrounding medullary interstitium. Vasopressin resistance has been studied in animal models of kidney disease, some of which (e.g. the 5/6 nephrectomy model) may not accurately mimic human kidney disease.

Vasopressin-independent defects in water permeability have been found in isolated perfused cortical collecting ducts obtained from uremic rabbits.[26] The defect is associated with decreased generation of c-AMP in response to vasopressin and with a decreased response to an analogue of c-AMP (indicative of a postreceptor signaling defect). Cultured inner medullary collecting tubular cells obtained from 5/6 nephrectomized rats also fail to generate c-AMP in response to vasopressin. They exhibit a marked decrease in the number of vasopressin receptors, decreased levels of mRNA for synthesis of the receptor, and reduced expression of AQPs 1, 2, and 3.[27,28] All three AQP play a role in the renal concentrating mechanism—AQP 1 in the descending limb of Henle's loop, AQP 2, in the luminal membrane of principal cells of the collecting duct, and AQP 3 in the basolateral membrane of the principal cells.[29] Decreased expression of AQP 2, but not AQP 1 and 3, would be the expected effect of a reduced number of vasopressin receptors.

Impaired Capacity to Concentrate Urea in Chronic Kidney Disease

In CKD, the capacity to concentrate urea in the medullary interstitium and in the urine is much more impaired than the capacity to concentrate other solutes. Hu et al. found a 30-fold decrease in the U/P urea concentration ratio after 5/6 nephrectomy, whereas the U/P osmolality ratio declined only fourfold. The selective impairment in urinary urea-concentration is explained by a large and early fall in collecting duct urea transporters.[30] Because of the almost complete disappearance of UT-A1 message and protein in this model, vasopressin cannot increase urea permeability of the terminal collecting duct, and urea can no longer be delivered to the papillary interstitium. The mRNA for urea transporters in the vasa recta and thin limbs of the loop also fell progressively after 5/6 nephrectomy, falling in established renal failure to 10% or less of that in control rats. These findings strongly suggest that the overall defect in urinary concentrating ability observed in CKD is caused by an almost complete loss of the capacity to accumulate and recycle urea in the medullary interstitium. The accumulation of sodium chloride, which depends on countercurrent multiplication of the single effect generated in thick ascending limbs, is probably much less affected, so that the urine can remain moderately hypertonic to plasma.

URINARY DILUTION IN CHRONIC KIDNEY DISEASE

In contrast to the extensive number of studies exploring the mechanism for impaired urinary concentration in kidney disease, urinary dilution has been given relatively little attention. Defects in urine dilution appear later in the course of kidney disease than diminished concentrating ability.

Urine osmolality indicates how dilute the urine is, but determination of free water clearance (C_{H2O}) provides a better estimate of the kidney's ability to generate solute-free water.[31] C_{H2O} is the difference between osmolar clearance (C_{osm}) and urine flow rate:

$$C_{H2O} = V - C_{osm} = V(1 - U_{osm}/P_{osm})$$

When the kidney is presented with increased solute loads during a water diuresis, with low levels of vasopressin, urine osmolality rises, approaching but remaining below plasma osmolality.[31] Although the urine becomes less dilute as osmolar clearance increases, free water clearance increases, reflecting the increasing urine flow rate caused by a combined osmotic and water diuresis.

In Kleeman's study, only 1 of the 27 patients responded normally by excreting urine with a urine osmolality <100 mOsm/kg H_2O. In eight patients, the minimum urine osmolality was ≥ 200 mOsm/kg H_2O.[14] However, C_{H2O}/GFR was actually higher in the patients with CKD. Similarly, eight of the subjects studied by Tannen et al. who were unable to elaborate a urine more concentrated than plasma in response to vasopressin reduced urine osmolality by 50–112 mOsm/kg H_2O in response to a water load (Figure 38.3).[20] However, none of these patients were able to attain a urine osmolality <100 mOsm/kg H_2O, which is the normal response to a water load.

Studies in dogs mimic findings in patients with CKD. In a model with unilateral renal dysfunction, the abnormal kidney had a lower C_{H2O} than the contralateral control following a 40–70 mL/kg intragastric water load administered after volume expansion with isotonic saline to increase solute excretion.[18] However, C_{H2O}/GFR was actually higher in the abnormal kidney, suggesting that remaining nephrons were diluting the urine normally, and that the overall limitation in water excretion was related to the decrease in GFR, which reflects a reduced population of functioning nephrons.

IMPAIRED WATER HOMEOSTASIS IN CKD PATIENTS

People without kidney disease and a normally functioning osmoregulatory system can increase urine osmolality to as high as 1200 mOsm/kg H_2O and decrease it

to as low as 50 mOsm/kg H_2O. On a typical Western diet providing 900 milliosmoles of solute daily, a maximally concentrated urine reduces daily urine volume to 0.75 L. A maximally dilute urine allows excretion of 18 L of urine, providing a robust defense against both dehydration and the development of hyponatremia.[31] Progressive loss of renal function narrows these options for patients (Figure 38.4).

A patient with CKD whose urine cannot be concentrated above 300 mOsm/kg H_2O must excrete at least 3 L of urine to excrete the 900 milliosmoles generated by a typical Western diet. Because bladder capacity is about 500 mL, the defect in urinary concentration results in nocturia. The defect also makes patients with CKD susceptible to the development of dehydration and hypernatremia if water is scarce, thirst is impaired, or patients are too ill to seek water for themselves.

If the urine cannot be diluted below 200 mOsm/kg H_2O, urine volume on a diet generating 900 milliosmoles of solute is limited to 4.5 L/day. On a protein restricted, low-salt diet generating only 400 milliosmoles of solute, maximum urine volume is reduced to 2 L/day (Figure 38.4). Thus, the inability to maximally dilute the urine makes patients with advanced CKD on a low-salt, low-protein diet, susceptible to the development of hyponatremia if they drink more water than is eliminated by extrarenal losses, or it they are infused with large volumes of hypotonic fluid.

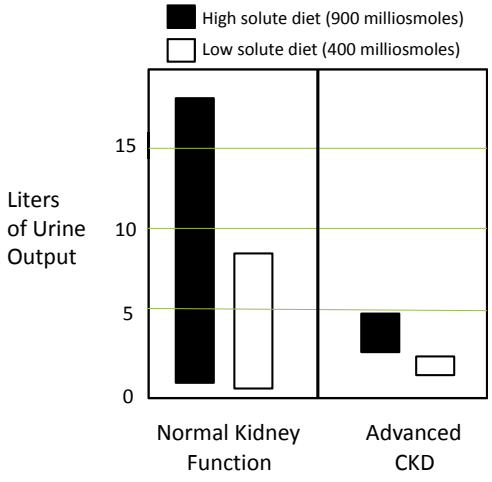


FIGURE 38.4 Restricted variation in urine volume in advanced chronic kidney disease (CKD). The figure illustrates the range of urine volumes when the urine is maximally concentrated and when it is maximally dilute. The panel of the left depicts urine volumes in a patient without kidney disease who is able to concentrate the urine to 1200 mOsm/kg H_2O. The panel on the right depicts urine volumes in a patient with kidney disease who is only able to concentrate the urine to 300 mOsm/kg H_2O and is unable to dilute the urine to a concentration below 200 mOsm/kg H_2O.

HYPONATREMIA AND HYPERNATREMIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Impaired ability to concentrate and dilute the urine would be expected to result in a higher than normal incidence of abnormal circulating sodium concentrations among ambulatory and hospitalized patients with CKD.

A study of 655,493 US Veterans with nondialysis-dependent CKD found that, at baseline, 13.5% were hyponatremic (serum sodium concentration <135 mEq/L) and 2% were hypernatremic (serum sodium concentration >145 mEq/L).[32] During a 5.5-year median follow-up, 26% of the patients had at least one episode of hyponatremia, and 7% had at least one episode of hypernatremia. The relatively high prevalence of hyponatremia may reflect the inclusion of hospitalized patients, the older age (mean 74 years) of the subjects, and comorbidities. Hyponatremia was twice as common in patients with early stages of CKD compared to CKD stages 3–5 (Figure 38.5). This finding suggests that hyponatremia in these patients was caused by nonosmotic release of vasopressin rather than an impaired ability to dilute the urine due to parenchymal kidney disease. Unlike hyponatremia, the prevalence of hypernatremia increased with the severity of renal impairment. These findings are consistent with the known defects in water homeostasis in CKD. The ability to concentrate the urine is lost sooner than the ability to dilute the urine during the course of progressive kidney disease. Therefore, the defense against hypernatremia is lost before the defense against hyponatremia. Consistent with this observation, a prospective study of 2182 ambulatory patients with CKD seen in outpatient

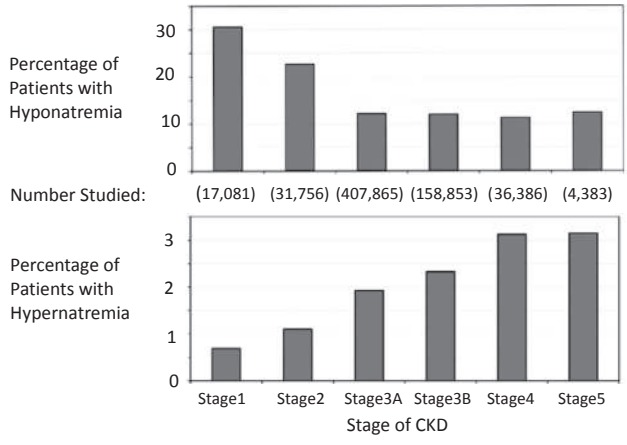


FIGURE 38.5 Incidence of hyponatremia and hypernatremia in a study of 655,493 US Veterans with nondialysis-dependent CKD. *Modified with permission from reference 32.*

clinics in the US followed for a mean of 1.8 years found hypernatremia to be more common than hyponatremia.[33]

In the general population, both hyponatremia and hypernatremia, even when mild, are associated with excess mortality.[34] Hyponatremia is associated with a poorer prognosis of several conditions, including heart failure, myocardial infarction, pulmonary infections, stroke, malignancy, and hepatic cirrhosis, but it is not known whether this means that hyponatremia results in mortality or that patients with more lethal conditions are more likely to develop hyponatremia. This observation is also true for patients with CKD.

A recent meta-analysis investigated the association of hyponatremia (serum sodium concentration <135−136) and hypernatremia (serum sodium concentration ≥145 to 144) with all-cause mortality risk in patients with CKD treated and untreated with dialysis.[34] From the seven included observational studies, the authors found that hyponatremia at the start of the studies (baseline hyponatremia or hypernatremia) and time-averaged sodium levels during the course of observation (time-dependent hyponatremia or hypernatremia) were independently associated with increased risk of all-cause mortality in patients with CKD. The risk of all-cause mortality increased by 41% for CKD patients with time-dependent hyponatremia and by 65% for patients with time-dependent hypernatremia. The mortality risk for CKD patients who had baseline hyponatremia increased by 34%. The association of baseline hypernatremia with all-cause mortality was not statistically significant. These findings suggest that in patients with CKD, the association between serum sodium concentration and all-cause mortality was U-shaped. In this study, the stage of kidney disease, among patients not requiring dialysis, did not affect mortality risk. However, the association between all-cause mortality and baseline hyponatremia was greater among patients undergoing dialysis than patients with CKD who did not require dialysis (hazard ratio 1.27 vs. 1.41). Among patients undergoing maintenance hemodialysis, a 4-mmol/L increase in baseline sodium level was associated with 19−28% lower risk of all-cause mortality in maintenance hemodialysis patients, but an elevated serum sodium level also conferred a higher risk of all-cause mortality (i.e. the association was U-shaped). The mechanism for the increased mortality associated with hyponatremia and hypernatremia is unknown. Currently there are no data demonstrating that correcting an abnormal serum sodium concentration reduces mortality.

Hyponatremia, even when mild and seemingly asymptomatic, has been shown to be associated with an increased risk of falls and fractures, abnormal gait, osteoporosis, and poorer performance on cognitive tests.[35] There is some evidence, albeit derived from extremely small studies, that correction of hyponatremia improves gait. A single case report convincingly showed that removal of a tumor causing chronic SIADH improved osteoporosis.[36,37]

Although evidence is lacking that correction of mild, chronic hyponatremia improves morbidity and mortality, many clinicians choose to treat the condition in patients without CKD. Some may also choose to treat mildly hyponatremic patients with CKD, but therapeutic options are more limited.

EVALUATION AND TREATMENT OF HYPONATREMIA IN CKD

Treatment of hyponatremia in patients who have impaired kidney function is similar to that in patients without kidney disease. Offending pharmacologic agents should be stopped, underlying endocrine disorders should be treated, and conditions that might be responsible for hyponatremia, such as liver disease and heart failure should be diagnosed and treated. However, some diagnostic approaches and therapeutic interventions must be modified.

Urinary sodium concentration is traditionally used as a marker to distinguish between the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and hypovolemic hyponatremia. Patients with CKD are unable to promptly reduce urine sodium losses when they become hypovolemic. Thus, patients with CKD who are hypovolemic may be misdiagnosed as having SIADH if the diagnosis is based on urine sodium concentrations. It is for this reason that normal kidney function is one of the criteria for making the diagnosis of SIADH. Normal saline solution is considered the treatment of choice for hypovolemic hyponatremia conditions. However, patients with CKD also have limitations in their ability to excrete sodium when volume overloaded. Also, unlike hypovolemic, hyponatremic patients without kidney disease, patients with advanced CKD may not respond by excreting maximally dilute urine when given isotonic saline. Thus, isotonic saline may be less effective in correcting hyponatremia in such patients, and its administration may be complicated by undesirable volume overload.

Water restriction, limiting isotonic saline to the amount needed to correct hypotension or prerenal azotemia, may be the best approach for treating hyponatremia in patients with advanced CKD. The effectiveness of water restriction can be predicted from the urine to plasma electrolyte (sodium + potassium) concentration ratio, as this ratio determines the fraction of urine volume that is electrolyte-free water.[31] As previously mentioned, C_{H2O} is the difference between urine

volume (V) and the urine to plasma osmolality ratio multiplied by V. This measurement helps quantify the kidney's processing of the glomerular filtrate. However, the serum sodium concentration is determined by the body's content of soluble sodium and potassium divided by total body water.[1] Changes in the body's content of urea, which contribute substantially to urine osmolality, do not change the serum sodium concentration. Therefore, to quantify losses that will change the serum sodium concentration, electrolyte-free water clearance (determined by urine concentrations of sodium and potassium) rather than C_{H2O}, (determined by urine osmolality), is the relevant measurement.[31]

$$\text{Electrolyte} - \text{free water clearance} = V[1 - \text{Urine}([Na + K]/\text{Plasma}[Na])].$$

If the electrolyte concentration of the urine is higher than the plasma sodium concentration, water restriction will predictably be ineffective.[31] However, this is unlikely to occur in patients with advanced kidney disease who excrete isosmolar or hypo-osmolar urine (fixed isosthenuria or hyposthenuria). Because urea comprises approximately one-third to one-half of excreted urinary solutes, urine electrolyte concentrations account for about half to two-thirds of the urine osmolality. With a urine osmolality equal to plasma osmolality, urine electrolyte concentration will be substantially lower than the serum sodium concentration, and urinary electrolyte-free water losses will contribute to correction of hyponatremia. Thus, fluid restriction can be expected to be a relatively effective therapy in hyponatremic patients with advanced CKD until patients become oliguric.

Consider a CKD patient with a serum sodium concentration of 120 mEq/L and a plasma and urine osmolality of 260 mOsm/kg H_2O. If dietary sodium and potassium provided 140 mEq of electrolytes (280 milliosmoles) for excretion, and dietary protein provided 240 milliosmoles of urea and ammonium salts, an isosmolar urine containing 520 milliosmoles of solute would be excreted in 2 L of urine. Each liter of urine would contain about 70 mEq of electrolyte (contributing 140 mOsm/kg H_2O to the total urine osmolality of 260 mOsm/kg), the urine to plasma electrolyte ratio would be 0.6, and electrolyte-free water clearance would be 0.4 times urine output ($0.4 \times 2\ L = 0.8\ L$ daily). Allowing for insensible losses, a 0.8 L fluid restriction would be expected to gradually increase the serum sodium concentration. Urinary electrolyte-free water losses diminish and water restriction becomes increasingly ineffective with lower dietary protein intakes and/or decreasing urine volumes associated with extremely low GFR.

Several pharmacologic agents have been used in the treatment of euvolemic hyponatremia. Demeclocycline has been used to treat SIADH because it acts on the collecting tubule cells to diminish their responsiveness to ADH. However, demeclocyline should be avoided in patients with kidney disease because it is nephrotoxic, particularly in patients with impaired liver function.[38]

Vasopressin V2R antagonists (a class of drugs known as "vaptans") have been shown to reliably increase serum sodium concentrations in a variety of clinical settings, but many trials have excluded enrollment of patients with moderate to severely decreased kidney function.[39] Preliminary pharmacodynamic studies with a single oral dose of 60 mg of tolvaptan demonstrated increased free water clearance in normonatremic patients with a creatinine clearance of 15–30 mL/min.[40] The response appears to be delayed, but it results in an increase in serum sodium concentrations similar to that in patients without kidney disease. Vasopressin V2R antagonists are likely to be less successful in patients with creatinine clearance <15 mL/min, but some response (increased urine flow and decreased urinary osmolality) was observed in patients with CKD stages 4 and 5, and congestive heart failure.[41] Although proven to be effective in maintaining a normal or near normal serum sodium concentration with long-term use, tolvaptan is extremely expensive and concerns about hepatotoxicity at high doses have led to mandates for monitoring liver function tests.

Although not formally studied, in CKD, high-dose loop diuretics can be used alone or in addition to water restriction to enhance water excretion. It is important to carefully monitor volume status and serum electrolyte levels on a regular basis to ensure that the patient does not become severely volume depleted, hypokalemic, or hypomagnesemic.

Oral urea promotes urinary electrolyte-free water losses, and urea has been used successfully to treat both acute and chronic hyponatremia. In a small unblinded, nonrandomized study in ambulatory patients with chronic hyponatremia, urea was found to be as effective as vasopressin antagonists in normalizing the serum sodium concentration and was comparably well tolerated.[42]

The use of urea to treat hyponatremia in patients with CKD has not been well studied. Administration of urea inevitably increases the BUN, and there is some concern that such an increase may have adverse effects.[10] At concentrations found in patients with CKD, urea forms cyanate, which causes protein carbamylation, a process that alters several enzymes and hormones, impairs leukocyte function, and aggravates oxidative stress. Increased urea levels can also interact with intestinal microbial flora with urease activity, potentially disrupting intestinal barrier dysfunction. Bankir has presented evidence that, like uric acid and ammonia, urea is probably actively secreted in the pars recta of the proximal

tubules by an energy-dependent process that increases active metabolic demand on the proximal tubular epithelium to raise the urea concentration in the lumen above that of the surrounding interstitial fluid.[5] GFR is markedly elevated in clinical situations of increased urea excretion associated with increased vasopressin secretion (an association that enhances intrarenal urea recycling and reduces the fractional excretion of urea). Administration of a large hypertonic urea load to rats, increasing urea excretion in a limited amount of urinary water results in a large increase in GFR, similar to the effect of a large protein load. The intrarenal mechanism that induces such vasopressin and urea-dependent hyperfiltration is not yet fully understood. The resulting high intraglomerular pressure and plasma flow could theoretically result in renal injury.[10]

Osmotic Demyelination in Kidney Disease

Osmotic demyelination syndrome can complicate overly rapid correction of hyponatremia (>8 mEq/L/day) in patients who have adapted for >48 hours to a serum sodium concentration <120 mEq/L.[43] The disorder presents in a delayed fashion one to several days after a large increase in serum sodium concentration. A variety of clinical findings emerge, including swallowing dysfunction and quadriparesis (symptoms of central pontine myelinolysis) and behavioral disturbances, movement disorders, and seizures (symptoms of extrapontine myelinolysis). Magnetic resonance images are often normal at the onset of neurological symptoms. After approximately two weeks, if symptoms persist, magnetic resonance images will show demyelinating lesions in the central pons and/or symmetrical extrapontine lesions in regions such as the basal ganglia, thalamus, and subcortex, where gray and white matter are closely admixed.

Many patients treated with maintenance hemodialysis who drink excessive amounts of water routinely experience large swings in serum sodium concentration with each dialysis. Despite this, there have not been any convincing published reports of osmotic demyelination after routinely scheduled hemodialysis. This may be because maintenance dialysis treatments are frequent enough that the brain has not yet fully adapted to the low serum sodium concentrations that develop between treatments. In addition, high levels of brain urea may protect against osmotic demyelination. Rapid correction of chronic hyponatremia results in cell injury because of cellular dehydration. During dialysis, urea is removed from the plasma more rapidly than it is removed from the brain, resulting in an osmotic gradient favoring water flow into brain cells.[44] After 5/6 nephrectomy in rats, expression of the urea transporter in brain, UT-B1, is reduced by half, whereas expression of brain AQP, AQP-4, is doubled.[45] These findings suggest that, during dialysis, the dehydration of brain cells caused by a rapid increase in serum sodium concentration is partially offset by brain cell swelling caused by rapid removal of urea.

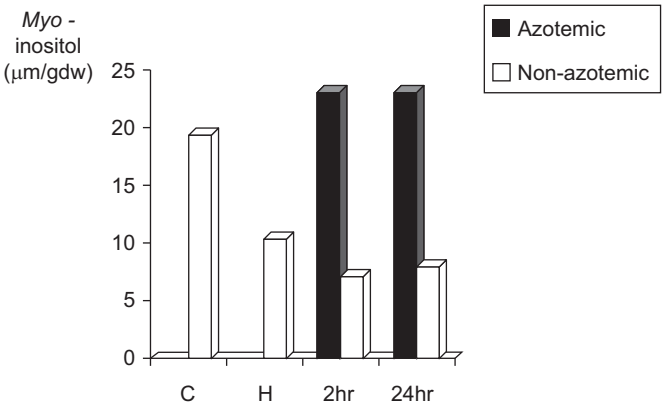


FIGURE 38.6 Enhanced brain uptake of myoinositol in uremia. The figure depicts the brain content of myoinositol in control rats without hyponatremia (C), after induction of hyponatremia (H), and 2 hours and 24 hours following rapid correction of hyponatremia. The brain content of myoinositol and other organic osmolytes is reduced comparably by hyponatremia in both uremic and nonuremic animals. After rapid correction of hyponatremia, uremic animals normalize the brain content of myoinositol and other organic osmolytes much more rapidly and uremic animals develop less severe osmotic demyelination than nonuremic animals. *From Figure 1 in reference 46 with permission.*

Depletion of organic osmolytes in response to hyponatremia is thought to make astrocytes vulnerable to injury when hyponatremia is corrected more rapidly than these solutes can be recovered.[1] In animal models, recovery of brain organic osmolytes, particularly myoinositol, occurs much sooner after rapidly correcting severe hyponatremia in uremic animals than in nonuremic controls (Figure 38.6). The uremic animals had a dramatic reduction in the incidence and severity of demyelinating brain lesions.[46]

However, uremia does not provide full protection from dialysis-related osmotic demyelination syndrome.[47,48] There have been a few case reports of osmotic demyelination syndrome with typical symptoms and imaging findings after correction of severe hyponatremia in peritoneal and hemodialysis patients.[49,50] The risk is likely to be much higher in severely hyponatremic patients with acute kidney injury, patients initially starting on dialysis therapy, and patients with end-stage renal disease (ESRD) who have not been dialyzed for some time.

When a patient who needs to be started on dialysis has severe hyponatremia, the dialysis regimen should be adjusted.[51] One option is to provide conventional dialysis, using a dialysate sodium concentration of 130 mEq/L and limiting blood flow to 50 mL/min, limiting dialysis time to two hours. Other options

include continuous venovenous hemodialysis, with a dialysate sodium concentration adjusted to 6 to 8 mEq/L above the serum sodium concentration or continuous hemofiltration with a similarly adjusted sodium concentration of the replacement fluid.[52] These latter options are preferred when the serum sodium concentration is <115 mEq/L, because in standard hemodialysis, dialysate sodium concentration cannot be decreased to <130 mEq/L. When these options are unavailable, or replacement fluid sodium concentration cannot be adjusted, an alternative approach is to prevent a rapid increase in serum sodium concentration by infusing 5% dextrose in water during the dialytic procedure.

Peritoneal dialysis can be used to increase the serum sodium concentration in hyponatremic patients with ESRD. Nolph et al. showed that during a hypertonic exchange with dextrose-based solutions, serum sodium concentrations increase with removal of an ultrafiltrate hyponatremic to extracellular fluid.[53] Therefore, treatment of hyponatremia with peritoneal dialysis is performed most effectively with repeated rapid exchanges of hypertonic dextrose solutions to promote electrolyte-free water removal.

EVALUATION AND TREATMENT OF HYPERNATREMIA IN PATIENTS WITH CKD

Patients with advanced CKD may develop hypernatremia when water losses caused by their inability to concentrate the urine are not replaced. In patients with normal kidney function, the failure to concentrate the urine in response to hypernatremia suggests a diagnosis of either neurogenic or nephrogenic diabetes insipidus.[1] In patients with advanced CKD, failure to concentrate the urine is the expected effect of the kidney disease and not a consequence of vasopressin deficiency. Treatment entails restoring water losses in the form of parenteral or enteric water intake. Administration of vasopressin is not helpful.

EFFECT OF WATER AND VASOPRESSIN ON PROGRESSION OF CKD

The kidney's role in maintaining water homeostasis has been understood for centuries. More recently, evidence has emerged that water balance and modulation of vasopressin levels or vasopressin action can affect renal function.[10]

Because vasopressin is unstable in the test tube and technically difficult to measure, vasopressin assays are unreliable unless done in research laboratories. Copeptin consists of the C-terminal portion of pro-AVP, the precursor of AVP. It is released with vasopressin in equimolar amounts. Copeptin has a longer half-life and is more stable and easier to measure than vasopressin. Plasma copeptin levels correlate with AVP levels and have been used as a surrogate measure for vasopressin secretion.[25] A study of renal transplant donors showed that copeptin levels do not change after nephrectomy (which results in a fall in GFR), suggesting that decreased clearance of copeptin does not account for changes in copeptin levels associated with kidney disease.[54]

The first evidence that vasopressin affects the progression of kidney disease was provided by experiments by Bouby et al. in 5/6 nephrectomized rats.[55] Vasopressin levels and urine osmolality were reduced by feeding the animals a water-rich gel. Animals provided with this regimen exhibited a significant reduction in proteinuria, kidney hypertrophy, glomerular lesions, interstitial injury, and mortality compared to animals with 5/6 nephrectomy that were fed dry food. Similarly, 5/6 nephrectomized Brattleboro rats, which are congenitally deficient in vasopressin, developed less kidney hypertrophy, hyperfiltration, and progression of CKD than 5/6 nephrectomized animals with normal vasopressin secretion. Administration of the synthetic vasopressin, desmopressin (a selective V2R agonist), to Brattleboro rats increased the rate of progression of CKD. Okada et al. showed selective blockade of vasopressin's V1a or V2Rs reduced protein excretion.[56] Histologic evidence of renal injury in rats with adriamycin-induced nephrotic syndrome and treatment of 5/6 nephrectomized rats with a selective V1a antagonist reduced proteinuria and progression of focal glomerulosclerosis.[57,58] Treatment of rats with puromycin aminonucleoside-induced nephropathy with the selective V2R antagonist, tolvaptan diminished proteinuria, decreased S[Cr], and reduced histologic evidence of podycyte injury.[59] Prolonged infusion of a V2R antagonist prevented albuminuria in rats with streptozotocin-induced diabetes mellitus.[60] Similarly, vasopressin-deficient Brattleboro rats with streptozotocin-induced diabetes mellitus do not develop an increase in GFR, and they have less albuminuria and less-intense kidney hypertrophy than diabetic Long Evans rats with intact vasopressin secretion.[61]

In animal models, maintaining a high urine osmolality causes glomerular hyperfiltration and kidney hypertrophy. The effect is analogous to the effect of high protein intake[10]. Animal models have shown that a high protein diet increases glomerular filtration. When increased intraglomerular pressure is sustained, it damages remaining glomeruli. GFR is markedly increased in rats when urine osmolality is raised by a one-week

infusion of the selective V2R agonist, desmopressin. Conversely, GFR falls when vasopressin secretion is inhibited by increasing water intake. Chronic infusion of vasopressin to Brattleboro rats (which lack the hormone) or chronic moderate dehydration in normal rats (which results in endogenous vasopressin secretion) results in kidney hypertrophy, with features that resemble those found in animals chronically fed a high protein diet.

The relationship between GFR and urine osmolality is "J-shaped," such that the rise in GFR with increasing osmolality is only observed when urine osmolality exceeds plasma osmolality. When urine osmolality is more dilute than plasma, vasopressin-dependent hyperfiltration disappears, or can even be reversed. If GFR were to decrease when there was a need to excrete excess water, it would be disadvantageous, because excretion of maximally dilute urine requires adequate delivery of fluid and solutes to the renal diluting sites.

Theoretically, water losses caused by the concentrating defect in CKD could lead to a compensatory increase of vasopressin, which then promotes progression of kidney disease because of hyperfiltration. Glomerular hyperfiltration induces a vicious cycle that leads to progressive renal damage.[10]

There is evidence that vasopressin may alter the progression of kidney disease in humans. A study of 979 patients with diabetes not taking renin–angiotensin–aldosterone inhibitors found that a higher baseline level of copeptin (a surrogate for vasopressin) is significantly associated with higher baseline urinary albumin:creatinine ratio and lower baseline estimated glomerular filtration rate (eGFR) values. Among 756 patients who were followed for an average of 6.5 years, higher copeptin levels were significantly associated with a more rapid decline in eGFR.[62] The association between copeptin and declining renal function was stronger than that for BMI or hemoglobin A1c levels. In three large prospective community-based European cohorts, high levels of plasma copeptin at baseline were associated with an increased incidence of microalbuminuria and stage 3 CKD, and more rapid decrease in eGFR over time during follow-up.[63] The risk associated with high plasma copeptin was similar to the risk associated with high blood pressure and arterial hypertension and was higher than the risk associated with high total cholesterol.

A 7-year prospective study of a community-based cohort of 2144 patients with preserved GFR found that kidney function declined significantly more slowly (odds ratio 0.46–0.66) in adults with the highest urine volumes (>3 L) than in those with the lowest urine volumes (<1 L), supporting a potential role of higher fluid intake in reducing the risk of kidney disease.[64] Similarly, a study of 273 patients with CKD stages 1–4 found that, adjusted for baseline creatinine clearance and use of diuretics, the risk of starting dialysis was approximately doubled for each doubling of urine osmolality, rising from a 15% risk when baseline urine osmolality was 315 mOsm/kg H_2O to a 34% risk when baseline osmolality was 775 mOsm/kg H_2O.[65]

In contrast to these findings, a *post hoc* analysis of the Modification of Diet in Kidney disease study found that higher urine volume patients with established CKD was associated with a faster decline in renal function.[66] However, the statistical association between rising S[Cr] and urine volume did not persist after controlling for use of diuretics and antihypertensive medications.[67]

A short-term pilot study showed that increased water intake can decrease plasma copeptin concentration in patients with stage 3 CKD.[68] Recently, in a randomized intervention study of patients with stage 3 CKD, coaching to increase water intake did not significantly slow the decline in kidney function after 1 year as compared to patients who were maintained on their baseline water intake.[69] However, in the high water intake group, 24-hour urine volumes were only modestly increased and plasma copeptin slightly lower during follow-up. The study may have been underpowered to detect a clinically important difference.

Autosomal Dominant Polycystic Kidney Disease

Vasopressin plays a pivotal role in the pathogenesis of adult dominant polycystic kidney disease (ADPKD). Vasopressin stimulates the formation of c-AMP, which is a potent stimulator of cyst growth in distal nephron segments that express V2Rs. By cross breeding vasopressin-deficient Brattleboro rats and rats with hereditary PKD, Wang et al. produced rats with PKD that produced no vasopressin. Compared to PKD rats with intact vasopressin secretion, the vasopressin-deficient PKD rats had lower renal c-AMP and almost complete inhibition of cystogenesis. Administration of desmopressin (a selective V2 receptor agonist) to the vasopressin-deficient animals increased renal c-AMP and restored the full cystic phenotype.[70] In an *in vitro* study, Reif et al. found the addition of the V2R antagonist, tolvaptan, to cultured human ADPKD cells inhibited vasopressin-stimulated cell proliferation and fluid secretion.[71]

Several lines of evidence in humans support the important role of vasopressin in the progression of PKD shown in animal models. The ability to concentrate the urine diminishes in ADPKD before GFR begins to decline.[25] It has been suggested that this is caused by cystic distortion of the medullary countercurrent mechanism that interferes with urea recycling. The urine to plasma urea concentration ratio (U/P urea) can be used to identify concentrating defects in patients with

ADPKD as it correlates strongly with maximum urine osmolality after water deprivation. There is a negative association between U/P urea and copeptin levels in patients with ADPKD whose GFR is normal, and total kidney volume is strongly associated with U/P urea and plasma osmolality. These findings suggest that as disease progresses in ADPKD, the cystic kidney develops a concentrating defect, leading to water loss and an increase in plasma osmolality. Responding to increased plasma osmolality, vasopressin levels rise to preserve water balance. Vasopressin then promotes cyst formation, further impairing the ability to concentrate the urine, creating a vicious cycle that results in progressive decline in kidney function. Higher copeptin levels are independently associated with more rapid disease progression in patients with early ADPKD.[72] This supports a causal role of vasopressin in progressive disease, but it could also mean that progressive disease, by impairing urinary concentration, results in higher levels of vasopressin (and copeptin).

Evidence for a causal role for vasopressin in disease progression in patients with ADPKD was provided by the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial, which found that in patients with early-stage ADPKD (mean eGFR 82 mL/min/1.73 m^2), administration of tolvaptan, an AVP-V2R antagonist, significantly slows the increase in total kidney volume by one-half and the decline in kidney function by about one-third after three years of follow-up.[73] An open label extension of the study showed that the beneficial effects of tolvaptan were maintained for an additional 2 years. The Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy Trial confirmed the efficacy and safety of tolvaptan in patients with CKD stages 2 to 4.[74] Tolvaptan (at an initial dose of 90 or 60 mg in the morning and 30 mg in the evening) resulted in a significantly slower decline in eGFR compared with placebo over the course of one year (-2.3 mL/min/1.73 m^2 vs. -3.6 mL/min/1.73 m^2, $p < 0.001$). It has been estimated that tolvaptan treatment started in a patient with ADPKD and an eGFR of 41 would extend the time to reach CKD stage 5 from 6.2 to 9.0 years. Tolvaptan has been approved for the treatment of ADPKD in several countries including the US. In addition to side effects from polyuria and thirst and the need for monthly monitoring of liver function tests, use of the drug may be limited by its high cost.

It has been hypothesized that ingestion of enough water to cause a water diuresis would lower vasopressin levels, and, like administration of a vasopressin antagonist, protect against progressive disease. It is difficult for patients to maintain a high enough fluid intake to suppress vasopressin secretion when eating a diet high in protein and salt. In a small randomized trial of patients with stage 1 and 2 CKD, Amro et al. showed that a low osmolar diet (1500 mg sodium and 0.8 g protein/kg body weight) led to a significant decrease in the water intake required to achieve the target urine osmolality of 280 mOsm/kg (from 2.5-5.02 L vs. 1.5–3.7 L).[75] Plasma copeptin levels fell in the 17 patients with a dietary intervention but not in 17 controls maintained on their customary diet. The reduction in mean urine osmolality achieved in this trial was equivalent to that reported in the TEMPO 3:4 trial (426 to 258 compared to 472 to 264 mOsm/kg H_2O).[73] A multicenter, prospective, randomized controlled trial is currently underway, which will study the effect of increased fluid intake and decreased dietary solute intake (designed to decrease urine osmolality to $\leq$270mOsmol/kg) on the progression of kidney volume, eGFR, and copeptin levels over a planned three years of follow-up.[76] Unfortunately, because of cost considerations, the study will not include a tolvaptan-treated comparison arm.

Acknowledgment

The author thanks Lise Bankir for stimulating discussions regarding the subject matter of this chapter.

References

1. Sterns RH. Disorders of plasma sodium—causes, consequences, and correction. *N Engl J Med* 2015;**372**:55–65.
2. Danziger J, Zeidel ML. Osmotic homeostasis. *Clin J Am Soc Nephrol* 2015;**10**:852–62.
3. Bankir L. Antidiuretic action of vasopressin: quantitative aspects and interaction between V1a and V2 receptor-mediated effects. *Cardiovasc Res* 2001;**51**:372–90.
4. Bachmann S, Mutig K. Regulation of renal Na-(K)-Cl cotransporters by vasopressin. *Pflueg Arch Eur J Physiol* 2017;**469**:889–97.
5. Bankir L, Yang B. New insights into urea and glucose handling by the kidney, and the urine concentrating mechanism. *Kidney Int* 2012;**81**:1179–98.
6. Bankir L, Kriz W. Adaptation of the kidney to protein intake and to urine concentrating activity: similar consequences in health and CRF. *Kidney Int* 1995;**47**:7–24.
7. Bankir L, Bouby N, Trinh-Trang-Tan M, et al. Direct and indirect cost of urea excretion. *Kidney Int* 1996;**49**:1598–607.
8. Bankir L, Roussel R, Bouby N. Protein- and diabetes-induced glomerular hyperfiltration: role of glucagon, vasopressin, and urea. *Am J Physiol Renal Physiol* 2015;**309**:F2–23.
9. Bankir L, Ahloulay M, Bouby N, et al. Is the process of urinary urea concentration responsible for a high glomerular filtration rate? *J Am Soc Nephrol* 1993;**4**:1091–103.
10. Bankir L, Bouby N, Ritz E. Vasopressin: a novel target for the prevention and retardation of kidney disease? *Nat Rev Nephrol* 2013;**9**:223.
11. Bankir L, Perucca J, Norsk P, et al. Relationship between sodium intake and water intake: the false and the true. *Ann Nutr Metab* 2017;**70**(Suppl. 1):51–61.
12. Platt R. Structural and functional adaptation in renal failure. *Br Med J* 1952;**1**:1372–7.

13. Roussel R, Fezeu L, Marre M, et al. Comparison between copeptin and vasopressin in a population from the community and in people with chronic kidney disease. *J Clin Endocrinol Metab* 2014;**99**: 4656–63.
14. Kleeman CR, Adams DA, Maxwell MH. An evaluation of maximal water diuresis in chronic renal disease. I. Normal solute intake. *J Lab Clin Med* 1961;**58**:169–84.
15. Baldwin DS, Berman HJ, Heinemann HO, Smith HW. The elaboration of osmotically concentrated urine in renal disease. *J Clin Investig* 1955;**34**:800–7.
16. Raisz LG, Au WY, Scheer RL. Studies on the renal concentrating mechanism. IV. Osmotic diuresis. *J Clin Investig* 1959;**38**:1725–32.
17. Rapoport S, Brodsky WA, West CD, Mackler B. Urinary flow and excretion of solutes during osmotic diuresis in hydropenic man. *Am J Physiol* 1949;**156**:433–42.
18. Bricker NS, Dewey RR, Lubowitz H, et al. Observations on the concentrating and diluting mechanisms of the diseased kidney. *J Clin Investig* 1959;**38**:516–23.
19. Dorhout Mees EJ. Role of osmotic diuresis in impairment of concentrating ability in renal disease. *Br Med J* 1959;**1**:1156–8.
20. Tannen RL, Regal EM, Dunn MJ, Schrier RW. Vasopressin-resistant hyposthenuria in advanced chronic renal disease. *N Engl J Med* 1969;**280**:1135–41.
21. Gilbert RM, Weber H, Turchin L, et al. A study of the intrarenal recycling of urea in the rat with chronic experimental pyelonephritis. *J Clin Investig* 1976;**58**:1348–57.
22. Finkelstein FO, Hayslett JP. Role of medullary structures in the functional adaptation of renal insufficiency. *Kidney Int* 1974;**6**: 419–25.
23. Hatch FE, Culbertson JW, Diggs LW. Nature of the renal concentrating defect in sickle cell disease. *J Clin Investig* 1967;**46**:336–45.
24. Giselson N, Heinegard D, Holmberg C, et al. Renal medullary cystic disease or familial juvenile nephronophthisis: a renal tubular disease: biochemical findings in two siblings. *Am J Med* 1970;**48**: 174–84.
25. Zittema D, Boertien WE, van Beek AP, et al. Vasopressin, copeptin, and renal concentrating capacity in patients with autosomal dominant polycystic kidney disease without renal impairment. *Clin J Am Soc Nephrol* 2012;**7**:906–13.
26. Fine LG, Schlondorff D, Trizna W, et al. Functional profile of the isolated uremic nephron. Impaired water permeability and adenylate cyclase responsiveness of the cortical collecting tubule to vasopressin. *J Clin Investig* 1978;**61**:1519–27.
27. Kwon T, Frøkiaer J, Knepper MA, Nielsen S. Reduced AQP1,-2, and-3 levels in kidneys of rats with CRF induced by surgical reduction in renal mass. *Am J Physiol Renal Physiol* 1998;**275**:F724–41.
28. Teitelbaum I, McGuinness S. Vasopressin resistance in chronic renal failure. Evidence for the role of decreased V2 receptor mRNA. *J Clin Investig* 1995;**96**:378–85.
29. Nielsen S, Agre P. The aquaporin family of water channels in kidney. *Kidney Int* 1995;**48**:1057–68.
30. Hu M, Bankir L, Michelet S, et al. Massive reduction of urea transporters in remnant kidney and brain of uremic rats. *Kidney Int* 2000; **58**:1202–10.
31. Berl T. Impact of solute intake on urine flow and water excretion. *J Am Soc Nephrol* 2008;**19**:1076–8.
32. Kovesdy CP, Lott EH, Lu JL, et al. Hyponatremia, hypernatremia, and mortality in patients with chronic kidney disease with and without congestive heart failure. *Circulation* 2012;**125**:677–84.
33. Han SW, Tilea A, Gillespie BW, et al. Serum sodium levels and patient outcomes in an ambulatory clinic-based chronic kidney disease cohort. *Am J Nephrol* 2015;**41**:200–9.
34. Sun L, Hou Y, Xiao Q, Du Y. Association of serum sodium and risk of all-cause mortality in patients with chronic kidney disease: a meta-analysis and sysematic review. *Sci Rep* 2017;**7**:15949.
35. Rondon-Berrios H, Berl T. Mild chronic hyponatremia in the ambulatory setting: significance and management. *Clin J Am Soc Nephrol* 2015;**10**:2268–78.
36. Renneboog B, Musch W, Vandemergel X, et al. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med* 2006;**119**:71 e1–8.
37. Sejling A, Thorsteinsson A, Pedersen-Bjergaard U, Eiken P. Recovery from SIADH-associated osteoporosis: a case report. *J Clin Endocrinol Metab* 2014;**99**:3527–30.
38. Miller PD, Linas SL, Schrier RW. Plasma demeclocycline levels and nephrotoxicity: correlation in hyponatremic cirrhotic patients. *J Am Med Assoc* 1980;**243**:2513–5.
39. Rozen-Zvi B, Yahav D, Gheorghiade M, et al. Vasopressin receptor antagonists for the treatment of hyponatremia: systematic review and meta-analysis. *Am J Kidney Dis* 2010;**56**:325–37.
40. Shoaf SE, Bricmont P, Mallikaarjun S. Pharmacokinetics and pharmacodynamics of oral tolvaptan in patients with varying degrees of renal function. *Kidney Int* 2014;**85**:953–61.
41. Otsuka T, Sakai Y, Ohno D, et al. The effects of tolvaptan on patients with severe chronic kidney disease complicated by congestive heart failure. *Clin Exp Nephrol* 2013;**17**:834–8.
42. Soupart A, Coffernils M, Couturier B, et al. Efficacy and tolerance of urea compared with vaptans for long-term treatment of patients with SIADH. *Clin J Am Soc Nephrol* 2012;**7**:742–7.
43. Sterns RH. Treatment of severe hyponatremia. *Clin J Am Soc Nephrol* 2018;**13**:641–9.
44. Silver S, Sterns R, Halperin M. Brain swelling after dialysis: old urea or new osmoles? *Am J Kidney Dis* 1996;**28**:1–13.
45. Trinh-Trang-Tan M, Cartron J, Bankir L. Molecular basis for the dialysis disequilibrium syndrome: altered aquaporin and urea transporter expression in the brain. *Nephrol Dial Transplant* 2005; **20**:1984–8.
46. Soupart A, Silver S, Schrooeder B, et al. Rapid (24-hour) reaccumulation of brain organic osmolytes (particularly myo-inositol) in azotemic rats after correction of chronic hyponatremia. *J Am Soc Nephrol* 2002;**13**:1433–41.
47. Sterns RH, Silver SM. Hemodialysis in hyponatremia: is there a risk? 1990;**3**:3–4.
48. Sirota JC, Berl T. Is osmotic demyelination a concern dialyzing hyponatremic patients? 2011;**24**:407–9.
49. Loo C, Fan K, Murad Z, Suleiman A. Pontine M yelinolysis following correction of nantraemia. *Med J Malaysia* 1995;**50**.
50. Huang W, Weng W, Peng T, et al. Central pontine and extrapontine myelinolysis after rapid correction of hyponatremia by hemodialysis in a uremic patient. *Ren Fail* 2007;**29**:635–8.
51. Rosner MH, Connor Jr MJ. Management of severe hyponatremia with continuous renal replacement therapies. *Clin J Am Soc Nephrol* 2018;**13**:787–9.
52. Yessayan L, Yee J, Frinak S, Szamosfalvi B. Treatment of severe hyponatremia in patients with kidney failure: role of continuous venovenous hemofiltration with low-sodium replacement fluid. *Am J Kidney Dis* 2014;**64**:305–10.
53. Nolph KD, Hano JE, Teschan PE. Peritoneal sodium transport during hypertonic peritoneal dialysis: physiologic mechanisms and clinical implications. *Ann Intern Med* 1969;**70**:931–41.
54. Zittema D, van den Berg E, Meijer E, et al. Kidney function and plasma copeptin levels in healthy kidney donors and autosomal dominant polycystic kidney disease patients. *Clin J Am Soc Nephrol* 2014;**9**:1553–62.
55. Bouby N, Bachmann S, Bichet D, Bankir L. Effect of water intake on the progression of chronic renal failure in the 5/6 nephrectomized rat. *Am J Physiol* 1990;**258**:F973–9.
56. Okada H, Suzuki H, Kanno Y, et al. Effects of vasopressin V1 and V2 receptor antagonists on progressive renal failure in rats. *Clin Sci (Lond)* 1994;**86**:399–404.

57. Windt WA, Tahara A, Kluppel AC, et al. Early, but not late therapy with a vasopressin V1a-antagonist ameliorates the development of renal damage after 5/6 nephrectomy. *J Renin-Angiotensin-Aldosterone Syst JRAAS* 2006;**7**:217−24.
58. Okada H, Suzuki H, Kanno Y, Saruta T. Evidence for the involvement of vasopressin in the pathophysiology of adriamycin-induced nephropathy in rats. *Nephron* 1996;**72**:667−72.
59. Okada T, Sakaguchi T, Hatamura I, et al. Tolvaptan, a selective oral vasopressin V2 receptor antagonist, ameliorates podocyte injury in puromycin aminonucleoside nephrotic rats. *Clin Exp Nephrol* 2009; **13**:438−46.
60. Bardoux P, Bruneval P, Heudes D, et al. Diabetes-induced albuminuria: role of antidiuretic hormone as revealed by chronic V2 receptor antagonism in rats. *Nephrol Dial Transplant* 2003;**18**:1755−63.
61. Bardoux P, Martin H, Ahloulay M, et al. Vasopressin contributes to hyperfiltration, albuminuria, and renal hypertrophy in diabetes mellitus: study in vasopressin-deficient Brattleboro rats. *Proc Natl Acad Sci USA* 1999;**96**:10397−402.
62. Boertien W, Riphagen I, Drion I, et al. Copeptin, a surrogate marker for arginine vasopressin, is associated with declining glomerular filtration in patients with diabetes mellitus (ZODIAC-33). *Diabetologia* 2013;**56**:1680−8.
63. El Boustany R, Tasevska I, Meijer E, et al. Plasma copeptin and chronic kidney disease risk in 3 European cohorts from the general population. *JCI Insight* 2018;**3**.
64. Clark WF, Sontrop JM, Macnab JJ, et al. Urine volume and change in estimated GFR in a community-based cohort study. *Clin J Am Soc Nephrol* 2011;**6**:2634−41.
65. Plischke M, Kohl M, Bankir L, et al. Urine osmolarity and risk of dialysis initiation in a chronic kidney disease cohort–a possible titration target? *PLoS One* 2014;**9**:e93226.
66. Hebert LA, Greene T, Levey A, et al. High urine volume and low urine osmolality are risk factors for faster progression of renal disease1. *Am J Kidney Dis* 2003;**41**:962−71.
67. Clark WF, Sontrop JM, Huang SH, et al. Hydration and chronic kidney disease progression: a critical review of the evidence. *Am J Nephrol* 2016;**43**:281−92.
68. Sontrop JM, Huang SH, Garg AX, et al. Effect of increased water intake on plasma copeptin in patients with chronic kidney disease: results from a pilot randomised controlled trial. *BMJ Open* 2015;**5**. e008634.
69. Clark WF, Sontrop JM, Huang S, et al. Effect of coaching to increase water intake on kidney function decline in adults with chronic kidney disease: the CKD WIT randomized clinical trial. *J Am Med Assoc* 2018;**319**:1870−9.
70. Wang X, Wu Y, Ward CJ, et al. Vasopressin directly regulates cyst growth in polycystic kidney disease. *J Am Soc Nephrol* 2008;**19**: 102−8.
71. Reif GA, Yamaguchi T, Nivens E, et al. Tolvaptan inhibits ERK-dependent cell proliferation, Cl- secretion, and in vitro cyst growth of human ADPKD cells stimulated by vasopressin. *Am J Physiol Renal Physiol* 2011;**301**:F1005−13.
72. Boertien WE, Meijer E, Zittema D, et al. Copeptin, a surrogate marker for vasopressin, is associated with kidney function decline in subjects with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant* 2012;**27**:4131−7.
73. Torres VE, Higashihara E, Devuyst O, et al. Effect of tolvaptan in autosomal dominant polycystic kidney disease by CKD stage: results from the TEMPO 3:4 trial. *Clin J Am Soc Nephrol* 2016;**11**: 803−11.
74. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med* 2017; **377**:1930−42.
75. Amro OW, Paulus JK, Noubary F, Perrone RD. Low-osmolar diet and adjusted water intake for vasopressin reduction in autosomal dominant polycystic kidney disease: a pilot randomized controlled trial. *Am J Kidney Dis* 2016;**68**:882−91.
76. Wong ATY, Mannix C, Grantham JJ, et al. Randomised controlled trial to determine the efficacy and safety of prescribed water intake to prevent kidney failure due to autosomal dominant polycystic kidney disease (PREVENT-ADPKD). *BMJ Open* 2018;**8**. e018794-2017-018794.

QUESTIONS AND ANSWERS

Question 1

A 25-year-old woman with Bartter's syndrome (a congenital disorder caused by dysfunction of sodium, potassium, and chloride transport in the ascending limb of the loop of Henle) develops progressive renal failure due to nephrocalcinosis and focal segmental glomerular sclerosis. She comes to you complaining of polyuria. She has been taking sodium and potassium supplements for her entire life. The need for potassium replacement has declined as her renal failure progressed. Blood pressure is 160/90 mm Hg, lungs are clear and cardiac examination is normal except for mild pretibial edema. Liver function tests are normal. Blood glucose is normal. eGFR is 15 mL/min/1.73 m^2, urine output is 8 L/day, plasma osmolality is 280 mOsm/kg H_2O, BUN is 60 mg/dL, and serum sodium concentration is 128 mEq/L.

A 24 hour urine reveals:

Osmolality 164 mOsm/kg H_2O
Sodium 41 mEq/L
Potassium 23 mEq/L
Chloride 45 mEq/L
Creatinine 13.9 mg/dL

Which of the following are TRUE regarding C_{H2O} and C_{osm} in this patient.

A. C_{H2O} and C_{osm} are equal
B. C_{H2O} is less than C_{osm}
C. C_{H2O} is more than C_{osm}
D. C_{H2O} is more than 50% of the patient's GFR
E. C_{osm} is more than 50% of the patient's GFR

Answer: B
The urine output (V) equals the sum of
$C_{H2O} + C_{osm.} = 8$ L/day
$C_{osm} = (U_{osm} \times V)/Posm = (164 \times 8)/280$
$= 4.7$ L/day
$C_{H2O} = V - C_{osm} = 8{-}4.7 = 3.3$ L/day
The GFR is 15 mL/min = 21.6 L/day; therefore, neither C_{H2O} nor C_{osm} is larger than GFR.

In this patient, the large urine output is due to an osmolar clearance (4.7 L/day) that is 1.7 L/day higher than the 3 L/day osmolar clearance found in patients on a typical Western diet. The high osmolar clearance (an osmotic diuresis) is due to sodium and potassium wasting caused by Bartter's syndrome, which is treated with sodium and potassium supplements. A pressure natriuresis, caused by the patient's high blood pressure and volume overload, may be contributing to the osmotic diuresis. Although free water clearance (C_{H2O}) is not as large as osmolar clearance (C_{osm}), it is markedly higher than the slightly negative free water clearance found in patients who are eating and drinking normally. It is indicative of a concurrent water diuresis.

Question 2

Which of the following statements are TRUE regarding the cause of the above patient's polyuria.

A. She has diabetes insipidus and administration of desmopressin will determine whether the cause is central or nephrogenic
B. She has diabetes insipidus and measurement of copeptin will determine whether the cause is central or nephrogenic
C. She has nephrogenic diabetes insipidus
D. The sole reason for her polyuria is an osmotic diuresis caused by sodium and potassium supplements
E. None of the above

Answer: E
The very high free water clearance (C_{H2O}), reflecting a dilute urine, with an osmolality lower than plasma osmolality, indicates that the patient's large urine output is, in part, due to a water diuresis. Therefore, although the patient also has an osmotic diuresis, Answer D is incorrect. A water diuresis can be caused by central diabetes insipidus, nephrogenic diabetes insipidus, or primary polydipsia. The low-serum sodium concentration indicates that primary polydipsia must be a major part of the explanation for her water diuresis. It is possible that she has central or nephrogenic diabetes insipidus as well, but these diagnoses cannot be entertained until the urine osmolality is reassessed after the plasma osmolality has normalized.

Question 3

Which of the following causes the above patient's urine osmolality to be lower than her plasma osmolality?

A. Impaired sodium, potassium, and chloride reabsorption in the ascending limb of the loop of Henle
B. Decreased urea reabsorption in the papillary collecting duct
C. Low levels of vasopressin
D. All of the above
E. None of the above

Answer: C

The patient's serum sodium concentration is low, which suppresses vasopressin secretion by the hypothalamus. This results in a low urine osmolality in both normal subjects and in patients with CKD. The ability to dilute the urine is preserved in patients with CKD until the GFR falls below 15 mL/min, and some patients with a GFR <15 mL/min will respond to a water load with a fall in urine osmolality. Answers A and B explain why this patient is unable to concentrate her urine. Concentration of the urine depends on sodium, potassium, and chloride transport in the ascending limb and urea reabsorption in the papillary collecting duct. Impaired function of the ascending limb actually reduces the ability to dilute the urine and cannot be the reason that the patient's urine is dilute. Decreased urea reabsorption in the collecting duct does not enhance the ability to dilute the urine.

Question 4

Which of the following causes the above patient's serum sodium concentration to be lower than normal?

A. The high BUN
B. Inability to concentrate the urine due to the defect in the ascending limb
C. Decreased urea absorption in the papillary collecting duct
D. SIADH
E. None of the above

Answer: E

The serum sodium concentration is lower than normal because, despite the retained ability to excrete urine more dilute than plasma, the patient is unable to dilute the urine maximally. Her urine electrolyte (Na + K) concentration is 64 mEq/L, half her serum sodium concentration. Therefore, her 8 L of daily urine output is half electrolyte-free water. She must be drinking more than 4 L of electrolyte-free water daily to have become hyponatremic.

Although the high BUN increases plasma osmolality, it does not affect the serum sodium concentration. This is because urea, unlike glucose or mannitol, is an ineffective osmole that does not dilute the serum sodium concentration by osmotically attracting water from the intracellular space.

Inability to concentrate the urine and decreased urea reabsorption in the papillary collecting duct, part of the processes involved in the generation of the medullary concentration gradient, do not affect the ability to dilute the urine.

The diagnosis of SIADH cannot be made in patients with advanced CKD.

Question 5

Which of the following would be appropriate counseling for this patient regarding her water intake:

A. A high water intake will delay progression of your kidney disease
B. Your polyuria will resolve if you decrease your water intake to 2 L/day.
C. Your serum sodium concentration will normalize if you decrease your water intake
D. All of the above
E. None of the above

Answer: C

As noted in the answer to question 4, the urine electrolyte concentration is half the serum sodium concentration, indicating that water restriction will be effective in raising the serum sodium concentration.

Although there is evidence in experimental animals that a high water intake delays progression of kidney disease, this has not yet been proven in humans.

Although polyuria will likely improve by decreasing water intake, it may not completely resolve for two reasons: (a) part of the diuresis is due to increased osmolar clearance, and (b) the patient may have fixed hyposthenuria due to her kidney disease. Hyposthenuria (even when the serum sodium concentration is normal or high) is a feature of some variants of Bartter's syndrome.

Question 6

A 30-year-old man with a family history of ADPKD is found to have S[Cr] of 1.4 mg/dL and multiple cysts in both kidneys. Which one of the following would be appropriate counseling for this patient regarding his water intake:

A. High water intake will definitely delay progression of your kidney disease
B. If you decide to treat your disease with a high water intake, a high-protein, high-salt diet will make it easier for you to suppress vasopressin secretion and achieve a target urine osmolality of 280 mOsm/kg H_2O.
C. Tolvaptan therapy has been shown to decrease progression of kidney disease in some patients like you
D. All of the above
E. None of the above

Answer C

Vasopressin promotes the growth of renal cysts in ADPKD. By suppressing vasopressin secretion, a high water intake would be expected to be effective in delaying progression of ADPKD; however, it has not been proven to do so. Tolvaptan, a vasopressin receptor antagonist, which blocks the effect of vasopressin on renal cyst growth, has been shown to delay progression of ADPKD in therapeutic trials.

A low-protein, low-salt diet makes it easier to lower the serum sodium concentration enough to suppress vasopressin secretion by drinking water. Higher protein intakes increase urine electrolyte-free water excretion, making it harder to drink enough water to achieve this goal.

CHAPTER

39

Sodium Metabolism in Chronic Kidney Disease

Surabhi Thakar, Mark S. Paller

University of Minnesota, Minneapolis, MN, United States

Abstract

Sodium balance is reasonably well maintained in chronic kidney disease (CKD) patients until renal function is extensively diminished. Patients do not usually develop either edema or sodium depletion during the early stages of CKD. The adaptive response to decreasing glomerular filtration rate (GFR) in the face of a constant (or high) sodium intake is an increase in the fractional excretion of sodium (FE_{Na}). This, in turn, requires a reduction in sodium reabsorption per nephron. In most circumstances, this is protective and prevents or limits sodium retention and extracellular fluid volume expansion. However, if dietary sodium intake is suddenly or greatly reduced, the chronically diseased kidney cannot immediately adjust. Distal nephron tubular function is not permanently impaired because the kidney can adequately adjust to decreases in sodium intake if the changes occur slowly. Hypertension is very common in CKD patients. Control of extracellular fluid volume through diet, and dialysis prescription in the case of end-stage renal disease, is the most effective means of controlling blood pressure. The KDOQI Clinical Practice Guidelines recommends that dietary sodium intake be limited to no more than 2.4 g/day.

SODIUM HOMEOSTASIS AND SODIUM METABOLISM

The body maintains homeostasis by protecting sodium balance more vigorously than it does water balance or acid–base balance. It should be no surprise then that sodium balance is reasonably well maintained in chronic kidney disease (CKD) until renal function is extensively diminished. In normal individuals, sodium balance is maintained by coordination of the afferent sensors and the efferent actions of the kidneys. In individuals with CKD, the same pathways are relevant.

The regulated (i.e. perceived) portion of total body sodium is the intravascular fluid volume. The afferent sensors for intravascular volume include baroreceptors in the arterial circulation, in the aortic arch and carotid sinuses, cardiac receptors in the atria, and receptors in the renal arteries. Sympathetic nerves to the kidney, as well as circulating norepinephrine, are the main communication mode between the arterial baroreceptors and the kidneys.[1] The renal baroreceptors also mediate renin release, and the subsequently generated angiotensin II becomes an additional circulating signal to the kidneys. Angiotensin II-stimulated aldosterone further influences renal sodium handling in the collecting duct. The cardiac baroreceptors release natriuretic peptides that alter distal nephron sodium handling.[2]

The intrarenal mechanisms whereby sodium handling and ultimately urinary sodium excretion can be altered include glomerular filtration, peritubular physical forces, renal sympathetic nerve activity, aldosterone, natriuretic peptides, prostaglandins, and other vasoactive substances, including vasopressin, endothelin, and nitric oxide.[2–8]

Since the 1960s, it has been recognized that glomerular filtration rate (GFR) and aldosterone are not the most important controlling factors for renal sodium excretion. Scientists sought the so-called third factor. Although the third factor was discovered to be an atrial natriuretic factor, in actuality there are several hormones, autacoids, and intrinsic vasoactive controllers of sodium excretion (see above).[9]

ALTERATIONS AND ADAPTATIONS IN CKD

Body Fluid Spaces

Total body water is increased in most patients with CKD.[10] Because total body water is expressed in units of body weight, this could reflect an absolute increase in water, a decrease in body fat, or a combination. Because water is distributed in lean body tissue, a decrease in fat tissue would be expressed as an increase in water per unit of body weight. Because CKD is often

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00039-5

associated with malnutrition and an expected loss in fat tissue, the extent of a true increase in total body water, if any, in patients is not precisely known.

Measurements of extracellular fluid volume, also expressed per unit of body weight, have also been reported as being increased when measured as exchangeable bromide or sulfate in CKD. Exchangeable sodium has also been employed as a measurement of extracellular fluid volume. However, unlike bromide, sulfate, or chloride, sodium does enter cells. In CKD, exchangeable sodium is usually elevated. On the other hand, the magnitude of total body potassium and intracellular potassium is either normal or low, suggesting a substitution of sodium for intracellular potassium. Circulating inhibitors of Na/K ATPase, including endogenous ouabain, accumulate in patients with CKD and may be the responsible for this electrolyte shift.[11] Therefore, in CKD, the exchangeable sodium measurement may not be an accurate predictor of extracellular fluid volume. Measurements of blood volume using chromium-labeled red cells or radio-iodinated albumin have usually been normal in CKD. In summary, although there are abnormalities of intracellular sodium levels and of total body sodium in CKD, extracellular fluid volume measured by older methods is usually normal, at least until profound decreases in renal function occur.

Bioelectrical impedance analysis (BIA) may detect early changes in the extracellular volume when other clinical indicators, such as edema, are not evident, especially in early stages of CKD. Bellizzi et al. performed anthropometry and BIA in an outpatient CKD population and found, compared with healthy subjects, patients with CKD had higher total body water, even in early phases of renal disease.[12] A recent prospective observational study using Chronic Renal Insufficiency Cohort, which included patients with mean estimated GFR of 20–70 mL/min/1.73 m^2, found BIA-derived measures of tissue hydration were significantly associated with death and incident heart failure.[13] More data are required, however, to validate these measures in patients with CKD.

CONTROL SYSTEMS

Several physiologic phenomena are involved in the normal control of sodium metabolism by the kidneys (Table 39.1). When renal function is reduced, there must be quantitative changes in these factors to maintain sodium balance.

Increased Fractional Excretion of Sodium

As patients develop CKD with a slowly progressive course, they do not usually develop either edema or sodium depletion. If sodium intake remains constant and the number of functioning nephrons decreases, then sodium excretion per nephron must increase.

TABLE 39.1 Factors Affecting Renal Sodium Excretion

1. Glomerular filtration rate
2. Aldosterone
3. Peritubular physical factors
4. Renal sympathetic nerve activity
5. Natriuretic peptides
6. Prostaglandins
7. Others (AVP, endothelin, nitric oxide)

Slatopolsky and colleagues studied subjects with CKD with GFR between 3 and 25 mL/min on a 1400 and a 2800 mg/day sodium diet.[14] The subjects were able to maintain external sodium balance without a change in GFR. Calculations suggested that small, imperceptible increases in GFR could not have accounted for the doubling of sodium excretion when switching from the lower to the higher sodium diet. Therefore, a decrease in tubular reabsorption, or increase in excretion, must have occurred. A similar response to saline infusion was observed.

Role of Mineralocorticoids

Aldosterone levels are often elevated in CKD. However, aldosterone *per se* is not responsible for adaptation to changes in sodium intake. In the studies by Slatopolsky and colleagues, half of the subjects were maintained on a high fixed dose of exogenous mineralocorticoid, and the ability to maintain sodium balance when increasing dietary sodium was preserved.[4] In CKD, increased aldosterone secretion is probably much more important for maintaining potassium homeostasis than sodium balance.[15]

Natriuretic Peptides

Three types of natriuretic peptides are involved in sodium homeostasis—atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide. The release of these peptides is caused by atrial and ventricular wall stretch, and they act to facilitate sodium excretion in the collecting tubule. Thus, to maintain sodium homeostasis in the face of decreasing renal function, increased secretion of natriuretic peptides occurs.

The most useful biomarkers to assess the status of the natriuretic peptide system in heart failure are BNP and NT-proBNP. Ventricular myocytes synthesize pre-proBNP, a 134 amino acid peptide, which is then cleaved to proBNP and a 26 amino acid fragment.

ProBNP, the secreted peptide, is cleaved by corin to yield BNP and an N-terminal, 76 amino acid fragment NT-proBNP. NT-proBNP has a longer circulating half-life than does BNP. It is often the biomarker of choice. However, NT-proBNP is cleared by the kidneys alone, and so accumulates as GFR declines. In most settings, NT-proBNP is a better reflection of GFR than of left ventricular function.[16] In studies of patients with end-stage renal disease (ESRD), essentially all patients have elevated ANP, BNP, and NT-proBNP.[17] These levels fall after hemodialysis, depending on the dialysis membrane used, but the decrease in levels does not correlate well with changes in volume status during dialysis. Still, Sommerer et al. found that NT-proBNP levels were 3247 pg/mL in hemodialysis patients with euvolemia, but 11,988 pg/mL in those with volume overload.[18] BNP should probably not be used as a screening tool for left ventricular dysfunction in CKD but can be used to serially follow a patient when GFR remains relatively constant.

"Magnification Phenomenon"

To explain how the kidneys maintain sodium, or other solute, homeostasis in the face of a decreasing number of functioning nephrons as would occur in CKD, Bricker and his colleagues developed the "magnification phenomenon" theory. "This transformation in nephron function in uremia constitutes the central and pivotal feature of the magnification phenomenon, which is defined as follows: *the addition or loss from extracellular fluid of any given amount of a substance that is actively regulated by the kidneys will evoke an excretory response per nephron that varies inversely with the number of surviving nephrons.*"[19] Epstein et al., who employed thermoneutral water immersion to the neck to acutely redistribute blood volume to the central circulation, provided one of the best demonstrations of the magnification phenomenon.[20] This maneuver is comparable in effect to a sudden volume expansion by infusion of 2 L of normal saline. At baseline, CKD subjects with GFR between 3 and 65 mL/min had FE_{Na} of 2.8% compared with FE_{Na} of 0.5% in control subjects. During 4 hours of water immersion, FE_{Na} increased to 6.9% in the CKD subjects, whereas FE_{Na} increased only to 1.4% in control subjects. Therefore, natriuresis in response to acute volume expansion was magnified. However, despite this adaptation, natriuresis was incomplete within this time frame. CKD subjects excreted only 28 mEq Na in 4 hours, whereas normal subjects excreted 51 mEq Na in 4 hours.

Adaptation to Changes in Sodium Intake

CKD has long been considered to be a "salt wasting" condition. Unlike normal individuals, those with CKD were observed to be unable to reduce urinary sodium concentration to near zero when sodium intake was severely restricted. In 1966, Coleman et al. carefully studied 14 subjects with GFR between 3 and 20 mL/min during sodium restriction and water diuresis.[21] They were interested in determining whether sodium wasting was the consequence of an "inadequate capacity of the distal nephron to reabsorb sodium" or "an inability to lower the concentration of sodium in distal tubular fluid below a relatively high fixed minimal value." Urine sodium concentration (U_{Na}) during sodium restriction was relatively high, 9–27 mEq/L. The lowest daily urinary sodium excretion ($U_{Na}V$) in any subject with CKD was 12 mEq/day. 11 of 14 subjects with CKD were in net negative Na balance during the two to three weeks of study. In contrast, normal subjects reduced U_{Na} to between 2 and 8 mEq/L. Water diuresis increased urine flow without changing urinary sodium concentration, so that sodium excretion rose in direct proportion to urine flow. Salt wasting in CKD was attributed to the failure of the patients with CKD to reduce U_{Na} below a relatively high fixed value.

Danovitch, Bourgoignie, and Bricker challenged the concept that CKD is an intrinsically salt-wasting condition and, instead, posited that an increase in sodium excretion per nephron is an adaptive response to falling GFR in the face of constant sodium intake.[22] They studied five people with CKD during a stepwise, rather than abrupt, reduction in sodium intake. These subjects had GFR between 5 and 16 mL/min and had dietary Na intake slowly reduced over a period of 1½ or more months. They all achieved a final U_{Na} of <10 mEq/L and $U_{Na}V$ <10 mEq/day as long as initial sodium losses were replaced.

These seemingly contradictory sets of observation can be synthesized as follows. The adaptive response to decreasing GFR in the face of a constant (or high) sodium diet is an increase in the FE_{Na}. This, in turn, requires a reduction in sodium reabsorption per nephron. The precise cellular and nephronal mechanisms for this decrease in sodium reabsorption in CKD have not been completely characterized but are likely to be qualitatively similar to those operative in normal kidneys. The renal response has the appearance of impaired distal nephron tubular function. In most circumstances, this is protective and prevents or limits sodium retention and extracellular fluid volume expansion. However, if dietary sodium is suddenly or greatly reduced, the kidney cannot immediately adjust. Then, there will be a large net negative sodium balance, or salt wasting. Distal nephron tubular function is not permanently impaired because the kidney can adequately adjust to decreases in sodium intake if the changes occur slowly enough.

CLINICAL IMPLICATIONS

Rate of Altering Sodium Intake or Excretion

Neither sodium retention nor sodium wasting is a major clinical problem in CKD under steady-state conditions until GFR is severely diminished (i.e. CKD stage 5). Abrupt increases in sodium intake cause volume expansion and edema, but not when similar increases in sodium intake are gradually introduced. Correspondingly, volume depletion does not occur when sodium intake is gradually reduced or when diuretics are gradually introduced. However, sudden decreases in sodium intake or increases in sodium loss cannot be completely defended in advanced CKD. This may explain the apparent frequency of episodes of acute reductions in renal function (prerenal azotemia) in CKD with gastrointestinal fluid losses caused by vomiting or diarrhea.

Sodium and HTN in CKD

Hypertension is very common in CKD, occurring in 60−100% of patients.[23] In ESRD patients, control of extracellular fluid volume (volume status) through diet and dialysis prescription is the most effective means of controlling blood pressure (BP). Hypertension in those with lesser degrees of CKD is also believed to be a consequence of sodium retention.

Vasavada and Agarwal performed balance studies in subjects with stage 2 or 3 CKD to examine the relationship between sodium balance and BP.[24] On a constant sodium diet, they found an inverse relationship between GFR and extracellular volume (measured as extracellular water [ECW]/lean body weight [LBW] by electrical impedance). A single administration of furosemide or torsemide caused natriuresis, an 8% decrease in ECW, and increased plasma renin activity. During three weeks of diuretic therapy, ECW partially returned to baseline, BNP decreased by 45%, and BP was significantly lower. The mean decrease in systolic BP was 9 mm Hg. Although these studies did not follow subjects beyond 3 weeks, some reasonable extrapolations can be made. In CKD, as GFR worsens there is expansion of the extracellular fluid space which is associated with an increase in BP. Diuretic therapy can partially reverse the sodium retention and decrease BP.

Blood pressure response to dietary sodium intake varies among individuals. The concept of salt sensitivity is that a meaningful change in BP results from a change in dietary salt intake. Salt sensitivity has recently been suggested to be a function of nonosmotic storage of sodium in the skin interstitium and of endothelial dysfunction caused by deterioration of the endothelial glycocalyx layer.[25,26] Luft et al. have extensively reviewed the regulatory mechanisms regarding sodium handling in the skin interstitium, such as the role of negatively charged glycosaminoglycans in sodium hemostasis, which is independent of renal function. Immune cells such as macrophages function as local osmoregulators and hence regulate the interstitial electrolyte composition mainly by lymphatic clearance.[27,28]

Lymphatic capillaries act as buffers by clearing the excess interstitial sodium.[29] In a recent study done in 99 patients with mild to moderate CKD, skin sodium content was measured using ^{23}Na magnetic resonance imaging. Skin sodium content strongly correlated with systolic pressure and LVH and was a better predictor of LVH than BP or total body hydration (measured by bioimpedance spectroscopy).[30] In another study, patients with refractory hypertension had increased skin sodium content.[31] Whether dietary sodium restriction or diuretic use can lead to a decrease in the skin sodium content has not yet been evaluated.

The glycocalyx is a protective layer on the endothelial (luminal) surface of blood vessels, which prevents adhesion of circulating red blood cells. The glycocalyx is a negatively charged biopolymer composed of heparan sulfate residues, which has a capacity to buffer sodium. The glycocalyx also selectively controls endothelial sodium permeability. A proposed mechanism for salt sensitivity is that a disrupted glycocalyx has a low buffering capacity and increased permeability that can lead to sodium accumulation in the interstitial space. Kumpers et al. found that CKD was associated with reduced endothelial glycocalyx integrity, which likely puts this population at increased risk of salt sensitivity.[32]

Sodium intake is also an important modulating factor for BP in patients being treated with antihypertensive medications. Heeg et al. examined the effect of the angiotensin-converting enzyme inhibitor lisinopril in nondiabetic, proteinuric kidney disease.[33] When subjects increase, sodium intake from 50 to 200 mmol/day, BP increased 3%. Importantly, high sodium intake also abolished the lisinopril-induced decrease in proteinuria.

PROGRESSION OF CKD

The links between hypertension and progression of CKD and between sodium and hypertension are well recognized. Higher BP is correlated with greater risk for progression of CKD.[34,35] As CKD worsens, a greater proportion of patients develop hypertension.[36] Therefore, sodium restriction would seem prudent in CKD. Some authors also suggest that sodium might have direct microcirculatory effects (i.e. glomerular) that would be harmful in CKD.[37,38]

A double-blind, placebo-controlled, randomized cross-over trial was conducted assessing the effect of high and low sodium diets on ambulatory BP and

extracellular volume.[39] Salt restriction of 60–80 mmol compared with 180–200 mmol resulted in a mean reduction in the BP of 10/4 mm Hg in three weeks. Extracellular fluid volume and body weight were reduced as well. Patients with CKD were more sensitive to this intervention. A larger study with longer follow-up needs to be conducted to confirm these findings. However, this study emphasizes the role of sodium restriction in patients with CKD as a modifiable risk factor.

Proteinuria is a generally accepted intermediate endpoint in studies of the risk for progression of CKD. In the above study, those randomized to a low salt diet also had a significant reduction in proteinuria and albuminuria.[38] The effects of lisinopril to reduce proteinuria can be abrogated by high sodium intake. The antiproteinuric effects of the calcium channel antagonist diltiazem can also be abrogated by a high sodium intake, apparently independent of any effect on BP.[40] In an important study of nondiabetic, proteinuric renal disease, Vogt et al. observed that losartan lowered proteinuria by about 30% and that a low sodium diet (1200 mg) decreased proteinuria by 22%.[41] Combining diet with angiotensin blockade lowered proteinuria by 55% such that sodium restriction and angiotensin blockade were additive. Hydrochlorothiazide (25 mg daily) could be substituted for the low sodium diet with equivalent benefits.

CLINICAL GUIDELINES

In CKD, sodium balance is best maintained by following the guidelines outlined in Table 39.2. The NKF KDOQI (National Kidney Foundation Kidney Disease Outcomes Quality Initiative) Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease recommends that dietary sodium intake be limited to no more than 2.4 g/day (100 mmol/day).[42] This recommendation is based on strong evidence that shows that the altered sodium handling in CKD has a major role in hypertension in CKD. The specific recommendation of <100 mmol/day is based on the results of the DASH-Sodium Trials.[43]

The KDIGO (Kidney Disease: Improving Global Outcomes) Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease recommends lowering sodium intake to <2 g/day (90 mmol/day), a level not very different from the KDOQI recommendation.[44] These guideline authors cite the observations that lowering sodium intake reduces blood pressure in the general population, and that CKD patients have sodium retention that is associated with an elevation in BP. Both guidelines warn that some patients with tubulointerstitial disease may have true salt wasting and need to be carefully observed for signs of volume depletion when dietary sodium is restricted.

There is a growing emphasis on reversing the metabolic acidosis that usually accompanies CKD to prevent bone and muscle disease. The 2003 KDOQI Guidelines state that in CKD patients "serum levels of total CO_2 should be maintained at ≥22 mEq/L (22 mmol/L). If necessary, supplemental alkali salts should be given to achieve this goal."[45] The KDIGO Guidelines make a nearly identical recommendation.[34] Sodium bicarbonate administration causes extracellular fluid expansion. Although almost all Na administered as sodium chloride is retained within the extracellular space, approximately three-fourth of Na administered as sodium bicarbonate remains in the extracellular space.[46,47] Practically speaking, there is little difference between NaCl and $NaCO_3$.[48] Therefore, if one prescribes three 650 mg sodium bicarbonate tablets daily to treat low serum bicarbonate, this represents a sodium load of about 500 mg.

TABLE 39.2 Clinical Guidelines for Maintenance of Sodium Balance in CKD

1. Limit dietary sodium intake to 2.0–2.4 g/day
2. Use diuretics to manage edema or hypertension
3. Do not make sudden or large changes in sodium intake or excretion. Rather, make stepwise changes to allow for renal adaptation

Use of Diuretics

In addition to dietary sodium restriction, diuretics have an important role in the treatment of hypertension and edema in CKD patients. The KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease states "Diuretics are useful in the management of most patients with CKD. They reduce ECF volume; lower blood pressure; potentiate the effects of ACE inhibitors, ARBs, and other antihypertensive agents; and reduce the risk of CVD in CKD."[25] Thiazide diuretics, given once daily, are recommended for those with GFR >30 mL/min. Loop diuretics, given once or twice daily, are recommended for those with GFR <30 mL/min. Loop diuretics can be combined with thiazides for those with ECF volume expansion and edema.

Effects of Other Drugs

Use of vasodilators for hypertension may result in the development of edema, even at higher levels of GFR. This effect can certainly be observed in patients with advanced CKD. Similarly, inhibition of cyclooxygenase by NSAIDS frequently causes sodium retention and edema in normal subjects. This effect can also occur in CKD patients. The effect in CKD may be magnified if NSAIDS result in a marked decrease in GFR.[49]

CONCLUSION

Sodium balance is reasonably well maintained in CKD until renal function is seriously diminished. Patients do not usually develop either edema or sodium depletion. The adaptive response to decreasing GFR in the face of a constant (or high) sodium diet is an increase in the fractional excretion of sodium (FE_{Na}). This, in turn, requires a reduction in sodium reabsorption per nephron. In most circumstances, this is protective and prevents or limits sodium retention and extracellular fluid volume expansion. However, if dietary sodium is suddenly or greatly reduced, the kidney cannot immediately adjust. Distal nephron tubular function is not permanently impaired because the kidneys can adequately adjust to decreases in sodium intake if the changes occur slowly. Hypertension is very common in CKD. Control of extracellular fluid volume through diet, and dialysis prescription in the case of ESRD, is the most effective means of controlling blood pressure. The KDOQI Clinical Practice Guidelines recommends that dietary sodium intake be limited to no more than 2.4 g/day in patients with CKD.

References

1. McDonald KM, Rosenthal A, Schrier RW, et al. Effect of interruption of neural pathways on renal response to volume expansion. *Am J Physiol* 1970;**218**:510–7.
2. Brenner BM, Stein JH, editors. *Atrial natriuretic peptide. Contemp issues nephrol*, vol. 21. Churchill Livingstone; 1989.
3. Lindheimer MD, Lalone RC, Levinsky NG. Evidence that an acute increase in glomerular filtration has little effect on sodium excretion in the dog unless extracellular volume is expanded. *J Clin Investig* 1974;**46**:256–65.
4. Davis JO. A critical evaluation of the role of receptors in the control of aldosterone secretion and sodium excretion. *Prog Cardiovasc Dis* 1961;**4**:27–46.
5. Wright FS. Flow-dependent transport processes: filtration, absorption, secretion. *Am J Physiol* 1982;**243**:F1–11.
6. Kirschenbaum MA, Stein JH. The effect of inhibition of prostaglandin synthesis on urinary sodium excretion in the conscious dog. *J Clin Investig* 1976;**57**:517–21.
7. Zeidel ML, Brady HR, Kone BC, et al. Endothelin, a peptide inhibitor of Na+-K+ -ATPase in intact renal tubular cells. *Am J Physiol* 1989;**257**:C1101–7.
8. Stoos BA, Carretero OA, Farhy RD, et al. Endothelium-derived relaxing factor inhibits transport and increases cGMP content in cultured mouse cortical collecting duct cells. *J Clin Investig* 1992; **89**:761–5.
9. de Wardener HE, Mills IH, Clapham WF, Hayter CJ. Studies on the efferent mechanism of the sodium diuresis which follows the administration of intravenous saline in the dog. *Clin Sci* 1961;**21**: 249–58.
10. Mitch WE, Wilcox CS. Disorders of body fluids, sodium and potassium in chronic renal failure. *Am J Med* 1982;**72**:536–50.
11. Stella P, Manunta P, Mallamaci F, et al. Endogenous ouabain and cardiomyopathy in dialysis patients. *J Intern Med* 2008;**263**: 274–80.
12. Bellizzi V. Early changes in bioelectrical estimates of body composition in chronic kidney disease. *J Am Soc Nephrol* 2006; **17**:1481–7.
13. Bansal N, Zelnick LR, Himmelfarb J, Chertow GM. Bioelectrical impedance analysis measures and clinical outcomes in CKD. *Am J Kidney Dis* 2018;**72**:662–72.
14. Slatopolsky E, Elkan IO, Weerts C, Bricker NS. Studies on the characteristics of the control system governing sodium excretion in uremic man. *J Clin Investig* 1968;**47**:521–30.
15. Keane WF, Anderson S, Aurell M, de Zeeuw D, Narins RG, Povar G. Angiotensin converting enzyme inhibitors and progressive renal insufficiency: current experience and future directions. *Ann Intern Med* 1989;**111**:503–16.
16. Mark PM, Stewart GA, Gansevoort RT, Petrie CJ, McDonagh TA, Dargie HJ, et al. Diagnostic potential of circulating natriuretic peptides in chronic kidney disease. *Nephrol Dial Transplant* 2006;**21**: 402–10.
17. Khalifeh N, Haider D, Horl WH. Natriuretic peptides in chronic kidney disease and during renal replacement therapy: an update. *J Investig Med* 2009;**57**:33–9.
18. Sommerer C, Beimler J, Schwenger V, et al. Cardiac biomarkers and survival in haemodialysis patients. *Eur J Clin Investig* 2007;**37**: 339–434.
19. Bricker NS, Fine LG, Kaplan M, Epstein M, Bourgoignie J, Light A. "Magnification phenomenon" in chronic renal disease. *N Engl J Med* 1978;**299**:1287–93.
20. Epstein M, Hoffman D, DeNunzio AG. Evidence for operation of the magnification phenomenon in patients with chronic renal insufficiency. *Miner Electrolyte Metab* 1983;**9**:62–8.
21. Coleman AJ, Arias M, Carter NW, Rector Jr FC, Seldin DW. The mechanism of salt wastage in chronic renal disease. *J Clin Investig* 1966;**45**:1116–25.
22. Danovitch GM, Bourgoignie J, Bricker NS. Reversibility of the "salt-losing" tendency of chronic renal failure. *N Engl J Med* 1977; **296**:14–9.
23. Buckalew Jr VM, Berg RL, Wang SR, et al. Prevelance of hypertension in 1,795 subjects with chronic renal disease: the modification of diet in renal disease study baseline cohort. Modification of diet in renal disease study group. *Am J Kidney Dis* 1996;**28**: 811–21.
24. Vasavada N, Agarwal R. Role of excess volume in the pathophysiology of hypertension in chronic kidney disease. *Kidney Int* 2003; **64**:1772–9.
25. Olde Engberink RHG, Rorije NMG, Homan van der Heide JJ, van den Born B-JH, Vogt L. Role of the vascular wall in sodium homeostasis and salt sensitivity. *J Am Soc Nephrol* 2015;**26**(4):777–83.
26. Oberleithner H, Wilhelmi M. Vascular glycocalyx sodium store – determinant of salt sensitivity? *Blood Purif* 2015;**39**:7–10.
27. Wiig H, Luft FC, Titze JM. The interstitium conducts extrarenal storage of sodium and represents a third compartment essential for extracellular volume and blood pressure homeostasis. *Acta Physiol* 2018;**222**.
28. Titze J, Luft FC. Speculations on salt and the genesis of arterial hypertension. *Kidney Int* 2017;**91**:1324–35.
29. Wiig H, Schröder A, Neuhofer W, et al. Immune cells control skin lymphatic electrolyte homeostasis and blood pressure. *J Clin Investig* 2013;**123**:2803–15.
30. Schneider MP, Raff U, Kopp C, et al. Skin sodium concentration correlates with left ventricular hypertrophy in CKD. *J Am Soc Nephrol* 2017;**28**:1867–76.

31. Kopp C, Linz P, Dahlmann A, et al. 23Na magnetic resonance imaging- determined tissue sodium in healthy subjects and hypertensive patients. *Hypertension* 2013;**61**:635–40.
32. Padberg JS, Wiesinger A, di Marco GS, et al. Damage of the endothelial glycocalyx in chronic kidney disease. *Atherosclerosis* 2014; **234**:335–43.
33. Heeg JE, de Jong PE, van der Hem G, de Zeeuw D. Efficacy and variability of the antiproteinuric effect of ACE inhibition by lisinopril. *Kidney Int* 1989;**36**:272–9.
34. Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. *N Engl J Med* 1996;**334**:13–8.
35. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of diet in renal disease study group. *N Engl J Med* 1994;**330**:877–84.
36. Blythe WB. Natural history of hypertension in renal parenchymal disease. *Am J Kidney Dis* 1985;**5**:A50–6.
37. Weir MR, Fink JC. Salt intake and progression of chronic kidney disease: and overlooked modifiable exposure? A commentary. *Am J Kidney Dis* 2005;**45**:176–88.
38. Krikken JA, Laverman GD, Navis G. Benefits of dietary sodium restriction in the management of chronic kidney disease. *Curr Opin Nephrol Hypertens* 2009;**18**:531–8.
39. McMahon EJ, Bauer JD, Hawley CM, et al. A randomized trial of dietary sodium restriction in CKD. *J Am Soc Nephrol* 2013;**24**: 2096–103.
40. Bakris GL, Smith A. Effects of sodium intake on albumin excretion in patients with diabetic nephropathy treated with long-acting calcium antagonists. *Ann Intern Med* 1996;**125**:201–4.
41. Vogt L, Waanders F, Boomsma F, de Zeeuw D, Navis G. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. *J Am Soc Nephrol* 2008;**19**:999–1007.
42. KDOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. http://www.kidney.org/professionals/KDOQI/guidelines_bp/index.htm on.
43. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. DASH-sodium collaborative research group. *N Engl J Med* 2001;**344**:3–10.
44. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Intl Suppl* 2012;**2**: 337–414.
45. KDOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. http://www.kidney.org/professionals/KDOQI/guidelines_bone/index.htm on.
46. Ernest D, Belzberg AS, Dodek PM. Distribution of normal saline and 5% albumin infusions in septic patients. *Crit Care Med* 1999; **27**:46–50.
47. Swan RC, Axelrod DR, Seip M, Pitts RF, Madiso H. Distribution of sodium bicarbonate infused into nephrectomized dogs. *J Clin Investig* 1955;**34**:1795–801.
48. Lorenz JM, Kleinman LI, Disney TA. Lack of anion effect on volume expansion natriuresis in developing canine kidney. *J Dev Physiol* 1986;**8**:395–410.
49. Toto RD, Anderson SA, Brown-Cartwright D, Kokko JP, Brater DC. Effects of acute and chronic dosing of NSAIDs in patients with renal insufficiency. *Kidney Int* 1986;**30**:760–8.

QUESTIONS AND ANSWERS

Question 1

A 73-year-old man has new complaints of ankle swelling. He has stable CKD stage 3, thought to be a consequence of long-standing hypertension, and a past history of myocardial infarction at age 69. He has otherwise been quite healthy and active and still works full time as a financial advisor. On physical examination, his BP is 143/89 mm Hg, heart rate 72 bpm, and O_2 saturation 98%. Because of a thick neck, it is difficult to estimate central venous pressure. His lungs have rare basilar rales and no wheezes, his heart rate rhythm is normal without murmurs, and his abdomen is obese without a palpable liver. His pulses are intact, and he has trace ankle edema.

Laboratory:

Electrolytes normal
Glucose 95 mg/dL
S[Cr] 1.7 mg/dL
Estimated GFR 44 mL/min/1.73 m^2
Urinalysis—no blood or protein

Which **one** of the following is true regarding his condition?

A. He should be treated for deep venous thrombosis
B. His edema is caused by impaired sodium excretion due to CKD
C. He should be given a prescription for furosemide 40 mg daily and told to return only if his edema worsens
D. He should be evaluated for liver disease or heart failure
E. Small amounts of peripheral edema are normal for men in this age group

Answer: D

A is incorrect because bilateral edema is rare in deep venous thrombosis and there is nothing in the history or examination to suggest that diagnosis. **B** is incorrect because sodium balance is usually preserved until greater losses of GFR. **C** is incorrect because one should not treat this patient without further consideration of the possible causes of sodium retention, which could be serious.

D is correct. Because mild to moderate CKD should not cause sodium retention, other possibilities must be considered. These include heart failure, especially in a patient with known coronary heart disease. Cirrhosis is also a possibility that needs to be further explored. **E** is not true and a specific etiology is usually responsible.

Question 2

A 59-year-old woman with a number of chronic illnesses complains of recent onset of exertional dyspnea. She has a history of type 2 diabetes mellitus, CKD stage 4, hypertension, mitral regurgitation, obesity, and asthma. Her dyspnea has not responded to her asthma inhaler. She has chronic leg swelling which has not worsened. Her diabetes has been under good control. She is an imprecise historian. Physical examination reveals BP 132/83 mm Hg, heart rate 77 bpm, respiratory rate 12 per minute, O_2 saturation 95%. She is obese and her neck veins are difficult to evaluate. Her lungs have a few rales in the mid-left without wheezes. Her heart sounds are distant with a grade 4/6 systolic murmur. An S3 is noted. She has 1−2+ lower extremity edema.

Laboratory:

Na 143 mEq/L
K 4.8 mEq/L
Cl 109 mEq/L
HCO_3 20 mEq/L
Glucose 139 mg/dL
S[Cr] 2.7 mg/dL (unchanged from baseline)
Estimated GFR 20 mL/min/1.73 m^2
NT-proBNP 2472 pg/mL (normal 0−125 pg/mL)

Which **one** of the following is true regarding her condition?

A. She has decompensated heart failure because her NT-proBNP is elevated, reflecting ventricular distension
B. She probably has asthma because her S[Cr] has not increased
C. The NT-proBNP is not useful in this setting
D. She has diabetic ketoacidosis because she has an elevated anion gap
E. Obesity can be ruled out because it does not cause dyspnea

Answer: C

A is incorrect. NT-proBNP is certainly elevated in decompensated heart failure and in a person with normal kidney function this value would be strong evidence for congestive heart failure. However, NT-proBNP is excreted by the kidneys. In patients with advanced CKD, NT-proBNP is a better indicator of GFR than of left ventricular function, and in such patients it should not be used to diagnose heart failure. **B** is incorrect because she has no wheezes and there is no constant relationship between asthma and renal function. **D** is incorrect because her blood glucose is not markedly elevated and she has only a small anion gap which is consistent with CKD alone. **E** is incorrect because obesity, often associated with deconditioning, is a frequent cause of dyspnea.

Question 3

A 46-year-old man with idiopathic membranous nephropathy and CKD stage 4 has more difficulty in controlling blood pressure. He has recently been taking lisinopril 40 mg daily, metoprolol 100 mg twice daily, and furosemide 40 mg daily. He has proteinuria less than 500 mg/24 h and BP greater than 150/95 mm Hg on several occasions. He does not wish to take additional medications. His physician counseled him to restrict his sodium intake, which was estimated to exceed 4 g daily because of a diet based on fast foods and canned goods.

The patient vowed to get his diet and blood pressure under control, started cooking all his own meals, and eliminated prepared foods, high sodium foods, and added salt from his diet. A dietician later estimated that his daily sodium intake was now less than 1500 mg. When he saw his physician three weeks later for reevaluation, his BP was 123/78 mm Hg but S[Cr] had increased from 3.0 mg/dL (estimated GFR 24 mL/min/1.73 m^2) to 4.5 mg/dL (estimated GFR 16 mL/min/1.73 m^2). He claims to feel well, but misses salty foods. Urinalysis shows trace protein, no cells or casts. Electrolytes were normal.

Which **one** of the following is true regarding the decrease in his kidney function?

A. He probably has acute interstitial nephritis from one of his medications
B. He probably has prerenal azotemia because of intravascular volume depletion
C. He would have developed the same problem even if he had gradually decreased his dietary sodium over a period of several weeks
D. He needs to start hemodialysis
E. He should be given one liter of normal saline immediately

Answer: B

A is incorrect because he is taking no new medications and his urinalysis is unchanged. **B** is correct. He decreased his sodium intake very rapidly and by a large amount. His kidneys could not adapt rapidly enough so he developed large urinary sodium losses and intravascular volume depletion leading to prerenal azotemia. **C** is incorrect because a gradual reduction in sodium intake would have allowed his kidneys to adapt without incurring large net sodium losses. **D** is incorrect because dialysis is not indicated at this level of renal function in the absence of symptoms and because the change in renal function should be reversible if his sodium intake is slowly liberalized. **E** is incorrect because there is no urgency to reverse the volume depletion and because sudden overcorrection could lead to edema or heart failure.

CHAPTER

40

Potassium Metabolism in Chronic Kidney Disease

Biff F. Palmer[a], *Deborah J. Clegg*[b]

[a]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, United States;
[b]University of California at Los Angeles, Medical Center, Los Angeles, CA, United States

Abstract

Adaptive increases in renal and gastrointestinal excretion of K^+ help to prevent hyperkalemia in patients with chronic kidney disease (CKD) as long as the glomerular filtration rate (GFR) remains >15–20 mL/min. In these patients K^+ balance is maintained by increased K^+ secretion per functioning nephron, which is mediated in part by elevated plasma K^+ concentration, aldosterone, increased flow rate, and enhanced Na^+–K^+-ATPase activity. Fecal losses of potassium also increase in CKD patients. These adaptive mechanisms are effective in preventing hyperkalemia, provided that urine output is in excess of 600 mL/day. However, limits of adaptation render the CKD patient susceptible to hyperkalemia with even minor perturbations in these factors. Such is the case in patients with diabetes, where decreased mineralocorticoid activity is often an early finding caused by hyporeninemic hypoaldosteronism, or in patients primarily with renal tubular injury, as in tubulointerstitial renal disease. In these settings, hyperkalemia often develops with only mild or moderate reductions in GFR. Once the GFR falls to <15 mL/min, an inflection point is reached whereby small incremental losses in renal function require progressively steeper rises in steady state S[K] to maintain total body K^+ balance. Certain medications can impair potassium handling and excretion in CKD patients. At this level of renal function the impact of factors known to adversely affect K^+ homeostasis is significantly magnified. In clinical practice hyperkalemia is usually the result of a combination of factors superimposed on renal dysfunction.

INTRODUCTION

This chapter deals with potassium (K^+) metabolism in patients with chronic kidney disease (CKD). After a description of the scope of the problem and brief discussion of normal renal K^+ homeostasis, the chapter outlines adaptations in renal K^+ handling, which characterize CKD. The approach to and treatment of K^+ disorders in CKD patients up to the point at which renal replacement therapy is required will be the focus of the chapter.

SCOPE OF THE PROBLEM

Hyperkalemia is typically defined as a serum potassium concentration (S[K]) of >5.0 or >5.5 mEq/L, with the upper limit of normal varying across guidelines and publications.[1–4] It is relatively uncommon to find hyperkalemia in individuals with normal renal function. In patients with CKD, however, the incidence ranges from 5% to 50%.[5] In patients with CKD loss of nephron mass is counterbalanced by an adaptive increase in the secretory rate of K^+ in remaining nephrons, such that K^+ homeostasis is generally well maintained until the glomerular filtration rate (GFR) falls below 15–20 mL/min.[6] More severe renal dysfunction invariably leads to K^+ retention and hyperkalemia unless dietary intake of K^+ is reduced. In a random sample of 300 CKD patients (serum creatinine concentration [S[Cr]] ranging from 1.5 to 6.0 mg/dL), excluding diabetics and those taking drugs that interfere with angiotensin II synthesis or effect, the incidence of hyperkalemia has been noted to be 55% (K^+ ≥5.5 mEq/L).[7]

The relationship between hyperkalemia and renal function has been documented in a large, retrospective Veterans Affairs (VA) study, where the incidence of hyperkalemia (≥5.5 mEq/L) was 8.9% in a control cohort (defined by an estimated glomerular filtration rate [eGFR] ≥60 mL/min/1.73 m^2) and increased to 20.7%, 42.1%, and 56.7% in patients with stage 3, 4, and 5 CKD, respectively.[8] Furthermore, the odds of hyperkalemia in patients with stage 3, 4, and 5 CKD were 2.24, 5.91, and 11.0, respectively. Comparable

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00040-1

results to the VA study were obtained from the Humedica database in an analysis of 1.7 million persons with S[K] measurements on 2 separate occasions from 2008 to 2012.[9,10] The prevalence of hyperkalemia, defined by the highest reported S[K] value ≥5.1 mEq/L during the study period, was 8.5% for subjects without CKD. By comparison the incidence of hyperkalemia progressively increased with advancing stages of CKD being 22.8%, 32.7%, 46.9%, 56.5%, and 68.7% in patients with CKD stage 3a, 3b, 4, 5, and end-stage renal disease (ESRD) respectively. The number of risk factors present in individuals significantly contributes to the variability in incidence rates, with the risk factors being increased age, diabetes mellitus, hypertension and/or heart failure, and the use of medications such as renin–angiotensin–aldosterone system (RAAS) inhibitors[11] (Table 40.1).

Although adaptive mechanisms in the CKD patient may attenuate cardiac toxicity from increased S[K], hyperkalemic events are still associated with an increased risk of death in this population.[8] The electrocardiogram in a hyperkalemic subject can progress from normal to ventricular tachycardia and asystole in a precipitous manner.[12] In the VA study, a hyperkalemic event increased the risk of death within 1 day across all groups, even those without CKD, because hyperkalemia can lead to cardiac arrhythmias and increased mortality.[8] There are data suggesting a U-shaped relationship between plasma K^+ and mortality, with mortality increasing at low and high plasma K^+, especially in those with cardiorenal manifestations including hypertension, CKD, and ESRD.[13] The frequency of hyperkalemia in the CKD patient makes a strong argument for early referral and management of these patients in a clinic environment focused on the management of this common electrolyte disorder.[14]

Although loss of kidney function is the single most important cause of hyperkalemia, in clinical practice this electrolyte disorder is usually the result of a combination of factors limiting renal K^+ excretion superimposed on renal dysfunction (Table 40.1). Such is the case in diabetic patients, where decreased mineralocorticoid activity is often an early finding due to hyporeninemic hypoaldosteronism or in advanced stages of heart failure with accompanying reductions in distal delivery of Na^+ combined with concurrent use of drugs that interfere with the RAAS. In these settings hyperkalemia is common and can develop with only mild or moderate reductions in the GFR. One study attempted to identify all of the factors known to interfere in K^+ homeostasis simultaneously present during a single clinic visit in a population of CKD patients.[5] These patients were receiving regular follow-up in a clinic specifically designed and structured to optimize the care of advanced CKD. Despite the focus of the clinic the mean S[K] was increased over 5.1 mEq/L in 54.2% of patients. Although the average eGFR of the entire study population was 14.4 mL/min/1.73 m^2, those with hyperkalemia had a significantly lower eGFR compared to those without (14.8 vs. 13.5 mL/min/1.73 m^2). In addition to worse renal function, hyperkalemic patients had significantly lower serum bicarbonate concentrations (22.5 vs. 24.1 mEq/L).

TABLE 40.1 Causes of Hyperkalemia

- Pseudohyperkalemia
- Cellular redistribution
  - Mineral Acidosis
  - Cell shrinkage (hypertonicity)
  - Deficiency of insulin
  - β-Blockers
  - Hyperkalemic periodic paralysis
  - Cell injury
- Excess Intake (very rare)
- Decreased Renal Excretion
  - Decreased distal delivery of Na^+ (oliguric renal failure)
  - Mineralocorticoid deficiency
  - Defect of cortical collecting tubule

NORMAL POTASSIUM HOMEOSTASIS

Potassium plays a key role in maintaining cell function. All cells possess a Na^+–K^+-ATPase, which pumps Na^+ out of the cell and K^+ into the cell. This leads to a K^+ gradient across the cell membrane ($K^+_{in} > K^+_{out}$), which is partially responsible for maintaining the potential difference across the membrane. This potential difference is important to the function of all cells, but it is especially important in excitable tissues such as nerve and muscle. For these reasons, the body has developed numerous mechanisms for defense of S[K]. Total body K^+ is approximately 50 mEq/kg, which in a 70 kg person would be 3500 mEq. The majority (98%) of this K^+ is within cells, with only 2% in the extracellular fluid. The normal concentration of K^+ in the extracellular fluid is 3.5–5.3 mEq/L. Large deviations from these values are not compatible with life. The typical American diet includes 50–100 mEq/day of K^+. Approximately 90% of the daily K^+ intake is excreted in the urine, while 10% is excreted in the GI tract. The kidney and gastrointestinal tract respond directionally when K^+ intake increases or decreases.

NORMAL RENAL POTASSIUM HANDLING

Potassium is freely filtered by the glomerulus. The bulk of filtered K^+ is reabsorbed in the proximal tubule and loop of Henle, such that only 10% of the filtered load

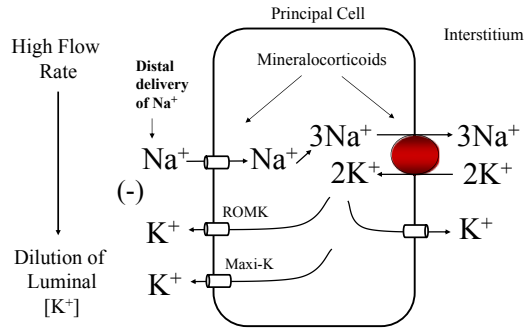


FIGURE 40.1 Model for renal regulation of K^+ secretion by the principal cell in the collecting tubule.

reaches the distal nephron. In the proximal tubule K^+ absorption is passive and is in rough proportion to Na^+ and water absorption. In the thick ascending limb of Henle, K^+ reabsorption occurs *via* transport on the apical membrane Na^+–K^+–$2Cl^-$ cotransporter. Secretion of K^+ occurs in the distal nephron primarily in the initial collecting duct and the cortical collecting duct. Under most physiologic and pathologic conditions, K^+ delivery to the distal nephron remains low and is fairly constant. By contrast, the rate of K^+ secretion by the distal nephron varies significantly and is highly regulated according to physiologic needs. K^+ secretion in the distal nephron is generally responsible for most of urinary K^+ excretion.

The specialized cell that is responsible for K^+ secretion in the initial collecting duct and the cortical collecting duct is the principal cell (Figure 40.1). The cellular determinants of K^+ secretion include the cell K^+ concentration, luminal K^+ concentration, transepithelial potential difference (voltage) across the luminal membrane, and the permeability of the luminal membrane for K^+. Two of the most important factors that influence these determinants are mineralocorticoid activity and the distal delivery of Na^+ and water.[15,16]

Aldosterone interacts with the intracellular mineralocorticoid receptor in the principal cell to stimulate K^+ secretion by affecting several of these cellular determinants. First, aldosterone stimulates Na^+ reabsorption across the luminal membrane by increasing the open probability of the epithelial sodium channel on the apical membrane, which increases the electronegativity of the lumen, thereby increasing the electrical gradient favoring K^+ secretion. Second, aldosterone increases intracellular K^+ concentrations by stimulating the activity of Na^+–K^+-ATPase in the basolateral membrane. Third, aldosterone directly increases the permeability of the luminal membrane to K^+. Thus, aldosterone increases the rate of K^+ secretion by increasing cell K^+ concentration, increasing luminal membrane K^+ permeability, and making the luminal potential more negative.

An increase in the distal delivery of Na^+ stimulates K^+ secretion by causing the luminal potential to become more negative. When K^+ is secreted in the collecting duct, the luminal K^+ concentration increases, which decreases the diffusion gradient and slows further K^+ secretion. At high luminal flow rates the same amount of K^+ secretion will be diluted by the larger volume, such that the increase in luminal K^+ concentration will be less, thus facilitating ongoing K^+ secretion.

Two populations of K^+ channels have been identified in the cells of the cortical collecting duct (Figure 40.1). The renal outer medullary K^+ channel is considered to be the major K^+ secretory pathway. This channel is characterized by having low conductance and a high probability of being open under physiologic conditions. The maxi-K^+ channel, or BK channel, is characterized by a large single channel conductance, which is relatively quiescent in the basal state. This channel becomes activated under conditions of increased flow. In addition to increased delivery of Na^+ and dilution of luminal K^+ concentration, recruitment of maxi-K^+ channels plays an important role in mediating flow-dependent increased K^+ secretion.

There are new data and evidence to suggest that the distal nephron can actually act as a "*K^+ sensor*," whereby small changes in extracellular K^+ concentration can lead to direct changes in the K^+ secretory mechanism through alterations in activity of the with no lysine family of kinases and their regulatory proteins SPAK and OxSR1.[17,18]

POTASSIUM HOMEOSTASIS IN ACUTE KIDNEY INJURY

There are a number of features characteristic of acute kidney injury (AKI), which makes hyperkalemia particularly common. When the cause is acute tubular necrosis or tubulointerstitial renal disease, there is often widespread injury to the late distal tubule and collecting duct, leading to direct injury of cells responsible for K^+ secretion. AKI is often associated with severe reduction in the GFR (<10 mL/min), which itself becomes rate limiting for K^+ secretion. The rapidity of renal functional loss precludes adequate time for normal renal and extrarenal adaptive mechanisms to adequately develop. In patients with more severe injury manifested clinically by oligoanuria, there is a marked reduction in distal delivery of salt and water, which contributes to decreased distal K^+ secretion. In nonoliguric AKI, hyperkalemia tends to be less common because distal delivery of salt and water is plentiful. Patients with AKI are more likely to have severe acidosis, increased catabolism, and tissue breakdown, all leading to release of intracellular K^+ into the extracellular compartment. This release of K^+ in the setting of impaired renal K^+

secretion makes life-threatening hyperkalemia a common occurrence in AKI patients.

POTASSIUM HOMEOSTASIS IN CKD

Potassium homeostasis is more complicated in CKD than in AKI. In addition to the decreased GFR and secondary decrease in distal delivery, there is nephron dropout and a smaller number of collecting ducts to secrete K^+. However, this is counterbalanced by an adaptive process in which the remaining nephrons develop an increased ability to excrete K^+. As a result hyperkalemia (S[K] >5.5 mEq/L) is uncommon in patients with CKD until the GFR falls below 15–20 mL/min.

Studies both in experimental animals and humans have provided insight into the nature and localization of the adaptive increase in renal K^+ secretion. In conscious dogs with a unilateral remnant kidney, K^+ secretion per nephron increases fourfold by 18 hours and approaches 85% of the control animals seven days after removal of the contralateral intact kidney[19] (Figure 40.2). The ability to maintain urinary K^+ secretion in the face of a marked reduction in functioning nephron mass requires the amount of K^+ excreted per unit GFR (fractional excretion of K^+) to markedly increase.

In a study of normokalemic patients with stage 4 CKD, the fractional excretion of K^+ was 126% compared with 26% in normal controls.[20] The fractional excretion of Na^+ in the two groups was 2.3% and 15%, respectively. Following the intravenous administration of amiloride, the fractional excretion of K^+ decreased by 87% in the patients with CKD compared with 19.5% in control patients. These findings support the idea that patients with CKD are able to maintain a normal S[K] through an adaptive increase in renal K^+ secretion that is largely amiloride sensitive.

Despite this adaptation, the ability to further augment K^+ secretion in response to an exogenous load is extremely limited, such that hyperkalemia can result from even modest increases in K^+ intake. When dogs with remnant kidneys are challenged with an acute intravenous infusion of K^+, the increment in renal K^+ secretion is approximately 50% less than in controls, and marked hyperkalemia develops.[21] In both the remnant and control groups renal K^+ excretion is directly related to the S[K], but the relationship is markedly attenuated in the remnant group. In the first 5 hours following the K^+ infusion, control animals excreted 65% of the K^+ load compared to only 35% in the remnant group. Nearly 24 hours is required to reestablish K^+ balance in dogs with reduced renal mass. During this time, plasma K^+ and aldosterone levels are significantly greater than in controls. Studies in patients

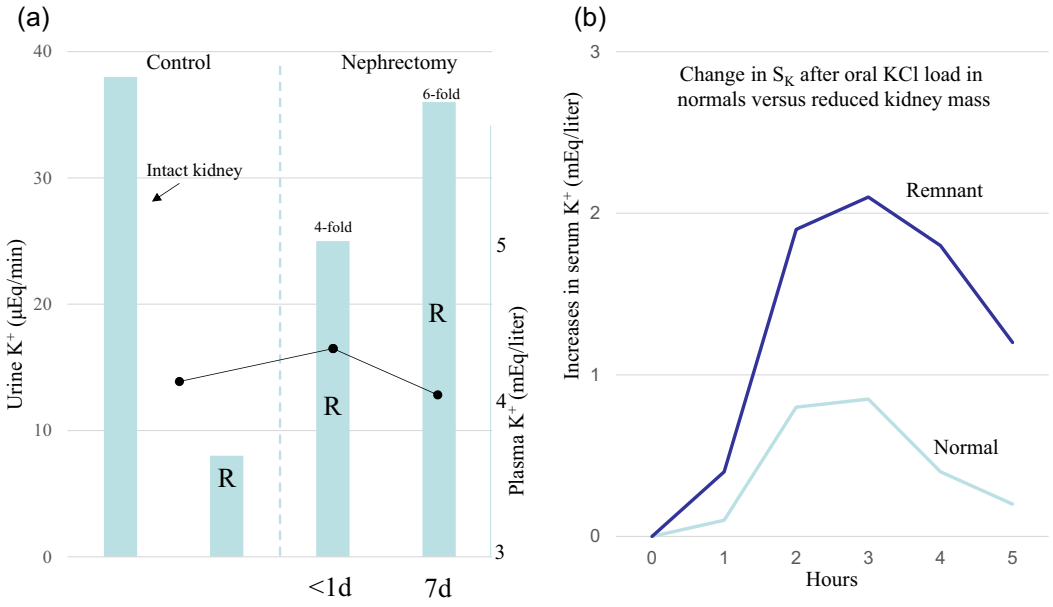


FIGURE 40.2 Studies in experimental animals show minimal change in the plasma potassium concentration following a reduction in renal mass due to an adaptive increase in potassium secretion by remaining nephrons (a). For this reason, hyperkalemia tends to be uncommon until the glomerular filtration rate (GFR) falls below 15 mL/min. The development of hyperkalemia with less severe reductions in GFR can be traced to one or all of the following: decreased distal Na^+ delivery, disturbances in the renin–angiotensin–aldosterone system, and/or abnormalities in the distal nephron. (b). Despite the adaptation, the ability to further augment K^+ secretion in response to an exogenous load is extremely limited, such that the increase in plasma K^+ concentration and time to normalization are both increased in the remnant kidney. *Adapted from references 21 and 23.*

with CKD also show a similar impairment in the ability to acutely excrete a K^+ load. Such patients develop more severe and prolonged hyperkalemia following a K^+ challenge.[22,23]

The nature of the adaptive process that facilitates K^+ excretion in patients with CKD is thought to be similar to the adaptive process that occurs in response to high dietary K^+ intake in normal subjects.[24] Chronic K^+ loading in animals augments the secretory capacity of the distal nephron so that renal K^+ excretion is significantly increased for any given plasma K^+ level. Increased K^+ secretion under these conditions occurs in association with structural changes characterized by cellular hypertrophy, increased mitochondrial density, and proliferation of the basolateral membrane in cells in the distal nephron and principal cells of the collecting duct. Increased S[K] and mineralocorticoids independently initiate the amplification process that is accompanied by an increase in Na^+–K^+-ATPase activity.

Studies in animal models show the cortical collecting duct is an important site of K^+ adaptation in surviving nephrons of animals with reduced renal mass. K^+ secretion is increased in perfused cortical collecting tubules taken from remnant kidneys of uremic rabbits fed a normal diet.[25] However, if dietary K^+ intake is reduced in proportion to the reduction in renal mass, this adaptation is prevented and K^+ secretory rates remain within the normal range. Reduction in renal mass leads to amplification of the basolateral membrane area and an increase in Na^+–K^+-ATPase activity similar to that described when dietary K^+ intake is increased in animals with intact kidneys.[26–28] Loss of renal mass also leads to an increase in Na^+ delivery and apical Na^+ transport in this segment.[29] Increased apical Na^+ entry provides a further stimulatory effect on Na^+–K^+-ATPase activity. Changes in S[K] and mineralocorticoids independently mediate these adaptive structural and functional changes.

Aldosterone plays an important role in the ability to augment K^+ secretion in the setting of CKD. Tubular hypertrophy, increased basolateral folding, and increased Na^+–K^+-ATPase activity in the collecting duct in remnant kidneys are similar to that in experimental models of chronic mineralocorticoid administration.[30] There is a wide variability in aldosterone levels in patients with CKD, with studies showing either increased, normal, or decreased values. Part of this variability is due to the failure to consider the prevailing plasma K^+ concentration and variations in Na^+ intake. In addition, many patients with CKD have low plasma renin activity. In this setting, impaired aldosterone secretion and hypoaldosteronism are the result of low circulating renin levels. When normalized for the plasma renin activity, levels of aldosterone are typically in the normal range when the GFR is $>50–60$ mL/min.[31] However, with more severe reduction in renal function there is a progressive increase in plasma aldosterone levels.

EXTRARENAL K^+ HOMEOSTASIS IN CKD

Under normal circumstances increases in plasma K^+ concentration following K^+ ingestion are minimized by physiologic mechanisms that shift K^+ into cells, before its excretion by the kidney. This maintenance of internal K^+ balance is primarily regulated by catecholamines, insulin, and to a lesser extent aldosterone. In pathologic states changes in blood pH and plasma tonicity also influence K^+ distribution within the body.

As renal function declines the cellular uptake of K^+ becomes an important defense against the development of hyperkalemia. Studies in humans and experimental models of reduced renal mass have produced conflicting results regarding whether disturbances in extrarenal K^+ disposal are a characteristic feature of CKD.[32] To the extent internal K^+ homeostasis is impaired, the defect cannot be attributed to increased cellular or total body K^+ content because these are either normal or often reduced.[33,34] Decreased intracellular K^+ content has been attributed to decreased activity of the Na^+–K^+-ATPase, which is a characteristic finding in uremia.[35,36] Studies in red blood cells taken from uremic patients show diminished activity of the pump, which can be reversed when cells are incubated in normal plasma. Pump activity has also been shown to improve following dialysis.[35,37–39] On the other hand, red blood cells taken from normal individuals and incubated in uremic plasma acquire the defect.

Studies in skeletal muscle from uremic patients show decreased K^+ concentration, increased Na^+ concentration, and decreased resting membrane potential.[40] After 7 weeks of hemodialysis, these physiologic parameters can be restored to normal, suggesting the presence of a circulating inhibitor of the Na^+-K^+-ATPase in some uremic patients.[41] In other patients, there may be a decrease in the number of pump sites rather than decreased activity. Decreased pump activity or decreased number of pumps may account for the impaired extrarenal K^+ disposal reported in some uremic patients.

Plasma norepinephrine and epinephrine concentrations as well as sympathetic nerve activity (at least to the leg muscles) are increased in patients with advanced CKD compared to normal controls.[42,43] In addition the metabolic clearance rate of insulin falls with loss of renal function.[44] The increase in circulating insulin and catecholamine levels may serve to attenuate uremia-induced alterations in cell function, which normally are responsible for sequestering K^+ in the intracellular compartment.[45]

By the time patients reach ESRD extrarenal K^+ homeostasis becomes more overtly impaired.[46] Fernandez et al. compared the disposition of an oral K^+ load (0.25 mEq/kg/body weight) in a group of dialysis patients and in normal controls.[47] The normal controls excreted 67% of the K^+ load within 3 hours and translocated 51% of the retained K^+ intracellularly. In contrast, the dialysis patients did not excrete any of the K^+ and only 21% of the retained K^+ was translocated intracellularly. The increment in plasma K^+ was significantly different between the two groups. The plasma K^+ concentration increased by 1.06 mEq/L in the dialysis patients, whereas only a 0.39-mEq/L increase was noted in the control group. The impairment in K^+ disposal persists even when the K^+ load is accompanied by oral glucose, although glucose-induced stimulation of insulin attenuates the maximal rise in S[K] levels.

GASTROINTESTINAL EXCRETION OF K^+ IN CKD

In patients with renal failure, a significant proportion of daily K^+ excretion occurs *via* the gastrointestinal tract. Gastrointestinal losses are important in maintaining K^+ balance in chronic dialysis patients because hemodialysis removes approximately 80−100 mEq/treatment (300 mEq/week) yet dietary K^+ intake is usually 400−500 mEq/week. In a balance study performed in patients treated with peritoneal dialysis, 25% of the daily K^+ intake was lost in the feces.[48,49] The amount of K^+ excreted in the stools correlates directly with the wet stool weight. Therefore, constipation should be avoided because it will decrease the gastrointestinal elimination of K^+ and increase the tendency toward hyperkalemia.

The mechanism of increased gastrointestinal K^+ loss is not known. The process appears to be due to active secretion, as it is unrelated to plasma K^+ or total body K^+.[50,51] Hemodialysis patients continue to have enhanced rectal K^+ secretion even after dialysis with their plasma K^+ being less than that of controls. Potassium transport in the large intestine was recently studied in ESRD patients using a rectal dialysis technique.[52] Rectal K^+ secretion was found to be threefold greater in ESRD patients compared to control patients with normal renal function. When barium (a K^+ channel inhibitor) was placed in the lumen, colonic K^+ secretion was reduced by 45% in the ESRD patients, whereas no effect was seen in the control group. Immunostaining using an antibody directed to the α-subunit of the high conductance K^+ channel protein revealed greater expression of the channel in surface colonocytes and crypt cells in the ESRD patients, whereas only a low level of expression was observed in the control group. These data are consistent with increased expression of K^+ channels as the mechanism for the adaptive increase in colonic K^+ secretion in ESRD patients.

Elevated levels of plasma aldosterone may play a role in stimulating the gastrointestinal excretion and cellular uptake of potassium in ESRD patients. Exogenous administration of mineralocorticoids decreases S[K] in anuric dialysis patients, presumably by increasing colonic potassium excretion.[53] In a prospective study, fludrocortisone administered at 0.1 mg/day was compared with no treatment in 21 hyperkalemic hemodialysis patients.[54] At the end of 10 months, the S[K] in the two groups was not statistically different. However, there was a decrease in S[K] compared with pretreatment values in patients who received the drug.

A recent study examined the effects of glycyrrhetinic acid food supplementation on the S[K] in a group of maintenance hemodialysis patients.[55] This substance inhibits the enzyme 11β-hydroxysteroid dehydrogenase II, which is found not only in the principal cells of the renal collecting duct but also epithelial cells in the colon. This enzyme converts cortisol to cortisone, thereby ensuring the mineralocorticoid receptor remains free to only interact with aldosterone, because cortisone has no affinity for the receptor. In 9 of 10 patients given the supplement there was a persistent decrease in measured predialysis S[K]. In addition, treatment with the supplement significantly decreased the frequency of severe hyperkalemia. These beneficial effects occurred without weight gain or increases in systemic blood pressure suggesting glycyrrhetinic acid supplementation may be of benefit in enhancing colonic K^+ secretion and minimizing the risk of hyperkalemia in dialysis patients.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) have both been reported to cause hyperkalemia in patients treated with hemodialysis and peritoneal dialysis.[56,57] The development of hyperkalemia with these drugs may be due to decreased colonic K^+ excretion resulting from lower circulating levels of aldosterone or decreased activity of angiotensin II. Enhanced colonic K^+ excretion in renal failure has been attributed to upregulation of angiotensin II receptors in the colon, suggesting that angiotensin II has a direct effect in stimulating colonic K^+ excretion.[58] Blocking the mineralocorticoid receptor with spironolactone given at a dose of 25 mg/day does not raise S[K] in hemodialysis patients.[59]

APPROACH TO THE HYPERKALEMIC PATIENT WITH CKD

Pseudohyperkalemia is an *in vitro* phenomenon due to the mechanical release of K^+ from cells during phlebotomy or specimen processing. This diagnosis is

made when the S[K] exceeds the plasma K^+ concentration by >0.5 mmol/L. Common causes of pseudohyperkalemia include fist clenching during phlebotomy, application of tourniquets, and use of small-bore needles. Pathologic causes of pseudohyperkalemia are mostly seen in the setting of hematologic disorders such as thrombocytosis and pronounced leukocytosis. The incidence of pseudohyperkalemia increases during the winter, when samples are likely to be exposed to lower ambient temperatures during transport. Higher ambient temperatures decrease the frequency of this complication. A spurious increase in plasma K^+ concentration should be considered when accompanied by a very low plasma Ca^{++} concentration. *In vitro* contamination with potassium ethylenediaminetetraacetic acid (K-EDTA), a liquid used as an anticoagulant in certain sampling tubes, can cause this problem through Ca^{++} chelation and simultaneous release of K^+.

After excluding pseudohyperkalemia, one must consider increased dietary intake of K^+ as the underlying cause of hyperkalemia. Dietary sources particularly enriched with K^+ include melons, citrus juice, and salt substitutes. Other hidden sources of K^+ reported to cause life threatening hyperkalemia include raw coconut juice (K^+ concentration of 44.3 mmol/L) and Noni juice (56 mEq/L). Although clay ingestion can cause hypokalemia due to binding in the gastrointestinal tract, river bed clay is K^+ enriched (100 mEq K^+ in 100 g clay) and can cause life-threatening hyperkalemia in CKD patients. Ingestion of burnt match heads (cautopyreiophagia) can also be a hidden source of K^+. This activity was found to add an additional 80 mmol of K^+ to one dialysis patient's daily intake and produced a plasma K^+ concentration of 8 mmol/L.

In the absence of pseudohyperkalemia or increased dietary K^+ intake, development of hyperkalemia in a previously stable CKD patient can be traced to one or more of three abnormalities: a primary decrease in distal delivery of salt and water, a primary decrease in mineralocorticoid levels, or an abnormal cortical collecting duct.[60]

Decreased Distal Delivery of Sodium

Mild to moderate reductions in renal perfusion do not typically cause distal delivery of Na^+ to fall to a level that impairs K^+ secretion sufficiently to result in clinically significant hyperkalemia. In untreated congestive heart failure S[K] is typically normal or high normal despite the reduction in distal Na^+ delivery as long as the impairment in cardiac function and renal perfusion is not severe. When such patients are treated with ACE inhibitors or ARBs, the fall in circulating aldosterone concentration will typically be counterbalanced by increased distal Na^+ delivery, so S[K] remains stable. The increase in distal Na^+ is due to the afterload-reducing effects of these drugs, causing an improvement in cardiac output and renal perfusion.

When renal perfusion becomes more severely reduced, as in intractable congestive heart failure, proximal reabsorption can become so intense that very little Na^+ escapes into the distal nephron. Lack of Na^+ availability can begin to impair renal K^+ secretion, particularly in the setting of CKD, where baseline aldosterone levels are often reduced and the capacity for increased production is limited.

Elderly patients are prone to intravascular volume depletion due to poor intake and impaired renal Na^+ conservation. The resultant decrease in distal Na^+ delivery put these patients at risk for hyperkalemia, because age is also associated with impaired release of renin and aldosterone in response to volume depletion.[61] This risk increases further with concurrent use of renin–angiotensin–aldosterone blockers.

Primary Decrease in Mineralocorticoid Activity

Decreased mineralocorticoid activity can result from disturbances that originate at any point along the RAAS. Such disturbances can be the result of a disease state or be due to effects of various drugs (Figure 40.3).

Hyporeninemic hypoaldosteronism is a common feature in CKD patients with a GFR of 20–60 mL/min, particularly in the setting of diabetes mellitus or interstitial renal disease. Hypoaldosteronism is primarily the result of reduced plasma renin and angiotensin II activity. In some patients plasma renin activity is normal, but the secretory response of aldosterone is blunted in response to angiotensin II infusion, suggesting an intra-adrenal defect.[62] In diabetic animals the impaired response of the zona glomerulosa cells to angiotensin II is caused by a postreceptor defect, specific to angiotensin II, because the aldosterone secretory response to ACTH is not diminished.[63]

In patients with normal renal function, hypoaldosteronism alone may not be sufficient to cause marked hyperkalemia, because any rise in S[K] will have a direct effect to enhance distal tubular K^+ secretion. This direct effect is diminished in the setting of CKD, suggesting hypoaldosteronism and decrease in renal function have synergistic effects in impairing renal tubular K^+ secretion.

Several factors have been proposed to cause both the renal and adrenal functional changes. These include a defect in prostaglandin production and/or the presence of volume expansion. Prostaglandins normally stimulate renin secretion by the juxtaglomerular cells in the kidney and facilitate the stimulatory effect of angiotensin II on aldosterone release in the adrenal gland.[64] Volume expansion promotes the release of atrial

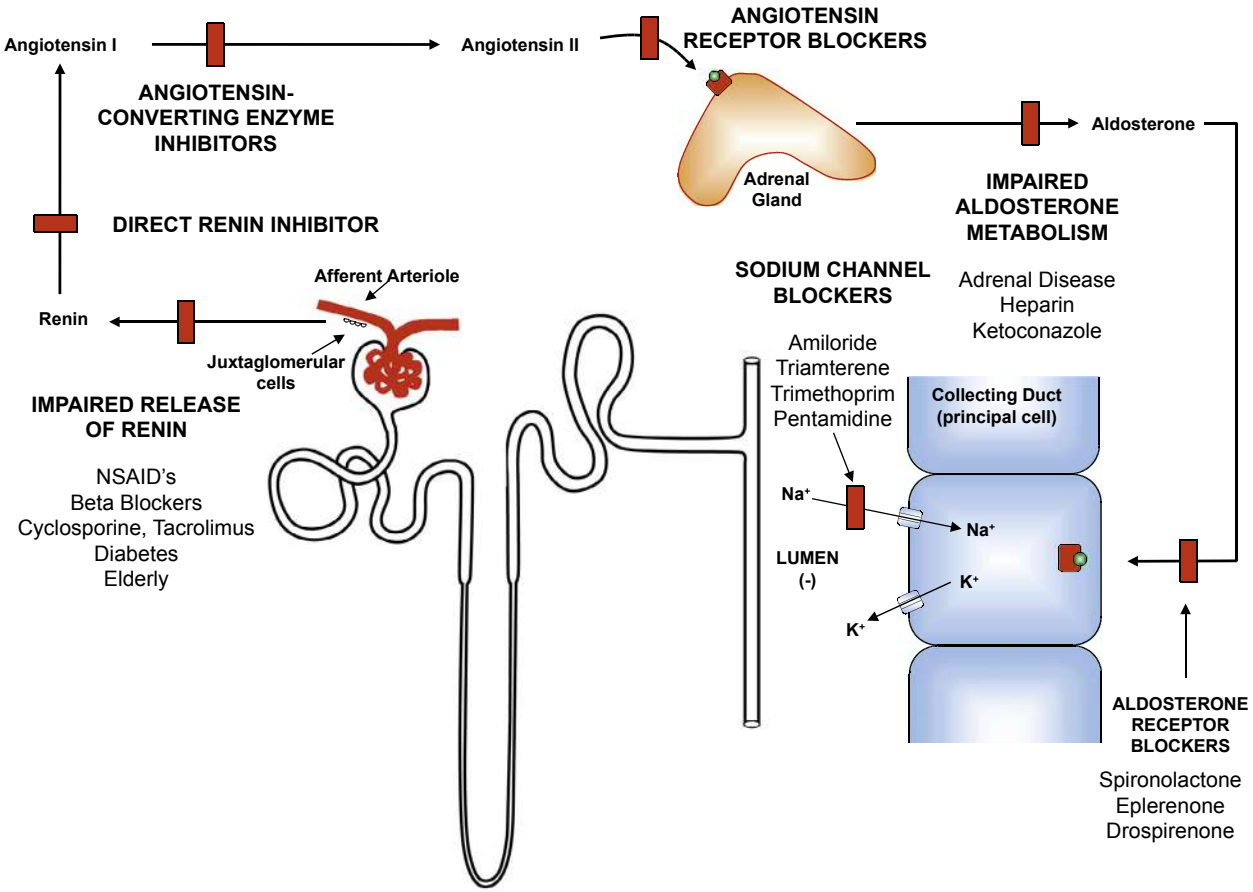


FIGURE 40.3 The renin–angiotensin–aldosterone system and regulation of renal K^+ excretion. Aldosterone binds to a cytosolic receptor in the principal cell and stimulates Na^+ reabsorption across the luminal membrane through a well-defined Na^+ channel. As Na^+ is reabsorbed the electronegativity of the lumen increases, thereby providing a more favorable driving force for K^+ secretion through an apically located K^+ channel. The permeability of the anion that accompanies Na^+ also influences K^+ secretion, with less permeable anions having a greater stimulatory effect on K^+ secretion. Disease states or drugs that interfere at any point along this system can impair renal K^+ secretion and increase the risk of hyperkalemia. In many patients this risk is magnified due to disturbances at multiple sites along this system.

natriuretic peptide, which in turn suppresses both renin secretion and aldosterone release.[65]

The ACE inhibitors and ARBs impair urinary potassium excretion by interfering with the stimulatory effect of angiotensin II on aldosterone secretion in the adrenal gland. The development of hyperkalemia is usually seen when mineralocorticoid levels are already decreased prior to the administration of the drugs, either as a result of a disease state or due to effects of other drugs (Table 40.2).

Hyperkalemia has been reported to develop in 44–73% of transplant patients treated with the immunosuppressive drugs cyclosporine or tacrolimus.[66] These drugs suppress renin release and directly interfere with renal K^+ secretion in the collecting duct.[67] Beta adrenergic blockade can predispose to the development of hyperkalemia through two potential mechanisms.[68] These drugs block the stimulatory effect of the sympathetic nervous system on renin release. In addition, these drugs can interfere with the cellular uptake of K^+ through decreased activity of Na^+–K^+-ATPase.[69]

DISTAL TUBULAR DEFECT

Certain interstitial renal diseases can affect the distal nephron specifically and lead to the development of hyperkalemia in the presence of only mild decreases in GFR and normal aldosterone levels. Amiloride and triamterene inhibit Na^+ transport, which makes the luminal potential more positive and secondarily inhibits K^+ secretion. A similar effect occurs with trimethoprim and accounts for the development of hyperkalemia following the administration of the antibiotic trimethoprim–sulfamethoxazole.[70] Spironolactone and eplerenone compete with aldosterone and thus block the mineralocorticoid effect.

TABLE 40.2 Risk Factors for Hyperkalemia

- Chronic kidney disease: risk is inversely related to GFR and increases substantially below an eGFR of 30 mL/min/1.73 m^2
- Diabetes mellitus*
- Decompensated congestive heart failure
- Medications
  - Inhibition of renin release from juxtaglomerular cells
    - Nonsteroidal anti-inflammatory drugs
    - Beta blockers
    - Calcineurin inhibitors: Cyclosporine, Tacrolimus
  - Inhibition of aldosterone release from the adrenal gland
    - Heparin
    - Ketoconazole
  - Mineralocorticoid receptor blockade
    - Spironolactone
    - Eplerenone
  - Blockade of epithelial sodium channel blocker in renal collecting duct
    - Amiloride
    - Triamterene
    - Trimethoprim
- K^+ supplements, salt substitutes, certain herbs, and K^+-enriched foods in setting of impaired renal excretion

**A spectrum of abnormalities in the renin–angiotensin–aldosterone system has been described in patients with diabetes mellitus, including hyporeninemic hypoaldosteronism as well as normal renin release but a diminished capacity to release aldosterone. Hypoaldosteronism combined with dysfunction of collecting ducts due to diabetic nephropathy and treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers put CKD patients at particularly high risk for hyperkalemia.* GFR, *glomerular filtration rate.*

TREATMENT OF HYPERKALEMIA IN THE CKD PATIENT

The initial approach is to review the patient's medication profile and whenever possible discontinue drugs that can impair renal K^+ excretion. Patients should be specifically questioned regarding the use of over-the-counter nonsteroidal anti-inflammatory drugs, as well as herbal remedies, because herbs may be a hidden source of dietary potassium. Patients should be placed on a low K^+ diet, with specific counseling against the use of K^+-containing salt substitutes. Diuretics are particularly effective in minimizing hyperkalemia. Diuretics enhance renal K^+ excretion by increasing the delivery of Na^+ to the collecting duct. In patients with a GFR greater than 30 mL/min, thiazide diuretics can be used. With more severe renal insufficiency loop diuretics are required.

In patients with CKD and metabolic acidosis, administration of sodium bicarbonate is an effective strategy to minimize increases in S[K]. Sodium bicarbonate increases renal K^+ excretion as a result of increased distal Na^+ delivery and will shift K^+ into cells as the acidosis is corrected. Ensuring that the patient is first on effective diuretic therapy will lessen the likelihood of developing volume overload as a complication of sodium bicarbonate administration.

The development of hyperkalemia after the administration of renin–angiotensin blockers is of particular concern because patients at highest risk for this complication are often the same ones who derive the greatest cardiovascular benefit. It is now commonplace to treat hypertension and decrease cardiovascular events in high-risk patients by using ACEIs and ARBs. After publication of the Randomized Aldactone Evaluation Study trial, which demonstrated a mortality benefit when an ACEI was added to an ARB, rates of hospitalization for hyperkalemia increased significantly, from 2.4/1000 patients in 1994 to 11.0/1000 patients in 2001.[71] Additionally, mortality related to hyperkalemia increased from 0.3 deaths/1000 patients to 2.0 deaths/1000 patients. This surge in hyperkalemia and its associated complications is in contrast to the relatively low rate of hyperkalemia of 2% noted in the trial, likely due to enrollment of patients at low risk for this complication. Additionally, study subjects had their laboratory values closely monitored, as well as were restricted from taking other drugs known to cause hyperkalemia. Given the positive findings obtained from the trial, physicians increased the number of prescriptions written for spironolactone. Unfortunately, similar precautions with respect to patient selection and monitoring were not employed in more general clinical settings.

Hyperkalemia resulting from RAAS blockers can pose a therapeutic dilemma because current guidelines for patients with CKD, heart failure, and hypertension recommend treatment with RAAS inhibitors, yet the risk of hyperkalemia often leads to modifications in dosing or even discontinuation of these effective medications.[1,3,72,73] For example, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines actually advocates use of ACEIs and ARBs at moderate to high doses because of their efficacy.[4] Despite these recommendations, most patients with CKD stage 3–4, heart failure, or diabetes mellitus are not receiving maximum/effective doses of RAAS inhibitors, due to the potential risk of hyperkalemia. In fact, data from a large retrospective analysis of a claims database in the US found that 62% of patients with at least one of these conditions received a lower than recommended dose of the RAAS inhibitor. Only 22% were receiving the recommended dose, and 15% had actually discontinued the medication.[9] The study found that those subjects receiving the labeled doses had their medication either down titrated or discontinued in 38% of cases, when the S[K] was 5.1–5.4 mEq/L. In 47% of cases the medications were modified when the S[K] was ≥5.5 mEq/L. Notably, adverse cardiorenal outcomes increased with RAAS inhibitor dose reduction or discontinuation, particularly in the cohorts with CKD and heart failure.[9] A similar adverse effect on outcomes

was observed in a cohort of 295 mostly elderly hospitalized heart failure patients with CKD.[74] One or more perceived contraindications to ACEI therapy was present in 52 of the patients. The cumulative 4-year survival in this subgroup of patients who did not receive therapy with ACEIs was only 3%. By contrast, when such patients were discharged on ACEIs, the cumulative survival increased sixfold from 3% to 19%. These findings are particularly important because more than 50% of patients with congestive heart failure have some level of CKD, which is among the strongest predictors of death in patients with underlying heart disease. In summary, optimizing the therapeutic dosage of RAAS inhibitors is critical to achieve the greatest cardiovascular benefit, but difficult to achieve due to the potential risk of hyperkalemia.

There are strategies the clinician should use to optimize RAAS blockers in patients at risk (Table 40.3). The initial approach is to better define the risk of hyperkalemia by accurately assessing the level of renal function. In general, this risk will increase as renal function declines. An eGFR of 30 mL/min/1.73 m^2 should be considered a threshold at which the likelihood of developing hyperkalemia substantially increases.[75] The clinician should review the patient's medication profile, and whenever possible discontinue drugs that can impair renal K^+ excretion. Use of over-the-counter nonsteroidal anti-inflammatory drugs is a common cause of hyperkalemia in this setting. Patients should be educated on sources of K^+ in the diet and should be strongly encouraged to avoid the use of K^+-containing salt substitutes, as well as herbal remedies, because herbs may be a hidden source of dietary K^+. Correction of metabolic acidosis in patients with CKD is an effective strategy to minimize the potential for developing hyperkalemia.[60] Ensuring the patient is first on effective diuretic therapy will lessen the likelihood of developing volume overload, although $NaHCO_3$ administration causes less sodium retention compared to NaCl in CKD patients.[76]

The level of renal function should not be the *sole* determinant regarding whether RAAS inhibitors should be initiated or continued. Withholding these drugs simply based on the level of renal function will unnecessarily deprive many patients of the cardiovascular benefit they would have otherwise received, particularly because numerous steps can be taken to minimize the risk of hyperkalemia. The successful implementation of these steps was demonstrated in a randomized, double blind study of 224 patients with S[Cr] of 3.1–5.0 mg/dL.[77] Administration of 20 mg/day of benazepril reduced the composite endpoint of doubling of the S[Cr], ESRD, or death compared to placebo. During the 3-year study, hyperkalemia (defined as a S[K] >6.0 mmol/L) developed in six patients treated with benazepril and five receiving placebo, resulting in only three withdrawn from the study. Hyperkalemia in the remaining eight patients was successfully treated with dietary modifications, diuretic therapy, and optimization of acid–base balance.

Close monitoring is required but not always implemented when prescribing drugs that interfere with the RAAS. In a retrospective cohort study conducted in 10 health maintenance organizations, the frequency of S[K] and S[Cr] monitoring was assessed in patients labeled as being treated with ACEIs or ARBs for at least 1 year.[78] More than two-thirds of the 52,906 patients were identified received laboratory monitoring. The likelihood of monitoring increased with advancing age, more frequent outpatient visits, recent hospitalizations, concomitant use of drugs such as potassium salts, diuretics, and digoxin, and comorbidities such as diabetes, congestive heart failure, and CKD. Of concern, nearly one-third of patients prescribed these drugs had no laboratory monitoring over a 1-year period.

Even the discovery of hyperkalemia during laboratory testing does not guarantee appropriate follow-up. In a retrospective observational cohort study of a large primary care practice, 109 instances of hyperkalemia (defined as S[K] >5.8 mEq/L) were identified in 86 patients.[79] Although more than half of the patients were recalled to the clinic for retesting, 25% of the cases had no repeat testing until they were seen on routine follow-up visits or when they came to the clinic for unrelated issues.

TABLE 40.3 Approach to Patients at Risk for Developing Hyperkalemia When Using Drugs That Interfere with the Renin-Angiotensin-Aldosterone System

- Accurately assess level of renal function to better define risk
- Discontinue drugs that interfere with renal K^+ secretion, inquire about herbal preparations, and discontinue nonsteroidal anti-inflammatory drugs, including the selective cyclooxygenase 2 inhibitors
- Low K^+ diet, inquire about K^+-containing salt substitutes
- Thiazide or loop diuretics (loop diuretics necessary when eGFR <30 mL/min/1.73 m^2)
- Sodium bicarbonate to correct metabolic acidosis in CKD patients
- Initiate therapy with low dose ACEI or angiotensin receptor blocker
  - Measure K^+ one week after initiation of therapy or after increasing dose of drug
  - For increases in S[K] up to 5.5 mEq/L, decrease dose of drug. If taking some combination of ACEI, angiotensin receptor blocker, and aldosterone receptor blocker discontinue one and recheck S[K]
  - The dose of spironolactone should not exceed 25 mg daily when used with an ACEI or angiotensin receptor blocker. This combination of drugs should be avoided with GFR <30 mL/min
  - For S[K] ≥5.6 mEq/L despite above steps, consider K^+ binding drug such as patiromer or ZS-9 before discontinuing RAAS blocker

ACEI, angiotensin-converting enzyme inhibitor; *GFR*, glomerular filtration rate; *RAAS*, renin–angiotensin aldosterone system.

The lack of appropriate follow-up is of particular concern because the electrocardiogram in a hyperkalemic patient can precipitously progress from normal to ventricular tachycardia and asystole. Most physicians are familiar with the findings of peaked T waves and the sine wave pattern that typify hyperkalemia. Profound bradycardia is a less well-appreciated manifestation of hyperkalemia. Particular attention should be given to patients with underlying disturbances of cardiac conduction because even mild degrees of hyperkalemia may precipitate heart block.

Once the decision has been made to initiate an ACEI or an ARB in a high-risk patient, one should begin with low doses and recheck S[K] within one week of starting the drug (Table 40.3). If S[K] is normal, then the dose of the drug can be titrated upwards, rechecking S[K] within one week following an increase in dosage. If S[K] rises to 5.5 mEq/L, in some cases, lowering the dose will reduce S[K] and allow the patient to remain on the RAAS blocker at a lower dose. In patients receiving some combination of an ACEI, ARB, and an aldosterone receptor blocker, discontinuation of one drug or the other may also be effective in lowering S[K]. In patients at risk for hyperkalemia, ARBs and direct renin inhibitors should be used with the same caution as ACEIs. When S[K] is greater than or equal to 5.6 mEq/L, despite following the above precautions, one can consider the use of a K^+ binding drug before making the decision to avoid the use of RAAS blockers.

POTASSIUM BINDING THERAPY

Pharmacological management of hyperkalemia has relied for over 50 years on chronic use of sodium-polystyrene sulfonate (Kayexalate), which binds K^+ in the gastrointestinal tract. This binder, however, is poorly tolerated and has been linked to gastrointestinal toxicity. Moreover, long-term administration is linked to serious side effects, such as rare cases of intestinal necrosis, resulting in a black-box warning by the Food and Drug Administration.[80] In addition, the ability of this drug to lower S[K] over and above the effect of increased stool volume brought about by the coadministration of sorbitol is minimal.[81] The efficacy of sodium-polystyrene sulfonate for the chronic treatment of hyperkalemia has not been well studied, and the drug is not formally approved for this indication. The drug was found to be superior to placebo in a 7-day study of mild hyperkalemia in outpatients with CKD.[82] Volume overload is a concern because use of sodium-polystyrene sulfonate exchanges sodium for potassium. There are new oral compounds, patiromer, and sodium zirconium cyclosilicate (ZS-9), which are K^+-binding drugs shown to be effective in preventing the development of hyperkalemia. Patiromer, and more recently, ZS-9, have been approved for clinical use. Both are indicated for the treatment of hyperkalemia. The use of these agents for emergent treatment of hyperkalemia has not been well studied.

Patiromer is a nonabsorbed free-flowing powder of small, spherical beads (~100 μm in diameter) that bind K^+ in the gastrointestinal lumen, thereby reducing luminal concentrations of free K^+ and increasing fecal excretion. Due to the use of calcium as the exchange ion, there were initial concerns that patiromer might increase calcium levels. A phase 1 study of healthy adult volunteers, however, indicated that only a small fraction of the calcium is available for absorption, whereas the remaining calcium is excreted through the gastrointestinal tract still bound to patiromer.[83] Calcium may form complexes with anions such as phosphate in the gastrointestinal lumen, accounting for the ability of the drug to modestly lower S[P] levels.[84] Patiromer effectively decreases S[K] in high-risk patients on RAAS blockers, including those with heart failure, CKD, and diabetic nephropathy.[85,86] In a study of over 300 patients with diabetic nephropathy with either mild to moderate hyperkalemia, patiromer lowered S[K] in a dose-dependent manner, with the greatest reduction in those with higher starting values. The drug remained effective in controlling plasma K^+ concentration over a 44-week maintenance phase despite ongoing administration of RAAS inhibitors. The drug was well tolerated, with the main adverse events being constipation (infrequent and self-limiting) and hypomagnesemia, which required magnesium replacement in a small number of subjects.

ZS-9 is a nonabsorbed microporous compound that binds K^+ throughout the gastrointestinal tract. The pore size renders it highly selective for K^+, compared to calcium or magnesium ions. The drug is effective in lowering plasma K^+ concentration in a dose-dependent manner, with the greater reductions in those with the highest levels.[87,88] The randomized, controlled, phase 3 Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance (HARMONIZE) trial, evaluated the safety and efficacy of ZS-9 in outpatients with hyperkalemia (S[K] $\geq$5.1 mEq/L). A total of 258 patients received ZS-9 at 10 g TID during an initial 48-h, open-label phase. The 237 patients achieving normokalemia (S[K] 3.5–5.0 mEq/L) were randomized to maintenance with ZS-9 at doses of 5, 10, or 15 g QD or placebo for 28 days. During the initial open-label phase, mean S[K] levels fell from 5.6 mEq/L at baseline to 4.5 mEq/L at 48 hours. During maintenance, S[K] remained significantly lower in all ZS-9 groups compared with the placebo group ($p < 0.001$). The early onset of action with ZS-9 is notable and has been observed consistently across clinical studies. Adverse event rates, including

events in the gastrointestinal tract, were generally comparable between ZS-9 and placebo. The compound does release sodium. This can be a concern when used in patients in heart failure, where edema and volume overload can become a clinical issue. Edema occurred more frequently with the 10-g and 15-g doses than with placebo, with most cases of edema reported in heart failure patients.[89] In comparison, evidence of increased edema was not seen in another phase 3 study in which ZS-9 was administered at doses ranging from 1.25 to 10 g TID during the first 48 hours and then QD during maintenance for 12 days.[88]

The ability of these drugs to allow ongoing use of RAAS blockers in patients with a history of hyperkalemia suggests these agents could prove useful in allowing patients at risk for hyperkalemia to liberalize their diets to be enriched in fruits and vegetables. It is important to note, however, that none of the trials so far have specifically tested dietary liberalization in patients with CKD. This would be an important area to explore, because dietary liberalization would improve the quality of life in patients at risk who are subjected to significant restrictions on foods that may ultimately benefit them.[90]

SUMMARY

Adaptive increases in renal and gastrointestinal excretion of K^+ help prevent hyperkalemia in patients with CKD as long as the GFR remains >15–20 mL/min. Once the GFR falls below these values, the impact of factors known to adversely affect K^+ homeostasis is significantly magnified. Impaired renal K^+ excretion can be the result of conditions that severely limit distal Na^+ delivery, decreased mineralocorticoid levels or activity, or a distal tubular defect. In clinical practice hyperkalemia is usually the result of a combination of factors, including administration of medications that interfere with normal K^+ handling, superimposed on renal dysfunction.

References

1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;**128**(16):1810–52.
2. National Institute for Health Care Excellence (NICE). *Chronic kidney disease in adults: assessment and management. Clinical guideline (CG182)*. Published July 23, 2014. Last updated January 2015. http://www.nice.org.uk/guidance/cg182.
3. McMurray JJV, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;**33**(14):1787–847.
4. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004; **43**(5 Suppl. 1):S1–290.
5. Sarafidis P, Blacklock R, Wood E, Rumjon A, Simmonds S, Fletcher-Rogers J, Ariyanayagam R, Al-Yassin A, Sharpe C, Vinen K. Prevalence and factors associated with hyperkalemia in predialysis patients followed in a low-clearance clinic. *Clin J Am Soc Nephrol* 2012;**7**(8):1234–41.
6. van Y persele de Strihou C. Potassium homeostasis in renal failure. *Kidney Int* 1977;**11**:491–504.
7. Gennari FJ, Segal AS. An adaptive response in chronic renal insufficiency. *Kidney Int* 2002;**62**:1–9.
8. Einhorn LM, Zhan M, Hsu VD, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med* 2009;**169**(12):1156–62.
9. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care* 2015;**21**(11 Suppl. l):S212–20.
10. Latts LM, Reaven NL, Funk SE, et al. Hyperkalemia in patients with cardiorenal comorbidities. In: *Poster presented at: ISPOR 20th annual international meeting; May 16–20, 2015; Philadelphia, PA*. https://www.ispor.org/research_pdfs/49/pdffiles/PCV33.pdf.
11. Lazich I, Bakris GL. Prediction and management of hyperkalemia across the spectrum of chronic kidney disease. *Semin Nephrol* 2014; **34**(3):333–9.
12. Montague BT, Ouellette JR, Butler GK. Retrospective review of the frequency of ECG changes in hyperkalemia. *Clin J Am Soc Nephrol* 2008;**3**:324–30.
13. Hughes-Austin J, Rifkin D, Beben T, Katz R, Sarnak M, Deo R, Hoofnagle A, Homma S, Siscovick D, Sotoodehnia N, Psaty B, de Boer I, Kestenbaum B, Shlipak M, Ix J. The relation of serum potassium concentration with cardiovascular events and mortality in community-living individuals. *Clin J Am Soc Nephrol* 2017; **12**(2):245–52.
14. Palmer BF. Hyperkalemia in predialysis patients. *Clin J Am Soc Nephrol* 2012;**7**:1201–2.
15. Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis. *Adv Physiol Educ* 2016;**40**:480–90.
16. Palmer BF. Renal physiology: regulation of potassium homeostasis. *Clin J Am Soc Nephrol* 2015;**10**:1050–60.
17. McCormick JA, Ellison DH. Distal convoluted tubule. *Comp Physiol* 2015;**5**(1):45–98.
18. Hadchouel J, Ellison DH, Gamba G. Regulation of renal electrolyte transport by WNK and SPAK-OSR1 kinases. *Annu Rev Physiol* 2016;**78**:367–89.
19. Schultze RG, Taggart DD, Shapiro H, Pennell JP, Caglar S, Bricker NS. On the adaptation in potassium excretion associated with nephron reduction in the dog. *J Clin Investig* 1971;**50**:1061–8.
20. Levy YN, Fellet A, Arranz C, Balaszczuk AM, Adrogué HJ. Amiloride-sensitive and amiloride-insensitive kaliuresis in advanced chronic kidney disease. *J Nephrol* 2008;**21**:93–8.
21. Bourgoignie JJ, Kaplan M, Pincus J, Gavellas G, Rabinovitch A. Renal handling of potassium in dogs with chronic renal insufficiency. *Kidney Int* 1981;**20**:482–90.
22. Gonick HC, Kleeman CR, Rubini ME, Maxwell MH. Functional impairment in chronic renal disease. 3. Studies of potassium excretion. *Am J Med Sci* 1971;**261**:281–90.
23. Perez GO, Pelleya R, Oster JR, Kem DC, Vaamonde CA. Blunted kaliuresis after an acute potassium load in patients with chronic renal failure. *Kidney Int* 1983;**24**:656–62.
24. Stanton BA. Renal potassium transport: morphological and functional adaptations. *Am J Physiol* 1989;**257**:R989–997.

25. Fine LG, Yanagawa N, Schultze RG, Tuck M, Trizna W. Functional profile of the isolated uremic nephron: potassium adaptation in the rabbit cortical collecting tubule. *J Clin Investig* 1979;**64**: 1033–43.
26. Zalups RK, Stanton BA, Wade JB, Giebisch G. Structural adaptation in initial collecting tubule following reduction in renal mass. *Kidney Int* 1985;**27**:636–42.
27. Scherzer P, Wald H, Czaczkes JW. Na-K-ATPase in isolated rabbit tubules after unilateral nephrectomy and Na^+ loading. *Am J Physiol* 1985;**248**:F565–573.
28. Mujais SK, Kurtzman NA. Regulation of renal Na-K-ATPase in the rat: effect of uninephrectomy. *Am J Physiol* 1986;**251**:F506–512.
29. Vehaskari VM, Hering-Smith KS, Klahr S, Hamm LL. Increased sodium transport by cortical collecting tubules from remnant kidneys. *Kidney Int* 1989;**36**:89–95.
30. Stanton B, Pan L, Deetjen H, Guckian V, Giebisch G. Independent effects of aldosterone and potassium on induction of potassium adaptation in rat kidney. *J Clin Investig* 1987;**79**:198–206.
31. Hené RJ, Boer P, Koomans HA, Mees EJ. Plasma aldosterone concentrations in chronic renal disease. *Kidney Int* 1982;**21**:98–101.
32. Salem MM, Rosa RM, Batlle DC. Extrarenal potassium tolerance in chronic renal failure: implications for the treatment of acute hyperkalemia. *Am J Kidney Dis* 1991;**18**:421–40.
33. Montanari A, Graziani G, Borghi L, Cantaluppi A, Simoni I, Lorenzano E, et al. Skeletal muscle water and electrolytes in chronic renal failure: effects of long-term regular dialysis treatment. *Nephron* 1985;**39**:316–20.
34. Bergstrom J, Alvestrand A, Furst P, Hultman E, Widstam-Attorps U. Muscle intracellular electrolytes in patients with chronic uremia. *Kidney Int* 1983;**24**(Suppl. 16):S153–60.
35. Cheng J-T, Kahn T, Kaji DM. Mechanism of alteration of sodium potassium pump of erythrocytes from patients with chronic renal failure. *J Clin Investig* 1984;**74**:1811–20.
36. Zannad F, Royer RJ, Kessler M, et al. Cation transport in erythrocytes of patients with renal failure. *Nephron* 1982;**32**:347–50.
37. Quarello F, Boero R, Guarena C, et al. Acute effects of hemodialysis on erythrocyte sodium fluxes in uremic patients. *Nephron* 1985;**41**:22–5.
38. Kramer HJ, Gospodinov D, Kruck D. Functional and metabolic studies on red blood cell sodium transport in chronic uremia. *Nephron* 1976;**16**:344–58.
39. Izumo H, Izumo S, DeLuise M, et al. Erythrocyte Na,K pump in uremia: acute correction of a transport defect by hemodialysis. *J Clin Investig* 1984;**74**:581–8.
40. Cotton JR, Woodard T, Carter NW, Knochel JP. Resting skeletal muscle membrane potential as an index of uremic toxicity. *J Clin Investig* 1979;**63**:501–6.
41. Kaji D, Kahn T. Na+-K+ pump in chronic renal failure. *Am J Physiol* 1987;**252**:F785–93.
42. Darwish R, Elias AN, Vaziri ND, et al. Plasma and urinary catecholamines and their metabolites in chronic renal failure. *Arch Intern Med* 1984;**144**:69.
43. Converse Jr RL, Jacobsen TN, Toto RD, et al. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992;**327**: 1912.
44. Adrogué HJ. Glucose homeostasis and the kidney. *Kidney Int* 1992; **42**:1266.
45. Alvestrand A, Wahren J, Smith D, DeFronzo RA. Insulin-mediated potassium uptake is normal in uremic and healthy subjects. *Am J Physiol* 1984;**246**:E174–180.
46. Alvo M, Krsulovic P, Fernandez V, et al. Effect of a simultaneous potassium and carbohydrate load on extrarenal K homeostasis in end-stage renal failure. *Nephron* 1989;**53**:133–7.
47. Fernandez J, Oster JR, Perez GO. Impaired extrarenal disposal of an acute oral potassium load in patients with endstage renal disease on chronic hemodialysis. *Miner Electrolyte Metab* 1986;**12**:125–9.
48. Hayes Jr CP, Robinson RR. Fecal potassium excretion in patients on chronic intermittent hemodialysis. *Trans Am Soc Artif Intern Organs* 1965;**11**:242.
49. Hayes Jr CP, McLeod ME, Robinson RR. An extrarenal mechanism for the maintenance of potassium balance in severe chronic renal failure. *Trans Assoc Am Phys* 1967;**80**:207.
50. Sandle GI, Gaiger E, Tapster S, Goodship TH. Enhanced rectal potassium secretion in chronic renal insufficiency: evidence for large intestinal potassium adaptation in man. *Clin Sci* 1986;**71**: 393–401.
51. Martin RS, Panese S, Virginillo M, Gimenez M, Litardo M, Arrizurieta E, Hayslett JP. Increased secretion of potassium in the rectum of humans with chronic renal failure. *Am J Kidney Dis* 1986;**8**:105–10.
52. Mathialahan T, Maclennan KA, Sandle LN, Verbeke C, Sandle GI. Enhanced large intestinal potassium permeability in end-stage renal disease. *J Pathol* 2005;**206**:46–51.
53. Imbriano LJ, Durham JH, Maesaka JK. Treating interdialytic hyperkalemia with fludrocortisone. *Semin Dial* 2003;**16**:5–7.
54. Dong-Min K, Chung J, Yoon S, Kim H. Effect of fludrocortisones acetate on reducing serum potassium levels in patients with end-stage renal disease undergoing haemodialysis. *Nephrol Dial Transplant* 2007;**22**:3273–6.
55. Farese S, Kruse A, Pasch A, et al. Glycyrrhetinic acid food supplementation lowers serum potassium concentration in chronic hemodialysis patients. *Kidney Int* 2009;**76**:877–84.
56. Knoll GA, Sahgal A, Nair RC, et al. Renin-angiotensin system blockade and the risk of hyperkalemia in chronic hemodialysis patients. *Am J Med* 2002;**112**:110–4.
57. Prakdeekitcharoen B, Leelasa-nguan P. Effects of an ACE inhibitor or angiotensin receptor blocker on potassium in CAPD patients. *Am J Kidney Dis* 2004;**44**:738–46.
58. Hatch M, Freel RW, Vaziri ND. Local up-regulation of colonic angiotensin II receptors enhances potassium excretion in chronic renal failure. *Am J Physiol Renal Physiol* 1998;**274**(43):F275–82.
59. Saudan P, Mach F, Perneger T, et al. Safety of low-dose spironolactone administration in chronic haemodialysis patients. *Nephrol Dial Transplant* 2003;**18**:2359–63.
60. Palmer BF. A physiologic based approach to the evaluation of a patient with hyperkalemia. *Am J Kidney Dis* 2010;**56**:387–93.
61. Weidmann P, De Myttenaere-Bursztein S, Maxwell M, de Lima J. Effect of aging on plasma renin and aldosterone in normal man. *Kidney Int* 1975;**8**:325–33.
62. Kigoshi T, Morimoto S, Uchida K, et al. Unresponsiveness of plasma mineralocorticoids to angiotensin II in diabetic patients with asymptomatic normoreninemic hypoaldosteronism. *J Lab Clin Med* 1985;**105**:195–200.
63. Azukizawa S, Kaneko M, Nakano S, et al. Angiotensin II receptor and postreceptor events in adrenal zona glomerulosa cells from streptozotocin-induced diabetic rats with hypoaldosteronism. *Endocrinology* 1991;**129**:2729–33.
64. Nadler JL, Lee FO, Hsuch W, et al. Evidence of prostacyclin deficiency in the syndrome of hyporeninemic hypoaldosteronism. *N Engl J Med* 1986;**314**:1015–20.
65. Clark BA, Brown RS, Epstein F. Effect of atrial natriuretic peptide on potassium-stimulated aldosterone secretion: potential relevance to hypoaldosteronism in man. *J Clin Endocrinol Metab* 1992;**75**:399–403.
66. Kaplan B, Wang Z, Abecassis M, Fryer J, Stuart F, Kaufman D. Frequency of hyperkalemia of simultaneous pancreas and kidney transplants with bladder drainage. *Transplantation* 1996;**62**: 1174–5.
67. Kamel K, Ethier J, Quaggin S, et al. Studies to determine the basis for hyperkalemia in recipients of a renal transplant who are treated with cyclosporine. *J Am Soc Nephrol* 1992;**2**:1279–84.

68. McCauley J, Murray J, Jordan M, Scantlebury V, Vivas C, Shapiro R. Labetalol-induced hyperkalemia in renal transplant recipients. *Am J Nephrol* 2002;**22**:347–51.
69. Castellino P, Simonson D, DeFronzo R. Adrenergic modulation of potassium metabolism during exercise in normal and diabetic humans. *Am J Physiol* 1987;**252**:E68–76.
70. Perazella MA. Trimethoprim is a potassium-sparing diuretic like amiloride and causes hyperkalemia in high-risk patients. *Am J Therapeut* 1997;**4**:343–8.
71. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the randomized Aldactone Evaluation Study. *N Engl J Med* 2004;**351**(6):543–51.
72. American Diabetes Association. Standards of medical care in diabetes—2016 abridged for primary care providers. *Clin Diabetes* 2016;**34**(1):3–21.
73. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults. Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *J Am Med Assoc* 2014;**311**(5):507–20.
74. Ahmed A1, Kiefe CI, Allman RM, Sims RV, DeLong JF. Survival benefits of angiotensin-converting enzyme inhibitors in older heart failure patients with perceived contraindications. *J Am Geriatr Soc* 2002;**50**(10):1659–66.
75. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N Engl J Med* 2004;**351**: 585–92.
76. Husted F, Nolph K, Maher J. NaHCO3 and NaC1 tolerance in chronic renal failure. *J Clin Investig* 1975;**56**:414–9.
77. Hou F, Zhang X, Zhang G, Xie D, Chen P, Zhang W, Jiang J, Liang M, Wang G, Liu Z, Geng R. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006;**354**(2): 131–40.
78. Raebel MA, McClure DL, Simon SR, Chan KA, Feldstein A, Andrade SE, Lafata JE, Roblin D, Davis RL, Gunter MJ, Platt R. Laboratory monitoring of potassium and creatinine in ambulatory patients receiving angiotensin converting enzyme inhibitors and angiotensin receptor blockers. *Pharmacoepidemiol Drug Saf* 2007; **16**(1):55–64.
79. Moore C, Lin J, O'Connor N, Halm E. Follow-up of markedly elevated serum potassium results in the ambulatory setting: implications for patient safety. *Am J Med Qual* 2006;**21**(2):115–24.
80. Sterns RH, Rojas M, Bernstein P, Chennupati S. Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? *J Am Soc Nephrol* 2010;**21**(5):733–5.
81. Emmett M, Hootkins RE, Fine KD, Santa Ana CA, Porter JL, Fordtran JS. Effect of three laxatives and a cation exchange resin on fecal sodium and potassium excretion. *Gastroenterology* 1995; **108**(3):752–60.
82. Lepage L, Dufour AC, Doiron J, Handfield K, Desforges K, Bell R, Vallée M, Savoie M, Perreault S, Laurin LP, Pichette V, Lafrance JP. Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. *Clin J Am Soc Nephrol* 2015;**10**(12):2136–42.
83. Bushinsky D, Spiegel D, Gross C, et al. Effect of patiromer on urinary ion excretion in healthy adults. *Clin J Am Soc Nephrol* 2016; **11**(10):1769–76.
84. Bushinsky DA, Rossignol P, Spiegel DM, Benton WW, Yuan J, Block GA, Wilcox CS, Agarwal R. Patiromer decreases serum potassium and phosphate levels in patients on hemodialysis. *Am J Nephrol* 2016;**44**(5):404–10.
85. Weir MR, Bakris GL, Bushinsky DA, , et alfor OPAL-HK Investigators. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 2015; **372**(3):211–21.
86. Bakris GL, Pitt B, Weir MR, , et alAMETHYST-DN Investigators. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease. The AMETHYST-DN randomized clinical trial. *J Am Med Assoc* 2015;**314**(2):151–61.
87. Kosiborod M, Rasmussen HS, Lavin P, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia. The HARMONIZE randomized clinical trial. *J Am Med Assoc* 2014;**312**(21):2223–33.
88. Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med* 2015;**372**(3):222–31.
89. Anker SD, Kosiborod M, Zannad F, et al. Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized, double-blind, placebo-controlled trial. *Eur J Heart Fail* 2015;**17**(10):1050–6.
90. Palmer BF, Clegg DJ. Achieving the benefits of a high-potassium, paleolithic diet, without the toxicity. *Mayo Clin Proc* 2016;**91**(4): 496–508.
91. Gabriels G, Stockem E, Greven J. Potassium-sparing renal effects of trimethoprim and structural analogues. *Nephron* 2000;**86**:70–8.
92. Quimby D, Brito MO. Fanconi syndrome associated with use of tenofovir in HIV-invected patients: a case report and review of the literature. *AIDS Read* 2005;**15**:357–64.
93. Koht A, Cane R, Cerullo L. Serum potassium levels during prolonged hypothermia. *Intensive Care Med* 1983;**9**:275–7.
94. Polderman KH, Girbes AR. Severe electrolyte disorders following cardiac surgery: a prospective controlled observational study. *Crit Care* 2004;**8**:R459–466.
95. Khoo M, Braden G, Deaton D, et al. Outcome and complications of intraoperative hemodialysis during cardiopulmonary bypass with potassium-rich cardioplegia. *Am J Kidney Dis* 2003;**41**: 1247–56.
96. Perazella MA, Biswas P. Acute hyperkalemia associated with intravenous epsilon-aminocaproic acid therapy. *Am J Kidney Dis* 1999;**33**:782–5.
97. Moratinos J, Reverte M. Effects of catecholamines on plasma potassium: the role of alpha- and beta-adrenoceptors. *Fundam Clin Pharmacol* 1993;**7**:143–53.
98. DeFronzo R, Bia M, Birkhead G. Epinephrine and potassium homeostasis. *Kidney Intl* 1981;**20**:83–91.
99. McAdams M, Staffa J, Pan G. The concomitant prescribing of ethinyl estradiol/drospiernone and potentially interacting drugs. *Contraception* 2007;**76**:278–81.
100. Eng P, Seeger J, Loughlin J, Oh K, Walker A. Serum potassium monitoring for users of ethinyl estradiol/drospirenone taking medications predisposing to hyperkalemia: physician compliance and survey of knowledge and attitudes. *Contraception* 2007;**75**: 101–7.
101. Schutt B, Kunz M, Blode H. Coadministration of estradiol/drospirenone and indomethacin does not cause hyperkalemia in healthy postmenopausal women: a randomized open-label crossover study. *J Clin Pharmacol* 2007;**47**(6):774–81.
102. Mirandi A, Williams T, Holt J, Kassotis J. Hyperkalemia secondary to a postobstructive uropathy manifesting as complete heart block in a hypertensive patient receiving multiple atrioventricular nodal blocking agents. *Angiology* 2008;**59**(1):121–4.
103. Segal A. A case of acute kidney injury due to complex partial, multifocal ureteral strictures. *Nat Clin Pract* 2008;**4**(2):102–8.

QUESTIONS AND ANSWERS

Question 1

A 23-year-old man is evaluated because of increasing dyspnea. He has HIV infection. During his most recent clinic visit 2 months ago he was found to have a CD4 count of 210 cells/μL and a HIV RNA level of 14,000 copies/mL. Highly active retroviral therapy was started at that time. He now presents with shortness of breath and a chest radiograph showing bilateral infiltrates. His BP on admission to the hospital is 120/76 mm Hg. Labs on admission show (mmol/L): Na 131, K 4.8, Cl 95, HCO_3 22, BUN 20 mg/dL, S[Cr] 1.3 mg/dL. Further evaluation leads to a diagnosis of pneumocystis carinii pneumonia. Due to a history of allergy to sulfa-containing drugs he is treated with pentamidine and continued on his antiretroviral therapy. Laboratory examination 1 week later shows (mmol/L): Na 132, K 6.2, Cl 100, HCO_3 18, BUN 21 mg/dL, S[Cr] 1.4 mg/dL. The urinalysis is normal.

Which ONE of the following is the most likely cause of the increased S[K] in this patient?

A. Rhabdomyolysis due to antiretroviral therapy—induced muscle toxicity
B. Cell shift due to development of antiretroviral therapy—induced lactic acidosis
C. Blockade of distal renal tubule potassium excretion due to pentamidine
D. Development of proximal RTA as a result antiretroviral therapy
E. Addison's disease due to adrenal HIV infection

Answer: C

Pentamidine in the tubular lumen of the collecting duct competes for Na movement on the epithelial Na channel. The decrease in Na reabsorption decreases luminal electronegativity, thus decreasing the driving force for potassium secretion. Although rhabdomyolysis (Choice A) can be a cause of hyperkalemia, there is no other evidence of this disorder. In particular the S[Cr] is unchanged and there is no mention of dipstick positive blood in the absence of red blood cells to indicate the excretion of myoglobin in the urine. Lactic acidosis (Choice B) can be associated with hyperkalemia due to leakage of K out of cells as a result of cell death or ischemia. The absence of an increased anion gap excludes this disorder. Highly active antiretroviral therapy (Choice D) can be associated with the development of proximal renal tubular acidosis. However, proximal RTA gives rise to hypokalemia. Adrenal insufficiency (Choice E) can occur in HIV-infected patients due to a variety of causes, often infectious in origin, such as cytomegalovirus-induced adrenalitis. The short time course in this case is inconsistent with this diagnosis. In addition, hyperkalemia due to adrenal insufficiency would be accompanied by other findings such as a normal gap metabolic acidosis, hyponatremia, and evidence of renal salt wasting.[75,91,92]

Question 2

A 67-year-old man with stage 3 CKD secondary to diabetic nephropathy underwent coronary artery bypass graft due to three-vessel coronary artery disease. The anesthetic regimen consisted of high-dose sufentanil and midazolum. Succinylcholine was used for muscular relaxation. Standard depolarization cardioplegia was used. Surgery was performed using nonpulsatile cardiopulmonary bypass under moderate hypothermia. Intravenous epsilon-aminocaproic acid (EACA) was given to decrease perioperative bleeding. Two units of packed red blood cells and 1200 mL of D5NS were given intraoperatively. During the final 30 minutes of the procedure peaked T waves were noted on the monitor. The S[K] was found to be 6.7 mmol/L.

Which ONE of the following is not in the differential diagnosis of the hyperkalemia that developed in this patient?

A. A potassium load from the cardioplegia solution used to stop the beating of the heart
B. Cell depolarization induced by succinylcholine leading to a K shift out of intracellular compartment
C. K shift out of intracellular compartment due to administration of EACA
D. K shift out of intracellular compartment due to hypothermia
E. Hemolysis due to a transfusion reaction

Answer: D

Hypothermia is associated with hypokalemia due to a shift of potassium into the intracellular fluid compartment. All of the other choices are potential causes of hyperkalemia in the case presented. Cardioplegia solutions (Choice A) are used to arrest the heart in bypass operations and are potassium enriched. Succinylcholine (Choice B) is a muscle relaxant used in the induction of anesthesia. In susceptible individuals the drug causes hyperkalemia due to widespread cell membrane depolarization. EACA (Choice C) is an antifibrinolytic agent used to stop bleeding. This agent is structurally similar to the cationic amino acids lysine and arginine. The cellular uptake of EACA in a manner similar to the effect of cationic amino acids leads to the efflux of K from the intracellular fluid space. A hemolytic reaction in association with blood transfusion (Choice E) during the operative procedure would be in the differential diagnosis of hyperkalemia.[93–96]

Question 3

A 38-year-old woman with ESRD due to diabetes is taken to the operating room for incision and drainage of a perirectal abscess. Meds: metoprolol 50 mg twice daily. VS: T 37.8 C, P 94, RR 18, BP 140/84 mm Hg. Labs: (mmol/L) Na 138, K 5.1, RR 103, HCO3 21, S[Cr] 9.4 mg/dL, BUN 65 mg/dL. She was last dialyzed one day prior to admission. In the operating room the BP drops to 90/60 mm Hg. A neosynephrine drip (phenylephrine) made up in a D5W-containing solution is started and continued throughout the procedure with stabilization of BP. In the recovery room profound weakness is noted preventing extubation of the patient. Repeat electrolyte measurements show a S[K] of 6.6 mmol/L.

Which ONE of the following is the most likely explanation for the development of hyperkalemia during the operative procedure?

A. Beta adrenergic stimulation leading to K efflux from the intracellular compartment
B. Alpha adrenergic stimulation leading to K efflux from the intracellular compartment
C. Metoprolol-induced suppression of renin leading to hypoaldosteronsim
D. Insulin resistance leading to impaired insulin mediated K uptake into the intracellular compartment
E. Rhabdomyolysis as a complication of malignant hyperthermia

Answer: B

Phenylephrine is an alpha adrenergic receptor agonist used to support blood pressure. Alpha adrenergic stimulation leads to K^+ efflux from the intracellular to extracellular fluid space. It is likely that the risk for hyperkalemia was further increased due to K^+ release from injured tissue during the abscess drainage procedure in a patient with limited renal function. Beta adrenergic stimulation (Choice A) causes hypokalemia by shifting K^+ into the intracellular fluid space. Beta receptor blockade (Choice C) can suppress renin and potentially cause hypoaldosteronism, but impairment of renal K^+ secretion through this mechanism would not be an issue in a dialysis patient. Insulin resistance (Choice D) is often present as a complication of uremia, but would not explain the acute development of hyperkalemia in this patient. Malignant hyperthermia (Choice E) can cause hyperkalemia as a result of rhabdomyolysis, but the absence of fever makes this diagnosis unlikely.[97,98]

Question 4

A 38-year-old woman with a strong family history of cardiovascular diseases and hypertension is recently diagnosed with essential hypertension. Her blood pressure on three separate measurements averaged 154/94 mm Hg. Current medications include a daily multivitamin and birth control pills. The physical examination and laboratory examination are normal. Because the patient was using birth control pills, her primary care physician was comfortable prescribing lisinopril 10 mg daily. One month later the patient returns for follow-up. Blood pressure is 142/88 mm Hg. Laboratory examination shows (mmol/L) Na 140, K 5.5, Cl 100, HCO_3 22, S[Cr] 0.8 mg/dL, BUN 10 mg/dL. The physician refers the patient to a nephrologist for evaluation of hyperkalemia.

Which ONE of the following is the MOST likely risk factor for the development of hyperkalemia after prescribing an ACEI in this patient?

A. High-grade bilateral renal artery stenosis
B. Underlying pseudohypoaldosteronism type II
C. Acquired adrenal insufficiency
D. Mineralocorticoid-blocking activity in birth control pill
E. Daily ingestion of bananas.

Answer: D

The oral contraceptive, Yasmin-28, contains the non–testosterone-derived progestin drospirenone, which possesses mineralocorticoid-blocking effects similar to what is seen with spironolactone. The product labeling recommends K^+ monitoring in the first month after prescribing the drug for those patients who are receiving K^+ supplements, renin–angiotensin blockers, or nonsteroidal anti-inflammatory drugs (NSAIDs). Despite this recommendation, there are many instances where monitoring does not occur or patients are prescribed the contraceptive in the setting of other drugs that either provide a K^+ load or interfere with renal K^+ secretion. There is nothing in the clinical history to suggest the disease states provided in Choices A, B, and C. The K^+ load contained in bananas would be unlikely to cause hyperkalemia in the setting of normal renal function, making Choice E incorrect.[99–101]

Question 5

A 65-yr-old man is referred for evaluation of an increased S[Cr] and hyperkalemia. The patient complains of intermittent abdominal pain over the last month. Medications: lisinopril/hydrochlorothiazide 10/25 mg daily for hypertension treatment for the last 7 years. His past medical history is only significant for a motor vehicle accident 8 months ago in which he suffered a retroperitoneal bleed. Laboratory studies at the time of discharge were normal. Physical examination BP 158/94 mm Hg, P 92 bpm. The remainder of the

examination is only significant for mild periumbilical tenderness. Laboratory examination: WBC 9.0, Hematocrit 32%; Na 138, K 5.9, Cl 108, HCO_3 19 (mmol/L); S[Cr] 2.3 mg/dL, BUN 38 mg/dL. UA: SG 1.010 trace protein, 0−1 RBC, 0−1 WBC. An abdominal sonogram shows normal sized kidneys with slight enlargement of the urinary pelvis on both sides. There is no hydroureter.

Which ONE of the following is the MOST likely cause of the development of hyperkalemia and renal failure in this patient?

A. Pseudohypoaldosteronism type 1
B. Use of over-the-counter NSAID
C. Urinary obstruction
D. Angiotensin-converting enzyme inhibitor therapy
E. Use of the herb Chan Su

Answer: C

This patient presents with renal failure of unclear etiology in the setting of unremarkable urine sediment. Even though the renal sonogram shows no evidence of hydronephrosis, urinary obstruction needs to still be excluded in this setting. The history of a retroperitoneal bleed makes this patient at risk for retroperitoneal fibrosis, which can lead to obstructive uropathy in the absence of hydroureter. Unexplained hyperkalemia in association with a normal gap hyperchloremic metabolic acidosis (type IV renal tubular acidosis) is a common feature of obstructive uropathy. Pseudohypoaldosteronism type I (Choice A) is characterized by salt wasting and hyperkalemia, typically presenting in childhood. It is not a consideration in this case. Use of NSAIDs (Choice B) can be a cause of hyperkalemia, and they can cause AKI, but usually when given to patients with a contracted extracellular fluid volume. The patient was taking an ACEI on a chronic basis and therefore is unlikely to have suddenly developed hyperkalemia, making Choice D incorrect. Chan Su (Choice E) is a herb containing a digoxin-like substance that when ingested in large amounts can be a cause of hyperkalemia. The features of the clinical case make this diagnosis unlikely.[102,103]

Question 6

A 55-year-old man with long-standing diabetes mellitus is referred for evaluation and treatment of diabetic nephropathy. His only medication is celecoxib 200 mg/day for treatment of mild degenerative joint disease. Physical examination is significant for a blood pressure of 146/92 mm Hg and trace pedal edema. Labs show (mmol/L) Na 142, K 5.7, Cl 108, HCO_3 18, S[Cr] 2.0 mg/dL, 4.6 g urinary protein/24 hours. His primary care physician has been reluctant to start either an ACEI or an ARB because of the increased S[K].

Which ONE of the following would be the BEST approach to this patient?

A. Make a note in the chart that this patient should never be treated with ACEI or ARB due to refractory hyperkalemia
B. Discontinue the COX-2 inhibitor and initiate therapy with hydrochlorothiazide
C. Discontinue COX-2 inhibitor
D. Discontinue the COX-2 inhibitor, initiate therapy with a loop diuretic, and add $NaHCO_3$ tablets
E. Start therapy with an angiotensin receptor blocker at schedule routine follow-up

Answer: D

The patient has diabetic nephropathy and would benefit from use of a renin−angiotensin system blocker to slow the progression of renal disease and to provide cardiovascular protection. Choice A is incorrect because several steps can be taken in such a patient to both correct and minimize the development of hyperkalemia, allowing the successful use of these drugs. Choice B is incorrect from the standpoint of using a thiazide diuretic. Thiazides are largely ineffective at an eGFR of <30 mL/min/1.73 m^2. Discontinuation of the COX-2 inhibitor would be of benefit but would not likely lower blood pressure to goal or fully correct the hyperkalemia. Angiotensin-receptor blockers should be used with the same caution as ACEIs in patients at risk for the development of hyperkalemia. Therefore Choice E is incorrect. Discontinuation of the COX-2 inhibitor along with use of a loop diuretic and administration of bicarbonate is the best answer. The loop diuretic will help lower S[K] through its effects on increasing distal Na delivery and flow rates. Loop diuretics will also be of benefit in treating the hypertension. $NaHCO_3$ is also of benefit in minimizing the risk of hyperkalemia by correcting metabolic acidosis. The salt load will not be problematic while being used in the setting of effective diuretic therapy.[75,77]

CHAPTER

41

Calcium, Phosphate, and Magnesium Metabolism in Chronic Kidney Disease

Silvia Ferrè[a,b], *Javier A. Neyra*[a,d], *Orson W. Moe*[a,b,c]

[a]Charles and Jane Pak Center for Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, Dallas, TX, United States; [b]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, United States; [c]Department of Physiology, University of Texas Southwestern Medical Center, Dallas, TX, United States; [d]Department of Internal Medicine, Division of Nephrology, Bone and Mineral Metabolism, University of Kentucky, Lexington, KY, United States

Abstract

Disturbances in calcium (Ca^{2+}), phosphate (Pi), and magnesium (Mg^{2+}) homeostasis contribute to Chronic Kidney Disease Mineral and Bone Disorders (CKD-MBD), which encompasses abnormalities in mineral metabolism and bone, extraskeletal calcification, and cardiovascular disease. Although the role of excess Pi is unequivocal in CKD-MBD, the role of Ca^{2+} and Mg^{2+} is less clear. Understanding how Ca^{2+}, Pi, and Mg^{2+} disturbances affect the onset and progression of CKD-MBD is essential to achieving the ultimate goal of developing individualized effective treatments that target different facets of CKD-MBD pathophysiology in each patient. Pi load to the organism can be reduced by dietary modifications, binders, and/or modifiers of intestinal epithelial transport. Ca^{2+} and/or Mg^{2+} supplements (or avoidance) should be prescribed only to those who will benefit based on Ca^{2+} and Mg^{2+} status. Multiple therapies targeting more than one pathophysiologic factor involved in Ca^{2+}, Pi, and Mg^{2+} balance will be required to treat CKD-MBD.

INTRODUCTION

Public Heath Scope

Chronic kidney disease (CKD) is a systemic condition with global public health impact affecting more than 10% of the general population.[1] CKD is characterized by progressive deterioration of renal function with progression to dialysis-dependence, end-stage renal disease (ESRD), or unfortunately very commonly to death. The "CKD phenotype" can be also viewed as a state of accelerating aging.[2] Cardiovascular disease (CVD) is the leading cause of death in patients with CKD, accounting for over 50% of deaths.[3] Unfortunately, there are few specific and effective therapies to retard CKD progression and prevent or ameliorate extrarenal complications, in particular CVD.

Mineral and bone disorders are common in patients with CKD and substantially contribute to the large burden of CVD observed in these patients.[4,5] CKD-Mineral and Bone Disorders (CKD-MBD) is a collective term encompassing a wide range of biochemical and pathological features (Figures 41.1 and 41.2).[6] Phosphate (Pi) assumes a central role in CKD-MBD with less well defined roles for calcium (Ca^{2+}) and magnesium (Mg^{2+}).

New "Players" in CKD Relevant to Mineral Balance

Three new molecules deserve introduction. α-Klotho is highly expressed in the kidney with a membrane-bound form serving as a coreceptor for fibroblast growth factor 23 (FGF-23). α-Klotho is cleaved and released from the kidney into the circulation.[7] CKD is a state of α-Klotho deficiency.[8] Soluble α-Klotho influences multiple cellular and endocrine pathways, protecting against kidney fibrosis and oxidative stress.[9,10] α-Klotho–deficient mice share similar features of CKD-MBD and exhibit more susceptibility and rapid progression of CKD, vascular calcification (VC), bone loss, neurodegeneration, and pathologic cardiac remodeling.[11] Better understanding of the molecular mechanisms of how α-Klotho deficiency dysregulates the CKD-MBD axis is direly needed.

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00041-3

Initially identified from rare genetic and acquired hypophosphatemic disorders, FGF-23 has emerged as a biomarker of morbidity and mortality in CKD patients.[12,13] As α-Klotho levels decline, FGF-23 resistance ensues.[14] The increased morbidity associated with FGF-23 is proposed but not yet proven to be due to its off-target effects, including left ventricular hypertrophy (LVH), inflammation, immune dysfunction, bone loss, and inhibition of erythropoiesis leading to anemia.[15,16]

A divalent cation that has received less attention is Mg^{2+}. Recent studies support that low serum Mg^{2+} concentration S[Mg] is a predictor of all-cause death—in particular CV death—in patients with different strata of CKD.[17] These findings opened new potential avenues of intervention in CKD patients at risk of CVD. Thus far, there are only small short studies suggesting beneficial effects of Mg^{2+} supplementation on surrogate markers of CVD in CKD patients.[18,19]

Although standard therapies targeting the reduction of CVD in CKD patients have mostly focused on traditional risks such as smoking cessation, blood pressure, cholesterol, and glycemic control, CVD remains a major burden in the debilitated CKD population.[6] We are in dire need of novel pathophysiology-based therapeutic strategies against the CKD-MBD–CVD disease complex.

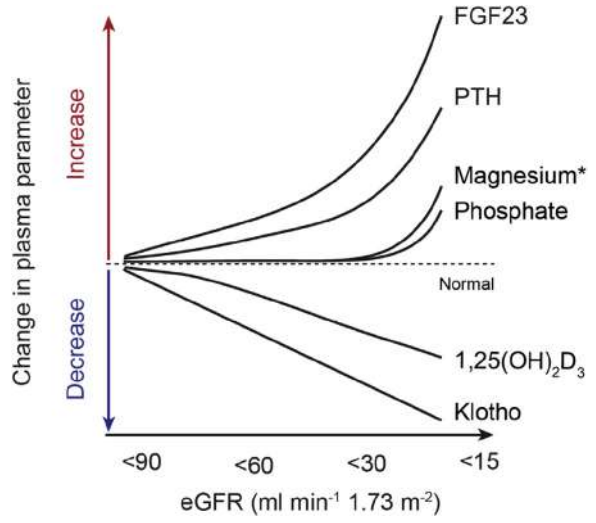


FIGURE 41.1 Proposed model of changes in plasma mineral parameters with different stages of CKD. FGF-23: Fibroblast growth factor 23; PTH: parathyroid hormone; $1,25(OH)_2D_3$: 1,25-dihydroxy-vitamin D_3; eGFR: estimated glomerular filtration rate. *Unlike hyperphosphatemia, hypermagnesemia is seen only in a fraction of patients near ESRD.

PATHOPHYSIOLOGY

Calcium (Ca^{2+}) Homeostasis

Maintenance of body Ca^{2+} homeostasis is important for many physiological functions including intracellular signaling, neuronal excitability, muscle contraction, and bone formation. The body houses 99% of the Ca^{2+} in bone, with 1% in the intracellular and extracellular space. Plasma Ca^{2+} levels (P[Ca]) are maintained within

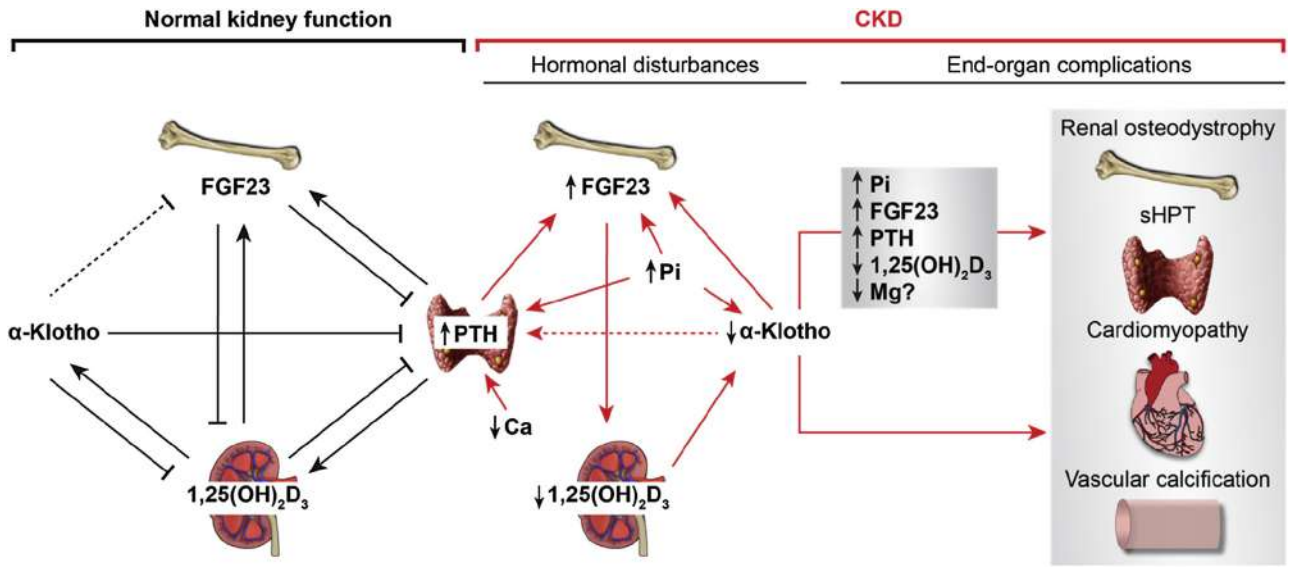


FIGURE 41.2 Regulatory network of mineral metabolism with normal kidney function and in chronic kidney disease (CKD). α-Klotho deficiency is the earliest abnormality in CKD and is likely the initiator of CKD-related mineral dysregulation that can lead to end-organ complications. The α-Klotho/Mg crosstalk is not currently defined. The conglomerate of abnormalities is believed to be pathogenic for multiple end organs complications. FGF-23: Fibroblast growth factor 23; PTH: parathyroid hormone; $1,25(OH)_2D_3$: 1,25-dihydroxy-vitamin D_3; Pi: phosphate; Ca: calcium; Mg: magnesium; sHPT: secondary hyperparathyroidism.

a narrow range, between 9–10 mg/dL (2.2–2.6 mM) *via* concerted actions of intestinal Ca^{2+} absorption, exchange of Ca^{2+} to and from bone, and renal Ca^{2+} excretion.

In the kidney, 50–60% of the total plasma Ca^{2+} is filtered, either in its ionized form or complexed with other ions.[20] After filtration, >95% of Ca^{2+} is reabsorbed along the tubules. Filtered Ca^{2+} is reabsorbed through paracellular pathways in the proximal tubule (PT) and the thick ascending limb (TAL) of Henle), where it is functionally coupled to Na^+ reabsorption.[20] Along the distal convolutions of the nephron, Ca^{2+} reabsorption is accomplished by transcellular transport. Approximately 10% of the filtered Ca^{2+} is reabsorbed in the late distal convoluted tubule (DCT2) and the connecting tubule *via* the epithelial Ca^{2+} channel, transient receptor potential vanilloid 5 (TRPV5).[21] Ca^{2+} is extruded in the renal interstitium to reenter the bloodstream by the Na^+/Ca^{2+}-exchanger and the plasma membrane Ca^{2+}-ATPase.[20] A few percent of the filtered Ca is excreted by the kidney into the urine.[20]

Intestinal Ca^{2+} absorption is the sum of two components.[22] The first is saturable, transcellular, active transport, which is largely regulated by the active form of vitamin D (1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$]). Transcellular Ca^{2+} absorption is highest in the proximal small intestine, mediated by the transient receptor potential vanilloid subtype 6 (TRPV6).[23] The second is unsaturable, paracellular, passive diffusion that is linearly related to dietary Ca^{2+} load. The relative contribution of the paracellular and transcellular pathway to the total amount of calcium that is absorbed from the intestine depends on dietary supply and bodily needs.[22] Finally, bone is a large exchangeable reservoir for Ca^{2+}, mostly as hydroxyapatite. The maintenance of mineral stores in bone depends on the balance between bone mineralization and resorption. Various TRP channels, including TRPV4, TRPV5, and TRPV6 are involved in calcium homeostasis in bone.[24] Expression studies have also reported calcium-sensing receptor (CaSR) transcripts in both osteoblasts and osteoclasts.[25]

Hormones classically involved in Ca^{2+} homeostasis are $1,25(OH)_2D_3$, parathyroid hormone (PTH), and calcitonin (CT).[26] In hypocalcemia, reduced binding of Ca^{2+} to the CaSR in the parathyroid glands induces rapid PTH release from the secretory granules, delays PTH degradation, and over the long term can result in parathyroid hyperplasia.[26] Increased levels of circulating PTH restore normal plasma Ca^{2+} level through Ca^{2+} resorption from bone, increase in Ca^{2+} reabsorption in the kidney *via* TRPV5,[27] and activation of $1,25(OH)_2D_3$ synthesis in the parathyroid glands,[20,26] which activates VDR-mediated enhanced intestinal Ca^{2+} absorption.[20,28] This regulatory system promotes a tri-organ network to restore Ca^{2+} levels.[20] As negative feedback, $1,25(OH)_2D_3$ represses the transcription of PTH and may have an indirect effect on PTH release by increasing the expression of CaSR. Hypercalcemia acts through CaSR to inhibit PTH release and stimulates the secretion of CT by the thyroid C cells, which counteracts hypercalcemia by decreasing osteoclast-mediated bone resorption.[29]

Phosphate (Pi) Homeostasis

Inorganic phosphate (Pi) is the third most abundant anion in the human body, accounting for about 1% of total body mass. Approximately 85% of total Pi is stored in bone in the form of apatite, contributing to bone structure. About 15% is distributed in soft tissues, and only 1% is contained in the rapidly exchangeable plasma pool. Pi balance depends on dietary intake and intestinal absorption, distribution among organs, and renal excretion.

Renal Pi excretion depends on the balance between filtration and reabsorption. Tubular Pi reabsorption occurs mainly in the PT, where at least three different Na^+-driven Pi transporters mediate the initial step of Pi reabsorption across the apical brush border membrane: NaPi-IIa (Npt2a, SLC34A1), NaPi-IIc (Npt2c, SLC34A3), and PiT2 (SLC20A2).[30] The basolateral exit pathway for Pi remains unknown. The three Pi transporters expressed in the PT exhibit different transport modes, sensitivity to pH, and dynamics of regulation by dietary Pi intake and phosphaturic hormones. Intestinal Pi absorption has dual pathways, consisting of a transcellular, transporter-dependent pathway, and a paracellular route. The transcellular route involves the Na^+-driven Pi transporter NaPi-IIb (Npt2b, SLC34A2), mostly expressed in the jejunum in humans.[31] The expression of NaPi-IIb is regulated by dietary Pi intake and $1,25(OH)_2D_3$.[32]

The main hormones regulating serum Pi are PTH, $1,25(OH)_2D_3$, and FGF-23 with its co-receptor α-Klotho. FGF-23 is a bone-generated humoral phosphaturic hormone.[33] Secretion of FGF-23 by bone is induced by Pi, $1,25(OH)_2D_3$, and PTH.[14] α-Klotho serves as a co-receptor for FGF-23.[14] *α-Klotho* gene expression is inducible by $1,25(OH)_2D_3$, in the distal convoluted tubule (DCT), and to a lesser extent in the PT and parathyroid glands.[34] Kidney and parathyroid α-Klotho expression mark these organs as FGF-23 targets, regulating both Pi and Ca^{2+}. In the kidney, both FGF-23 and α-Klotho suppress Pi reabsorption and $1,25(OH)_2D_3$ synthesis. In the parathyroid, FGF-23 suppresses PTH secretion, which may also contribute to the ability of FGF-23 to reduce $1,25(OH)_2D_3$ synthesis.[35] Thus, FGF-23 is both a phosphaturic hormone and the counter-regulatory hormone to $1,25(OH)_2D_3$,[35] which jointly promote negative Pi balance. *α-Klotho*-deficient mice show high levels of circulating FGF-23, likely caused by resistance, and

phenotypically similar to *Fgf-23*$^{-/-}$ mice with severe growth retardation, accelerated aging, vascular and ectopic calcifications, bone mineralization defects, increased serum Pi, and increased $1,25(OH)_2D_3$ levels.[34,36] Deletion of *Fgf-23* from *α-Klotho*$^{-/-}$ mice does not worsen the phenotype, confirming that FGF-23 requires α-Klotho.[37] The extracellular domain of membrane α-Klotho is shed by secretases and released into the circulation, cerebrospinal fluid, and urine as soluble α-Klotho.[35] Soluble α-Klotho exerts multiple biological actions on distant organs, including increase in renal Ca^{2+} reabsorption through modulation of the TRPV5 channel.[38] Thus, α-Klotho's action on the kidney is to promote Pi excretion and prevent renal Ca^{2+} loss.

Magnesium (Mg^{2+}) Homeostasis

There are approximately 24 g of Mg^{2+} in the body, of which 53% is stored in bone, 46% is in tissues, and the remaining 1% is in the extracellular space. Plasma Mg^{2+} levels are maintained around 1.6–2.6 mg/dL (0.7–1.1 mmol/L). Approximately 60–70% of the total plasma Mg^{2+} is filtered through the glomeruli, with 10–20% reabsorbed by the PT. The majority (65–70%) is taken up in the cortical TAL *via* the paracellular route, facilitated by the tight junction proteins, claudin-16, and claudin-19.[39] Of the filtered Mg^{2+}, 10–15% reaches the early DCT (DCT1), where Mg^{2+} is actively transported, which is critically influenced by cellular energy metabolism. The DCT1 determines the final urinary Mg^{2+} excretion by reabsorbing Mg^{2+} *via* the epithelial Mg channel, transient receptor potential melastatin 6 (TRPM6).[40] Families with monogenetic forms of hypomagnesemia have allowed the identification of a complex network of genes involved in active renal Mg^{2+} handling.[41] Up to now the gene/protein encoding for the basolateral Mg^{2+} extrusion in the kidney remains unknown. No significant Mg^{2+} reabsorption occurs in the more distal nephron segments. Overall, less than 5% of the filtered Mg^{2+} normally appears in the urine.

Between 25% and 75% of the Mg^{2+} from dietary sources is absorbed in the intestine, depending on the bioavailability and the needs of the body. When Mg^{2+} intake is normal, the transcellular pathway, involving TRPM6, is responsible for approximately 30% of total absorption, a fraction that increases when dietary intake is low.[22] Paracellular transport is responsible for approximately 70% of Mg^{2+} absorption when luminal concentrations are normal to high.[22] However, Mg^{2+}-specific intestinal paracellular channels are not yet elucidated.

Our understanding of the molecular mechanisms underlying Mg^{2+} handling in bone is limited. Dietary depletion leads to reduced bone Mg^{2+} content without affecting plasma Mg^{2+} levels, indicating that bone acts as a storage compartment from which Mg^{2+} is released in the situation of low Mg^{2+} supply. TRPM6 and TRPM7 are expressed in various osteoblast cell lines.[42] The physiological relevance of this observation for Mg transport in bone is not yet clear.

A comprehensive model describing systemic Mg^{2+} regulation is still missing. Thus far, epidermal growth factor, insulin, and estrogens have been suggested as magnesiotropic hormones by increasing renal reabsorption *via* TRPM6.[40] Mg^{2+} can bind and influence the activity of the CaSR, albeit with a much lower affinity than Ca^{2+}, and therefore may influence parathyroid PTH release.[43] However, hypomagnesemia is associated with a paradoxical block of PTH secretion and hypoparathyroidism, possibly secondary to impaired signaling downstream from the CaSR, secondary to intracellular Mg^{2+} deficiency.[43] Segmental Mg^{2+} transport experiments conducted in mice along the gastrointestinal tract showed that $1,25(OH)_2D_3$ does not affect Mg^{2+} absorption.[22]

Ca^{2+}, Pi, and Mg^{2+} Disturbances in CKD

With progression of CKD, the normal homeostatic mechanisms in Ca^{2+}, Pi, and Mg^{2+} balance are altered. Currently, CKD is often considered a state of accelerated aging associated with α-Klotho deficiency and Pi retention.[44,45] It is hypothesized that α-Klotho deficiency is the earliest biomarker of CKD and the initiator of CKD-related mineral dysregulation.[44,45] As α-Klotho levels declines progressively in CKD, FGF-23 expression increases. High serum phosphate concentration (S[P]) and PTH levels and low $1,25(OH)_2D_3$ levels accompany these changes (Figure 41.1). The first measurable decline in urinary α-Klotho levels occurs as early as stage 1 CKD[46] and is directly correlated with estimated glomerular filtration rate (eGFR),[47] suggesting that urinary soluble α-Klotho may be a good biomarker for early CKD detection. The reduction of serum α-Klotho starts at stage 2 CKD,[48] preceding the elevation of serum FGF-23, PTH, and S[P]. Serum α-Klotho levels progressively lower with more advanced CKD stages.[45,49] One study estimated the fall in serum α-Klotho to be 3.2 pg/mL for each 1 mL/min/1.73 m^2 decrease in eGFR.[50] *α-Klotho* mRNA in the kidney is decreased and positively correlates with eGFR.[51,52] CKD in rodents showed serum α-Klotho decrease that was comparable in magnitude to that of decreased α-Klotho protein in kidney and urine.[46] In CKD, low α-Klotho confers FGF-23 resistance contributing to a compensatory increase in blood FGF-23 levels to maintain Pi homeostasis (Figures 41.1 and 41.2). Preclinical studies show that both FGF-23 and α-Klotho levels are both predictive and pathogenic for kidney disease progression, extrarenal complications such as uremic cardiomyopathy, and mortality.[50,53–55] As CKD progresses, the increase in FGF-23 suppresses

$1,25(OH)_2D_3$ production, leading to $1,25(OH)_2D_3$ deficiency (Figures 41.1 and 41.2). Low $1,25(OH)_2D_3$ and high plasma Pi increase PTH, which contributes to the high FGF-23 levels in advanced CKD (Figures 41.1 and 41.2). By stage 4 CKD and ESRD, most patients exhibit frank hyperphosphatemia and secondary hyperparathyroidism (sHPT), marked elevations of FGF-23, and $1,25(OH)_2D$ deficiency (Figure 41.1).

Hypocalcemia is a late event in CKD that is sometimes seen in stage 5 CKD and ESRD. One major cause is reduced $1,25(OH)_2D_3$ that diminishes intestinal Ca^{2+}absorption (Figure 41.2). In addition, there is reduced mobilization of Ca^{2+} from bone due to decreased sensitivity to PTH in conjunction with $1,25(OH)_2D_3$ deficiency. Hyperphosphatemia and the secondary increase in FGF-23 levels inhibit 25-hydroxyvitamin D 1-hydroxylase in the kidney. This is combined with the loss of renal tissue and the consequent reduction in the enzyme availability and $1,25(OH)_2D_3$ production (Figure 41.2). There is a dramatic decrease in urine Ca^{2+} excretion in CKD, which represents the appropriate homeostatic response to maintain balance in the setting of decreased intestinal Ca^{2+} absorption.[20] However, many patients receive Ca^{2+} in the form of Ca^{2+}-containing Pi binders or $1,25(OH)_2D_3$, which can result in positive Ca^{2+} balance and net retention of Ca^{2+}.[56,57] Both negative and positive Ca^{2+} balance constitute potential health threats in CKD. Negative balance may increase risk for osteoporosis and fractures, which compounds the various CKD-specific bone complications. Positive calcium balance may increase risk for extraskeletal calcification. Management of altered mineral metabolism in CKD and ESRD has focused on the control and prevention of sHPT by treating hyperphosphatemia and $1,25(OH)_2D_3$ deficiency.

Compared to our knowledge of Ca^{2+} and Pi metabolism in CKD, regulation of Mg^{2+} homeostasis in CKD is poorly understood. When renal function declines, the fractional excretion of Mg^{2+} is increased to maintain normal S[Mg] concentrations. Therefore, patients with stages 1–3 CKD generally have normal S[Mg]. In stages 4 and 5 CKD, raising fractional excretion eventually fails to compensate for reduced filtered Mg^{2+}, which can cause hypermagnesemia (Figure 41.1). Ultimately, in dialysis patients, S[Mg] is variable and often depends on the dialysate Mg^{2+} concentration.[58] The use of the Pi binder sevelamer hydrochloride has been associated with hypermagnesemia in CKD.[59] It may be caused by sevelamer binding to bile salts, leaving more free Mg^{2+} available for absorption. Contrary to common belief, hypomagnesemia is not a rare finding among CKD patients.[60] In addition to the CKD-related pathophysiology, drugs that cause hypomagnesemia are often prescribed to patients with kidney disease,[61] such as proton pump inhibitors. The changes in intestinal pH induced by PPIs can reduced bioavailability of Mg^{2+} and the activity of TRPM6, thus contributing to the development of hypomagnesemia. Hypomagnesemia is also associated with the use of diuretics,[62] antimicrobials, the immunosuppressive agent cyclosporine, and the anticancer drugs cetuximab and cisplatin, which mostly affect the renal reabsorption of Mg^{2+}.[61] Other factors such as low dietary Mg^{2+} intake and comorbidities such as diabetes type II, greatly affect S[Mg] in CKD patients. S[Mg] levels have been found to be lower in diabetics who are at high risk for CKD development compared to nondiabetics.[63] Whether low S[Mg] is causative or a consequence of diabetes is under debate. Epidemiologic findings are consistent with a potential causal role of low S[Mg] in the development of diabetes, possibly through increased insulin resistance, and/or inflammation.[64] Low S[Mg] levels also independently associate with incidence and progression of CKD in patients with or without diabetes, as well as CV events and mortality in patients with CKD or undergoing hemodialysis.[17] The molecular mechanisms underlying deleterious effects of low S[Mg] on renal function are largely unknown. Low S[Mg] levels aggravate hyperphosphatemia-induced kidney injury.[65,66] In a small group of nondiabetic CKD patients, subjects with high S[P] had a higher risk of ESRD when they had concomitant low S[Mg] levels at baseline.[65] This dramatic finding can be explained by multiple mechanisms. Firstly, low-dietary Mg^{2+} favors positive Pi balance by increasing intestinal Pi absorption and decreasing urinary Pi excretion.[66] Secondly, low Mg^{2+} and high Pi have interactive and synergistic deleterious effects directly on renal tubular cells. Increase in extracellular Mg^{2+} concentration *in vitro* suppressed Pi-induced apoptosis of cultured renal tubular cells by inhibiting the expression of profibrotic and proinflammatory cytokines.[65] Thirdly low Mg^{2+} and high Pi increase the CV burden, which in turn increase peripheral and intrarenal resistance.

Ca^{2+}, Pi, and Mg^{2+} and CKD-MBD

Disturbances in Ca^{2+}, Pi, and Mg^{2+} homeostasis, and their regulatory hormones are part of the pathogenesis of CKD-MBD, which encompasses impaired mineral metabolism biochemistries, bone abnormalities, extraskeletal calcification, and CVD.[67] Cardiomyopathy (hypertrophy and fibrosis) and vasculopathy (VC), contribute significantly to morbidity and mortality in CKD.[3,67] Understanding how Ca^{2+}, Pi, and Mg^{2+} disturbances affect the development and progression of CKD-MBD at the molecular level is essential for better patient management and the development of new therapeutic targets. Although the role of Pi is unequivocal in CKD-MBD, the role of Ca^{2+} and Mg^{2+} are less well defined.

Cardiomyopathy

Cardiomyopathy occurs in >90% of patients with CKD and contributes to mortality. Disturbances in Ca^{2+} and Pi balance in CKD may induce cardiac abnormalities through several mechanisms (Figure 41.3). First, direct effects on cells due to disturbances in intracellular Ca^{2+} and/or Pi secondary to changes in function and/or expression of Ca^{2+} and Pi transporters may occur. Secondly, induction of cardiomyocyte hypertrophy through abnormal levels of hormones and extraskeletal deposition of calcioprotein particles (CPPs) occurs. Thirdly, increased VCs result in an increase in peripheral resistance. Ca^{2+} regulates cardiomyocyte contraction, growth, and remodeling. Abnormal Ca^{2+}-dependent cardiac ion channels have been reported in animal models of hypertrophic cardiomyopathy, which predispose to arrhythmias.[68] Rat cardiomyocytes incubated with PTH have a rapid increase in intracellular Ca^{2+} and undergo apoptosis. Incubation with uremic serum reproduced these findings, but not if the animal had undergone parathyroidectomy.[69] Epidemiologic studies in humans confirm that high-plasma PTH and FGF-23 levels are associated with cardiac hypertrophy (Figure 41.3).[15,70,71]

Hyperphosphatemia is a risk factor for progression of CVD and mortality in CKD/ESRD (Figure 41.3).[72,73] In rodents with normal renal function, long-term high Pi intake induced cardiac remodeling and was associated with decreased renal and systemic α-Klotho, and increased levels of plasma PTH and FGF-23.[74] Elevations in FGF-23 in CKD patients are independently associated with progression of LVH.[15] FGF-23 can directly induce LVH and cardiomyocyte hypertrophy in mice through FGFR-dependent activation of the calcineurin-NFAT signaling pathway (Figure 41.3).[15] This effect is independent of transmembrane α-Klotho, which is not expressed in heart.[15] Circulating soluble α-Klotho protects against uremic cardiomyopathy independently of FGF-23 and Pi (Figure 41.3).[75] Dietary Pi restriction rescues premature aging and death in both *Fgf-23*$^{-/-}$ and *kl/kl* mice, but does not abrogate cardiac hypertrophy in *kl/+* CKD mice, suggesting an independent role of α-Klotho in cardiac remodeling.[36,75,76] *kl/kl* mice have elevated FGF-23 levels and develop LVH, whereas *kl/+* mice manifest FGF-23 levels and an LVH phenotype that are intermediate between those of wild-type and *kl/kl* mice.[15] Administration of soluble α-Klotho to *kl/+* or wild-type mice with CKD, or transgenic overexpression of α-Klotho ameliorate cardiac hypertrophy and fibrosis *via* suppressed phosphorylation of Smad2/3 and Erk (Figure 41.3).[74,75,77] Moreover, soluble α-Klotho protects against cardiac remodeling by inhibiting TRPC6 channel−mediated Ca^{2+} signaling in the heart and suppressing reactive oxygen species production (Figure 41.3).[78] α-Klotho also inhibits TGF-β1−, angiotensin II−, or high Pi−induced fibrosis in cardiac fibroblasts *in vitro* and abolishes TGF-β1− or angiotensin II−induced hypertrophy of cultured neonatal cardiomyocytes.[74] The collective evidence supports a direct protective role of soluble α-Klotho on cardiac tissue beyond effects on renal function and mineral parameters.

The role of Mg^{2+} in cardiomyopathy in CKD is not well characterized. Mg^{2+} plays an important role in cardiac function by influencing myocardial metabolism, Ca^{2+} homeostasis, vascular tone, peripheral vascular resistance, and cardiac output.[39] Mg^{2+} exerts its effects in three ways (Figure 41.3). First, Mg^{2+} regulates the activity of ion channels in cardiac cells, thereby affecting the electrical properties of the myocardium. Secondly,

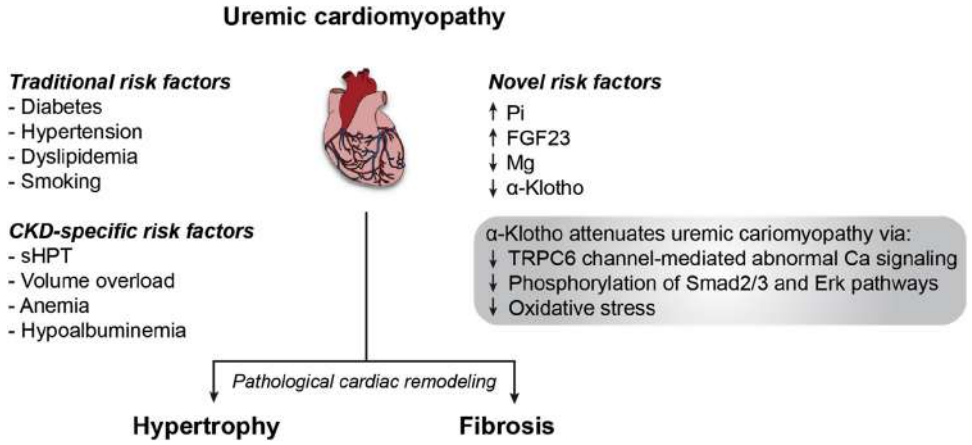


FIGURE 41.3 Risk factors for uremic cardiomyopathy. Mineral disorders along with high FGF-23 and α-Klotho deficiency are novel risk factor for uremic cardiomyopathy. Rodent models suggest that α-Klotho restoration is beneficial. The role of Mg supplementation on uremic cardiomyopathy is unclear. sHPT: secondary hyperparathyroidism; Pi: phosphate; FGF-23: fibroblast growth factor 23; Mg: magnesium; TRPC6: transient receptor potential canonical-6.

Mg^{2+} regulates myocardial contractility by influencing intracellular Ca^{2+} mobility. Finally, Mg^{2+} has anti-inflammatory and vasodilatory effects.[39] In the general population, low S[mg] is associated with higher risk of arrhythmias, coronary artery disease, myocardial infarction, congestive heart failure, and risk of sudden cardiac death.[79,80] Observational studies report that low S[Mg] is a significant predictor of CV events and CV death in patients with predialysis CKD or in patients treated with hemodialysis.[17]

Vascular Calcification

In CKD-MBD, elevated S[P], formation of CPP, and diminished levels of circulating inhibitors of VC, such as fetuin-A, matrix gla protein, and osteoprotegerin, initiate the trans-differentiation of vascular smooth muscle cells (VSMCs).[81] VSMC trans-differentiation is accelerated by the expression of osteogenic genes and amplified by the VSMCs through the release of exosomes and apoptotic bodies (Figure 41.4).[81]

Mounting evidence supports a protective role for soluble α-Klotho on VC that goes beyond its effect on amelioration of renal function and hyperphosphatemia.[44] Administration of exogenous recombinant α-Klotho, α-Klotho gene delivery, and increased endogenous circulating α-Klotho significantly reduced VC.[82–84] *In vitro* studies using endothelial cells and VSMCs show that α-Klotho improves endothelial function and suppresses uptake of Pi and mineralization induced by high S[P] (Figure 41.4).[46,85] The role of the FGF-23/α-Klotho signaling in endothelium and VSMC during CKD is still under investigation.

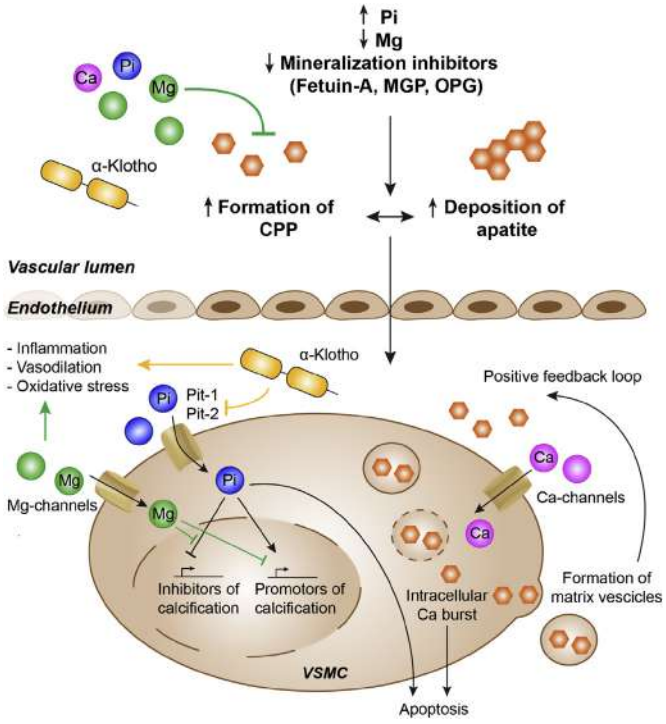


FIGURE 41.4 (Patho)physiology of vascular calcification during Ca, Pi, and Mg disturbances in CKD. Molecular mechanisms of vascular calcification in chronic kidney disease (CKD). The putative protective roles of Mg and α-Klotho on the endothelium and VSMC in the course of vascular calcification are depicted. MGP: matrix gla protein; OPG: osteoprotegerin; Pi: phosphate; Ca; calcium; Mg: magnesium; Pit-1: Na-Pi co-transporter-1; Pit-2: Na-Pi co-transporter-2; VSMC: vascular smooth muscle cells; CPP: calcioprotein particles.

There is increased circulating CPPs and serum calcification propensity in patients with CKD.[86,87] CPP are soluble colloidal protein−mineral nanoparticles, wherein Ca^{2+} and Pi are organized with various proteins with the main component being fetuin-A. CPP might initiate cardiomyopathy and VC[88] by inducing various cellular responses, including production of reactive oxygen species, mitochondrial dysfunction, cell cycle arrest, and cell death (Figure 41.4).[89] Serum CPP correlate positively with CV events,[86,90] worsening of kidney function,[86] and all cause and CV mortality in patients with CKD and renal transplant recipients.[91]

Low S[Mg] is independently associated with vascular disease in patients with CKD and treated with dialysis.[92,93] Low extracellular Mg^{2+} is proatherosclerotic in cultured endothelial cells, as it enhances the production of vasoconstrictor agents and cytokines, decreases the production of endothelial-derived vasodilators, and increases oxidative stress.[39] Mg^{2+} supplementation reverses these effects and reduces VC and osteogenic transdifferentiation of VSMC induced by high Pi both *in vitro* and *in vivo* (Figure 41.4).[94] Moreover, Mg^{2+} inhibits mineralization by directly suppressing apatite crystal formation or maturation in the extracellular space and maturation of CPP in uremic serum.[87,95] Increasing dialysate Mg^{2+} decreases calcification propensity in patients treated with maintenance hemodialysis.[96] Thus, Mg^{2+} seems to be useful to alleviate the Pi-induced calcification stress (Figure 41.4).

Renal Osteodystrophy

Fractures are more common in both predialysis CKD and stage 5D CKD compared to the general population, and the incidence increases with the progression of CKD.[97,98] The term renal osteodystrophy (ROD) is used to define alterations in bone morphology quantifiable by histomorphometry of bone biopsy.[99] Major classifications of ROD are based on histological findings. Osteitis fibrosa is associated with high turnover due to PTH stimulation of osteoblasts that are coupled to osteoclastic-mediated bone resorption. Osteomalacia is characterized by defective mineralization. Adynamic bone disease comprises low turnover due to low PTH and/or excessive treatment with vitamin D. The type of bone disease can influence S[Ca] and S[P] levels. High bone turnover contributes to elevated S[Ca] and

S[P] through increased release from bone. Low-turnover states can also make patients more susceptible to developing hypercalcemia after dietary loads or vitamin D therapy, due to the diminished buffering capacity for Ca^{2+} from the diminished bone remodeling.[100] Adynamic bone disease may increase the risk of vascular and soft tissue calcification, possibly due to limited Ca^{2+} buffering capacity or to a Ca^{2+} surfeit state.[101] Other examples of the impact of bone turnover on S[Ca] and S[P] in ESRD are hungry bone syndrome following parathyroidectomy, hypercalcemia observed with immobilization, and hypocalcemia following treatment with antiresorptive therapies. Osteoporosis may be observed with either high turnover or low turnover forms of ROD.

Whether FGF-23 acts directly on bone is a complex question to address because *in vivo* modifications of FGF-23 levels also disrupt S[P] and $1,25(OH)_2D_3$ levels. Direct action of FGF-23 on bone mineralization still remains to be clarified. *Fgf-23/NaPi2a* double knockout mice had completely normal S[P] levels compared with hyperphosphatemic *Fgf-23*$^{-/-}$ mice. Interestingly, these mice showed the same defects in bone mineralization, suggesting a direct action of FGF-23 on bone independent of S[P] levels.[102] It was proposed that increased osteopontin, a mineralization inhibitor, in bone is a pathogenic factor mediating the mineralization defect and alterations in bone metabolism observed in *Fgf-23*$^{-/-}$ mice.[103] However, *in vitro* experiments showed the opposite, with FGF-23 overexpression inhibiting matrix mineralization and osteoblast differentiation independent of its systemic effect on Pi metabolism,[104] while stimulating osteoclast activity.[105]

Recent investigations discovered α-Klotho in osteocytes.[106] Contrary to *kl/kl* mice that exhibit low-turnover osteoporosis, the deletion of *α-Klotho* from osteocytes resulted in a marked increase in bone formation and bone volume, along with the enhanced expression of osteoblastic marker genes.[107] The difference may be explained by the fact that the bone phenotype in *kl/kl* mice is not a direct result of the loss of α-Klotho in osteocytes, but of the inhibition of PTH secretion by hypercalcemia and hypervitaminosis D that leads to attenuated bone remodeling.

The role of Mg^{2+} in ROD is largely undefined. In bone, Mg^{2+} ions bind at the surface of hydroxyapatite crystals. Crystals are larger in Mg^{2+}-deficient bone, and the bone may be brittle and susceptible to fractures.[108] In a meta-analysis of population-based cohort studies, dietary Mg^{2+} intake was positively associated with the bone mineral density (BMD) of the femoral neck, total hip, and forearm.[109] Several studies showed that low S[Mg] is associated with osteoporosis.[110,111] Two large prospective cohort studies reported that both low serum and dietary Mg^{2+} levels are associated with increased risk of fractures.[112,113] Recently, it was found that patients undergoing hemodialysis with higher [Mg] levels have a lower risk of hip fractures.[114]

DIAGNOSIS

In adults, levels of S[Ca] (ionized Ca^{2+} or total Ca^{2+} corrected for albumin), S[P], PTH, serum bicarbonate, and alkaline phosphatase should be monitored in early stages of CKD (stage 3A). The frequency (every 1–3 to 12 months) should be based on the stage of CKD, the degree of abnormality, and the rate of CKD progression, with more frequent monitoring for patients with advanced CKD or rapid deterioration of eGFR.[115] As vitamin D deficiency (<10 ng/mL or 25 nmol/L) or insufficiency (10 to <20–32 ng/mL or 50–80 nmol/L) contributes to the pathogenesis of sHPT, levels of serum 25(OH) vitamin D should be routinely measured at baseline and to monitor therapeutic interventions.[116] The rate of change and severity of abnormalities in these analytes are highly variable among patients. Further, assay precision and accuracy may affect interpretation, specifically for PTH and 25(OH) vitamin D.[115] To diagnose CKD-MBD, one or more of these laboratory analytes should be abnormal. The interpretation of these abnormalities should also account for normal postprandial, diurnal, and seasonal variations. Laboratory tests should be performed at similar times of the day using the same assays whenever possible. The trend of changes rather one single measurement is also important for interpretation.

Calcium (Ca^{2+})

Measurement of S[Ca] is generally precise and reproducible, with minimal diurnal variation.[117] In patients with CKD, S[Ca] levels vary due to altered homeostasis and concomitant therapy. These fluctuations are more pronounced in CKD stage 5D (ESRD) patients due to dialysis-induced changes. Only 1% of total body Ca^{2+} is in the extracellular compartment. Serum ionized Ca^{2+} is physiologically active and constitutes 40–50% of total S[Ca]. Nonionized Ca^{2+} is bound to albumin and anions such as citrate, bicarbonate, and phosphate. Measurement of total serum Ca^{2+} concentration—even when corrected by S[Alb] levels—is less specific that ionized Ca^{2+} for the assessment of Ca^{2+} status, but it is more pragmatic.[118]

Phosphate (Pi)

The sum of bivalent (HPO_4^{-2}) and monovalent $(H_2PO_4^-)$ constitutes serum inorganic phosphate (Pi) concentration at pH 7.4, which is the compound measured in clinical practice by automated colorimetric

methods but commonly reported as "phosphorus" even though there is no elemental phosphorus in blood. Phosphate is mostly intracellular and serum levels are generally precise and reproducible. Diurnal and postprandial variations in S[P] and urinary phosphorus excretion have been documented (lower in the morning and higher late at night).[119]

Magnesium (Mg^{2+})

The assessment of Mg^{2+} status is complex as this cation is present mostly in the intracellular compartment, primarily in the skeleton and soft tissues. Only 1% of the total body Mg^{2+} is present in serum and the interstitium. Currently, measurement of S[Mg] by photometric methods is routine to evaluate Mg^{2+} status. However, levels of S[Mg] can be influenced by levels of S[Alb], other anions, and changes in blood pH.[120] Further, low levels of intracellular Mg^{2+} have been described in patients with diabetes, alcoholism, and malabsorption syndromes despite normal levels of S[Mg].[121] Overall, there is poor correlation between serum and intracellular Mg^{2+} levels.[122] Therefore, S[Mg] levels—although testing is readily available in clinical practice—is not the most reliable metric of total body Mg^{2+} status. Other measurements of Mg^{2+} status, such as serum free (ionized) Mg^{2+} or intracellular Mg^{2+} content by nuclear magnetic resonance and fluorescence probes are still under investigation. Functional tests such as the Mg^{2+} tolerance test to assess urinary excretion of Mg^{2+} in relation to parenteral load have been used in healthy subjects to assess magnesium deficiency but are of limited utility in patients with CKD due to the impaired renal functional excretory capacity.[123]

Parathyroid Hormone

PTH is stored in the parathyroid gland for pulsatile secretion and is cleaved at different sites (N-terminal, C-terminal, and mid-region fragments). The circulating 1−84 amino-acid protein has a half-life of 2−4 minutes. The extracellular ionized Ca^{2+} is a main determinant of minute-to-minute secretion of PTH. There are multiple PTH assays. Earlier assays measured C-terminal fragments lacking accuracy due to impaired renal excretion of these inactive peptides in CKD. N-terminal assays also detected inactive metabolites. Second generation PTH assays (two-site immunoradiometric capture at the amino- and carboxy-termini) can better detect active full-length PTH but can still pick up accumulated large C-terminal fragments, particularly in patients with advanced CKD.[124,125] Third generation bioactive PTH assays truly detect the 1−84-amino-acid, full-length PTH molecule.[126] Overall, the bioactive PTH assays yield lower PTH concentrations compared with intact PTH assays in CKD. Their use in clinical practice has not been fully implemented and further investigation is warranted.[127] The source of sample (serum vs. plasma) and sample handling also add variability to PTH assays.[128] Therefore, standardization in the methods of sample handling and processing is recommended. Analysis of trajectory of PTH levels rather than single-point interpretation and complementary CKD-MBD data should better guide the overall and comprehensive clinical management of patients with CKD-MBD.

Vitamin D and Metabolites

25-Hydroxyvitamin D

The term vitamin D collectively includes ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) compounds (Table 41.1). These compounds are lipophilic, have short half-life (~24 hours), and are not easy to quantify in serum or plasma. D_2 and D_3 are metabolized in the liver to 25(OH)D_2 (ercalcidiol) and 25(OH)D_3 (calcidiol) and are collectively named 25-hydroxyvitamin D or 25(OH)D, which has a longer half-life of ~3 weeks, and is considered the best clinical metric of vitamin D status from both nutritional and skin sources. The most common methods of measurement of 25(OH)D levels are automated chemiluminescence/radioimmunoassays for both 25(OH)D_2 and 25(OH)D_3 simultaneously, and liquid chromatography-tandem mass spectrometry, which can quantify 25(OH)D_2 and 25(OH)D_3 separately.[129] However, the utility of the latter in clinical practice has been questioned and may not necessarily guide management, as both metabolites have similar biological effects.[130]

1,25-Dihydroxyvitamin D

The dihydroxylated compounds 1,25$(OH)_2D_2$ and 1,25$(OH)_2D_3$ have a short half-life of approximately

TABLE 41.1 Vitamin D_2 and D_3 and Related Compounds

	D_2 Compounds	D_3 Compounds
Parent compound	Vitamin D_2 (ergocalciferol)	Vitamin D_3 (cholecalciferol)
After first hydroxylation	25-hydroxy D_2 (ercalcidiol)	25-hydroxy D_3 (calcidiol)
After second hydroxylation	1,25-dihydroxyvitamin D_2 (ercalcitriol)	1,25-dihydroxyvitamin D_3 (calcitriol)

4–6 hours and collectively constitute $1,25(OH)_2D$ (Table 41.1). Current commercial assays cannot distinguish between these two compounds. It is not known if these measurements—particularly in late stages of CKD—can substantially alter clinical decisions. Overall, circulating levels of $1,25(OH)_2D$ are approximately 1/1000 of total 25(OH)D levels. Furthermore, levels of $1,25(OH)_2D$ are influenced by substrate 25(OH)D storage and the enzymatic conversion of 25(OH)D to $1,25(OH)_2D$ by 25(OH)D-1α-hydroxylase renal enzyme (CYP27B1). CYP27B1 is stimulated by PTH, estrogen, calcitonin, growth hormone, prolactin, low Ca^{2+}, and low Pi and inhibited by FGF-23, metabolic acidosis, and its product $1,25(OH)_2D$.[131]

Alkaline Phosphatase

Alkaline phosphatases remove the phosphate moiety from phosphoproteins, phospholipids, nucleic acids, nucleotides, and other organic molecules and function optimally at alkaline blood pH. Total levels of alkaline phosphatases are measured by standardized automated colorimetric assays. These enzymes originate from the liver and bone but other organs such as the intestines, placenta, and kidneys are sources as well. Elevated levels of alkaline phosphatases are typically related to bone disease such as bone metastases, primary or secondary hyperparathyroidism, osteomalacia, and Paget's disease or liver dysfunction.[131] Therefore, liver function tests should be examined to exclude liver disease if elevated alkaline phosphatase is encountered. Bone-specific alkaline phosphatases can be isolated by an immunoradiometric assay, which further assists in the diagnosis of bone disease in the context of CKD-MBD, although the utility of this more specific test has not been fully elucidated for standardization in clinical practice.

Fibroblast Growth Factor 23

Initial studies showed *Fgf-23* mRNA expression in multiple organs[132] but later studies show osteocytes and osteoblasts to be the major source of elevated circulating FGF-23.[133] *Fgf-23* mRNA is still present in liver, kidneys, heart, spleen, and bone marrow.[132] In CKD patients, plasma FGF-23 levels are significantly elevated and inversely related to kidney function.[12,13] Measurement of circulating intact FGF-23—the biologically active form—is lower than levels reported using FGF-23 assays with C-terminal reagents (nondiscriminatory between full length and C-terminal fragments) in human CKD. Studies with simultaneous measurements of FGF-23 using both the intact and C-terminal assays are useful in assessing relative amounts of FGF-23 production and cleavage because cleavage will reduce circulating levels of intact FGF-23 but will not affect C-terminal FGF-23 levels. Currently, FGF-23 levels are not part of clinical assessments.

α-Klotho

α-Klotho expression is downregulated by inflammation, uremic toxins, hyperphosphatemia, low $1,25(OH)_2D$, oxidative stress, and by activation of the renin–angiotensin–aldosterone-system (RAAS), and upregulated by peroxisome proliferator-activated receptor gamma agonists, RAAS blockers, and statins.[44] The mechanisms by which α-Klotho expression is decreased include promoter hypermethylation and hyperacetylation.[134] Humans with lower eGFR also have lower circulating α-Klotho levels,[45] although some studies have reported no change in α-Klotho depending on level of kidney function.[50] These discrepancies are, in part, due to sample preparation errors and inaccurate measurement with commercial α-Klotho assays.[47,48,135] Serum α-Klotho is not currently measured in routine clinical practice.

Bone Health

Bone examination in patients with CKD stages 3 or above and evidence of CKD-MBD and/or risk factors for osteoporosis is now recommended for diagnosis and prognosis.[115] Dual-energy X-ray absorptiometry (DXA) measures of BMD—specifically femoral neck and total hip—predict pathologic fracture risk in CKD patients with stages 3 or above, particularly when levels of PTH are low or normal.[136] Other tools such as quantitative CT are available, but further research is needed to confirm their utility in fracture prediction. Overall, the observation of low or declining BMD can lead to timely interventions to improve outcomes in high-risk CKD patients. Noninvasive examination of bone disease is not fully informative for the classification of low, normal, and high bone turnover in some patients with CKD-MBD, yielding low negative predictive values and low positive predictive values for differentiating low-turnover vs. non low-turnover and high-turnover vs. nonhigh-turnover bone disease, respectively.[137]

Bone biopsy is not routinely performed for the evaluation of CKD-MBD. It is important to recognize that the ultimate pathologic diagnosis of ROD can only be achieved with a bone biopsy, the diagnostic gold standard. Bone biopsy should be strongly considered in patients with pathological fractures, suspicion of osteomalacia, refractory hypercalcemia, or erratic therapeutic response to standard CKD-MBD therapy.[115]

Vascular Calcification

In CKD patients, coronary artery and generalized VC are more prevalent, more severe, and more rapidly progressive than the general healthy population. Therefore, patients with CKD stages 3 or above and known vascular or valvular calcification should be considered at very high risk of cardiovascular morbidity and mortality. Other tests such as lateral abdominal radiograph, pulse wave velocity measurements of arterial stiffness, echocardiogram, or computed tomography-based imaging to estimate coronary artery calcification (CAC) metrics (CT-based CAC score) are alternatives.[131] CT-based CAC scores can be up to fivefold higher in patients on maintenance hemodialysis than in age-matched non-CKD controls.[138] Rather than indiscriminate testing of VC in all CKD patients, an individualized approach to assess severity, progression, and response to CKD-MBD therapy is recommended using noninvasive tests.[131]

THERAPY

Of the three ions under discussion, the one with the best data to support current therapeutic regimens is Pi. Pi restriction and Pi binding in the gut lumen are deployed routinely in clinical practice. The indications for Ca^{2+} and Mg^{2+} supplementation or restriction are much less clear, although both divalent cations are often given to CKD patients, primarily as Pi binders in the gut lumen. It is unknown whether the amount of Ca^{2+} and Mg^{2+} absorbed when given as Pi binders confers additional benefit. Practitioners largely rely on consensus guidelines that are based on expert opinion rather than randomized control trials with hard clinical outcomes. There is no reason why pathophysiology-driven consensus from experts in the absence of data on hard outcomes should not be acceptable in clinical practice.

Two points deserve mention. First, there are no single therapies that will work in CKD-MBD. There will always be integrated multiple therapies targeting more than one pathophysiologic factor—such as a specific type of Pi binder, calcimimetic, vitamin D replacement, and Mg^{2+} supplementation. The list of therapeutic agents will only increase as we learn more about the pathophysiology. Second, there will never be two patients that are identical, so treatment options will have to individualized for a given patient.

Calcium (Ca^{2+})

Ca^{2+} in acetate or carbonate form is still the most widely used Pi binder. Whether CKD and ESRD patients need more or less Ca^{2+} is a highly debatable subject. There is good consensus that osteoporosis in CKD should be treated.[139] Ca^{2+} supplementation has not received general support. In addition to its Pi-chelating properties in the gut lumen, some have argued that judicious Ca^{2+} absorption can contribute to suppression of PTH and also provides a Ca^{2+} load to counteract osteoporosis.[140] A counterpoint is an opposing view that ingested Ca^{2+} actually promotes soft tissue calcification (based mostly on acute balance studies) and hence is detrimental to health in CKD.[141] This is not a dichotomous situation as these models are not mutually exclusive. The skeleton of a CKD patient may indeed need Ca^{2+} for bone strength, but the problem is regulation of internal Ca^{2+} balance. The absorbed Ca^{2+} may undergo an ectopic destination. This is clearly a situation that will require tailored therapy for each patient. The Ca^{2+} preparations shown in Table 41.2 are designed for Pi binding. For more bioavailable oral Ca^{2+}, citrate will be more appropriate but currently, there is no indication for Calcium Citrate therapy in CKD.

Phosphate (Pi)

Phosphate is ubiquitous in the diet in the developed world. The impact of reduction of phosphotoxicity in preclinical animal models is excellent in showing causality. Human data are less strong, but high S[P] is clearly linked to VC, high FGF-23 and PTH, and cardiac remodeling; therapies to lower S[P] successfully ameliorate these intermediate phenotypes.[142] Randomized trials have documented the comparative efficacy between different protocols.[143,144] What is missing amidst these powerful data is the absence of assessments of hard clinical outcomes such as survival in well-designed randomized clinical trials. Nonetheless the beneficial effects of lowering Pi are still overall convincing. To achieve the goal, one can decrease Pi absorption or increase Pi excretion. Currently, we do not have practical means to achieve the latter in humans.

Intestinal Pi absorption can be reduced by several methods (Table 41.3). Dietary restriction is effective when properly executed but compliance is a formidable problem. A frequently ignored point is the highly diverse bioavailability of Pi ranging from highly easily absorbed (inorganic phosphate as food additives), to moderately absorbed (organic phosphate in its natural form needs to be hydrolyzed to free Pi), to phytates (found in plants and seeds) that are not absorbed by humans.[145] Ingested food with an equivalent amount of phosphate (e.g. 1000 mg of elemental phosphorus) delivers a vastly different amount of Pi to the circulation, depending on whether the Pi was ingested as inorganic, organic, or phytates. Therefore, in addition to restriction of the amount of dietary Pi, the modification of the type of dietary Pi is very important and often ignored.

Unfortunately, the conventional diet in the developed world is heavily laced with added inorganic Pi. Most patients are ingesting a high proportion of Pi as part of food additives, so the daily Pi load can be as high as twice the requirement.

There are many luminal binders of Pi that lower absorption (Tables 41.2 and 41.3). The principle is very similar despite different modes of action. The choice is largely driven by national guidelines, practice habit, cost, and accessibility. There is an array of bivalent (Ca^{2+}, Mg^{2+}, Fe^{2+}) and trivalent (Al^{3+}, La^{3+}) cations that function as anion exchangers to bind dietary and secreted Pi while releasing an anion such as carbonate or acetate. Synthetic polymeric cations such as sevelamer can bind Pi in exchange for chloride (sevelamer hydrochloride) or carbonate (sevelamer carbonate). Carbonate or metabolizable anions (acetate or citrate) when released also confers an alkali load. The perfect example is that sevelamer hydrochloride lowers serum bicarbonate concentration while sevelamer carbonate does not.

Pi binders reduce the available luminal Pi for absorption. Alternative methods modify the epithelial absorptive mechanisms that have evolved to be powerful means of extracting dietary Pi. Nicotinamide (niacin), which is already approved for human use for other indications, can inhibit the NaPi-2b transporter and transcellular transport.[146] Direct inhibition of the Na-coupled Pi transporter NaPi-2b is promising but may suffer from the large paracellular component that limits its efficacy.[147] In contrast, an unexpected downstream effect of an inhibitor of apical Na/H exchanger NHE3, originally designed to reduce gut Na^+ absorption, led to secondary effects of reduction of paracellular permeability to Pi and a substantial reduction of transepithelial Pi

TABLE 41.2 Phosphate Binders in Clinical Use

Cation	Formulation	Adverse Effects	Cost per Dose
Al^{3+}	Aluminum hydroxide	Osteomalacia Encephalopathy Microcytic anemia	$5
La^{3+}	Lanthanum carbonate	GI upset Unknown effect on bone	$12
Ca^{2+}	Calcium acetate Calcium carbonate	Hypercalcemia Ectopic calcification Adynamic bone disease	$1 $0.1
Mg^{2+}	Magnesium carbonate	Diarrhea Hypermagnesemia	$1.5
Fe^{2+}	Sucroferric oxyhydroxide Ferric citrate	Diarrhea Nausea	$11 $5
Sevalemar	Sevelamer hydrochloride Sevelamer carbonate	Diarrhea Constipation Metabolic acidosis	$7 $6

TABLE 41.3 Methods to Reduce Intestinal Pi Absorption

		Evidence	
Therapy	**Mode of Action**	**Preclinical**	**Humans**
Dietary modification	Reduce oral intake Reduce bioavailability	■	■
Gut lumen binder • Divalent/trivalent metal • Polymers	Binds dietary and secreted Pi in the gut lumen to be excreted in stool	■	■
NaPi-2b inhibitors	Inhibits transcellular absorption	■	
Nicotinamide (Niacin)	Inhibits transcellular absorption	■	■
NHE3 inhibitor	Inhibits paracellular absorption	■	■

absorption.[148] The reduction in intestinal Pi uptake will evolve very quickly to increasingly effective binders and inhibitors of both transcellular and paracellular Pi absorption, and treatment may be individualized.

Magnesium (Mg^{2+})

There is increasing appreciation regarding the potential deleterious effects of magnesium deficiency and the benefit of magnesium repletion in CKD. However, Mg^{2+} supplementation is not a routine practice, and there are no guidelines regarding how to achieve this goal. The data regarding the benefits of Mg^{2+} are well shown in animal models. Clinical epidemiologic data also support the detrimental effects of Mg^{2+} deficiency and the inferred beneficial effects of Mg^{2+} supplementation on diabetes, hyperparathyroidism, progression of CKD, cardiac arrhythmias, heart failure, hypertension, arterial calcification, and endothelial dysfunction.[17,149] Mg^{2+} is currently not routinely prescribed in the management of CKD, due mainly to lack of clinical guidelines, but other contributing factors include lack of clinically frank hypomagnesemia even in the presence of total body depletion, variations in interindividual and intraindividual longitudinal levels, variation in dialysis bath [Mg^{2+}], coexistence of compounding comorbid conditions, and side effects of therapy.

Oral Mg^{2+} supplementation is prescribed in various forms (oxide, chloride, lactate, gluconate, aspartate, citrate). Oxide has the lowest (<4%) and citrate the highest (~15%) absorption based on rise in S[Mg] and urinary Mg^{2+} excretion after an oral dose. The single factor most limiting Mg^{2+} therapy is diarrhea.

CONCLUSION

Disturbances in Pi, Ca^{2+}, and Mg^{2+} in CKD are part of the CKD-MBD syndrome, with grave cardiovascular complications that drive mortality, and skeletal complications that affect quality of life. The most important message is that there is not any automatic mobile phone-fit diagnostic algorithm or "one-size-fits-all" therapeutic regimen. There will be individualized treatments that are tailored to each patient's pathophysiology. Phosphate load to the organism should be restricted by dietary modifications and binders, and modifier of intestinal epithelial transport. Ca^{2+} supplements (or avoidance) should be prescribed only to those who will benefit from it based on individualized pathophysiology. Mg^{2+} therapy will have a similar scenario. We must have diagnostic capabilities to assess the Mg^{2+} status and guide whether to restrict or supplement Mg^{2+} to improve renal, cardiovascular, and metabolic outcomes.

References

1. Hill NR, Fatoba ST, Oke JL, et al. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. *PLoS One* 2016;**11**(7):e0158765.
2. Stenvinkel P, Larsson TE. Chronic kidney disease: a clinical model of premature aging. *Am J Kidney Dis* 2013;**62**(2):339–51.
3. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**(13):1296–305.
4. London GM, Marchais SJ, Guerin AP, Metivier F. Arteriosclerosis, vascular calcifications and cardiovascular disease in uremia. *Curr Opin Nephrol Hypertens* 2005;**14**(6):525–31.
5. Kestenbaum B, Belozeroff V. Mineral metabolism disturbances in patients with chronic kidney disease. *Eur J Clin Investig* 2007;**37**(8):607–22.
6. Covic A, Vervloet M, Massy ZA, et al. Bone and mineral disorders in chronic kidney disease: implications for cardiovascular health and ageing in the general population. *Lancet Diabetes Endocrinol* 2018;**6**(4):319–31.
7. Imura A, Iwano A, Tohyama O, et al. Secreted Klotho protein in sera and CSF: implication for post-translational cleavage in release of Klotho protein from cell membrane. *FEBS Lett* 2004;**565**(1–3):143–7.
8. Hu MC, Kuro OM, Moe OW. Klotho and chronic kidney disease. *Contrib Nephrol* 2013.
9. Sugiura H, Yoshida T, Tsuchiya K, et al. Klotho reduces apoptosis in experimental ischaemic acute renal failure. *Nephrol Dial Transplant* 2005;**20**(12):2636–45.
10. Zhou L, Li Y, Zhou D, Tan RJ, Liu Y. Loss of Klotho contributes to kidney injury by derepression of Wnt/beta-catenin signaling. *J Am Soc Nephrol* 2013;**24**(5):771–85.
11. Hu MC, Kuro-o M, Moe OW. Renal and extrarenal actions of Klotho. *Semin Nephrol* 2013;**33**(2):118–29.
12. Isakova T. Fibroblast growth factor 23 and adverse clinical outcomes in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2012;**21**(3):334–40.
13. Gutierrez OM, Mannstadt M, Isakova T, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008;**359**(6):584–92.
14. Kuro OM, Moe OW. FGF23-alphaKlotho as a paradigm for a kidney-bone network. *Bone* 2017;**100**:4–18.
15. Faul C, Amaral AP, Oskouei B, et al. FGF-23 induces left ventricular hypertrophy. *J Clin Investig* 2011;**121**(11):4393–408.
16. Rossaint J, Oehmichen J, Van Aken H, et al. FGF-23 signaling impairs neutrophil recruitment and host defense during CKD. *J Clin Investig* 2016;**126**(3):962–74.
17. Leenders NHJ, Vervloet MG. Magnesium: a magic bullet for cardiovascular disease in chronic kidney disease? *Nutrients* 2019;**11**(2).
18. Spiegel DM, Farmer B. Long-term effects of magnesium carbonate on coronary artery calcification and bone mineral density in hemodialysis patients: a pilot study. *Hemodial Int* 2009;**13**(4):453–9.
19. Mortazavi M, Moeinzadeh F, Saadatnia M, Shahidi S, McGee JC, Minagar A. Effect of magnesium supplementation on carotid intima-media thickness and flow-mediated dilatation among hemodialysis patients: a double-blind, randomized, placebo-controlled trial. *Eur Neurol* 2013;**69**(5):309–16.
20. Hoenderop JG, Nilius B, Bindels RJ. Calcium absorption across epithelia. *Physiol Rev* 2005;**85**(1):373–422.
21. Hoenderop JG, van der Kemp AW, Hartog A, et al. Molecular identification of the apical Ca2+ channel in 1,25-dihydroxyvitamin D3-responsive epithelia. *J Biol Chem* 1999;**274**(13):8375–8.
22. Lameris AL, Nevalainen PI, Reijnen D, et al. Segmental transport of Ca(2)(+) and Mg(2)(+) along the gastrointestinal tract. *Am J Physiol Gastrointest Liver Physiol* 2015;**308**(3):G206–216.

23. Nijenhuis T, Hoenderop JG, Bindels RJ. TRPV5 and TRPV6 in Ca(2+) (re)absorption: regulating Ca(2+) entry at the gate. *Pflügers Archiv* 2005;**451**(1):181–92.
24. van Goor MKC, Hoenderop JGJ, van der Wijst J. TRP channels in calcium homeostasis: from hormonal control to structure-function relationship of TRPV5 and TRPV6. *Biochim Biophys Acta Mol Cell Res* 2017;**1864**(6):883–93.
25. Chang W, Tu C, Chen TH, et al. Expression and signal transduction of calcium-sensing receptors in cartilage and bone. *Endocrinology* 1999;**140**(12):5883–93.
26. Moe SM. Calcium homeostasis in health and in kidney disease. *Comp Physiol* 2016;**6**(4):1781–800.
27. de Groot T, Lee K, Langeslag M, et al. Parathyroid hormone activates TRPV5 via PKA-dependent phosphorylation. *J Am Soc Nephrol* 2009;**20**(8):1693–704.
28. Hoenderop JG, Dardenne O, Van Abel M, et al. Modulation of renal Ca2+ transport protein genes by dietary Ca2+ and 1,25-dihydroxyvitamin D3 in 25-hydroxyvitamin D3-1alpha-hydroxylase knockout mice. *FASEB J* 2002;**16**(11):1398–406.
29. Kantham L, Quinn SJ, Egbuna OI, et al. The calcium-sensing receptor (CaSR) defends against hypercalcemia independently of its regulation of parathyroid hormone secretion. *Am J Physiol Endocrinol Metab* 2009;**297**(4):E915–923.
30. Biber J, Hernando N, Forster I. Phosphate transporters and their function. *Annu Rev Physiol* 2013;**75**:535–50.
31. Nishimura M, Naito S. Tissue-specific mRNA expression profiles of human solute carrier transporter superfamilies. *Drug Metab Pharmacokinet* 2008;**23**(1):22–44.
32. Radanovic T, Wagner CA, Murer H, Biber J. Regulation of intestinal phosphate transport. I. Segmental expression and adaptation to low-P(i) diet of the type IIb Na(+)-P(i) cotransporter in mouse small intestine. *Am J Physiol Gastrointest Liver Physiol* 2005;**288**(3): G496–500.
33. Yamashita T, Yoshioka M, Itoh N. Identification of a novel fibroblast growth factor, FGF-23, preferentially expressed in the ventrolateral thalamic nucleus of the brain. *Biochem Biophys Res Commun* 2000;**277**(2):494–8.
34. Kuro-o M, Matsumura Y, Aizawa H, et al. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature* 1997; **390**(6655):45–51.
35. Hu MC, Shiizaki K, Kuro-o M, Moe OW. Fibroblast growth factor 23 and Klotho: physiology and pathophysiology of an endocrine network of mineral metabolism. *Annu Rev Physiol* 2013;**75**: 503–33.
36. Shimada T, Kakitani M, Yamazaki Y, et al. Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF-23 in phosphate and vitamin D metabolism. *J Clin Investig* 2004; **113**(4):561–8.
37. Nakatani T, Sarraj B, Ohnishi M, et al. In vivo genetic evidence for klotho-dependent, fibroblast growth factor 23 (Fgf-23)-mediated regulation of systemic phosphate homeostasis. *FASEB J* 2009; **23**(2):433–41.
38. Wolf MT, An SW, Nie M, Bal MS, Huang CL. Klotho up-regulates renal calcium channel transient receptor potential vanilloid 5 (TRPV5) by intra- and extracellular N-glycosylation-dependent mechanisms. *J Biol Chem* 2014;**289**(52):35849–57.
39. de Baaij JH, Hoenderop JG, Bindels RJ. Magnesium in man: implications for health and disease. *Physiol Rev* 2015;**95**(1):1–46.
40. van der Wijst J, Bindels RJ, Hoenderop JG. Mg2+ homeostasis: the balancing act of TRPM6. *Curr Opin Nephrol Hypertens* 2014;**23**(4): 361–9.
41. Ferre S, Hoenderop JJ, Bindels RJ. Role of the distal convoluted tubule in renal Mg2+ handling: molecular lessons from inherited hypomagnesemia. *Magnes Res* 2011;**24**(3):S101–108.
42. Abed E, Labelle D, Martineau C, Loghin A, Moreau R. Expression of transient receptor potential (TRP) channels in human and murine osteoblast-like cells. *Mol Membr Biol* 2009;**26**(3):146–58.
43. Ferre S, Hoenderop JG, Bindels RJ. Sensing mechanisms involved in Ca2+ and Mg2+ homeostasis. *Kidney Int* 2012;**82**(11):1157–66.
44. Neyra JA, Hu MC. alphaKlotho and chronic kidney disease. *Vitam Horm* 2016;**101**:257–310.
45. Shimamura Y, Hamada K, Inoue K, et al. Serum levels of soluble secreted alpha-Klotho are decreased in the early stages of chronic kidney disease, making it a probable novel biomarker for early diagnosis. *Clin Exp Nephrol* 2012;**16**(5):722–9.
46. Hu MC, Shi M, Zhang J, et al. Klotho deficiency causes vascular calcification in chronic kidney disease. *J Am Soc Nephrol* 2011; **22**(1):124–36.
47. Yamazaki Y, Imura A, Urakawa I, et al. Establishment of sandwich ELISA for soluble alpha-Klotho measurement: age-dependent change of soluble alpha-Klotho levels in healthy subjects. *Biochem Biophys Res Commun* 2010;**398**(3):513–8.
48. Barker SL, Pastor J, Carranza D, et al. The demonstration of alpha-Klotho deficiency in human chronic kidney disease with a novel synthetic antibody. *Nephrol Dial Transplant* 2015;**30**(2):223–33.
49. Scholze A, Liu Y, Pedersen L, et al. Soluble alpha-klotho and its relation to kidney function and fibroblast growth factor-23. *J Clin Endocrinol Metab* 2014;**99**(5):E855–861.
50. Kim HR, Nam BY, Kim DW, et al. Circulating alpha-klotho levels in CKD and relationship to progression. *Am J Kidney Dis* 2013; **61**(6):899–909.
51. Koh N, Fujimori T, Nishiguchi S, et al. Severely reduced production of klotho in human chronic renal failure kidney. *Biochem Biophys Res Commun* 2001;**280**(4):1015–20.
52. Sakan H, Nakatani K, Asai O, et al. Reduced renal alpha-Klotho expression in CKD patients and its effect on renal phosphate handling and vitamin D metabolism. *PLoS One* 2014;**9**(1): e86301.
53. Drew DA, Katz R, Kritchevsky S, et al. Association between soluble klotho and change in kidney function: the health aging and body composition study. *J Am Soc Nephrol* 2017;**28**(6): 1859–66.
54. Portale AA, Wolf MS, Messinger S, et al. Fibroblast growth factor 23 and risk of CKD progression in children. *Clin J Am Soc Nephrol* 2016;**11**(11):1989–98.
55. Isakova T, Cai X, Lee J, et al. Longitudinal FGF-23 trajectories and mortality in patients with CKD. *J Am Soc Nephrol* 2018;**29**(2): 579–90.
56. Moe SM. Calcium as a cardiovascular toxin in CKD-MBD. *Bone* 2017;**100**:94–9.
57. Hill KM, Martin BR, Wastney ME, et al. Oral calcium carbonate affects calcium but not phosphorus balance in stage 3-4 chronic kidney disease. *Kidney Int* 2013;**83**(5):959–66.
58. Floege J. Magnesium concentration in dialysate: is higher better? *Clin J Am Soc Nephrol* 2018;**13**(9):1309–10.
59. Mitsopoulos E, Griveas I, Zanos S, et al. Increase in serum magnesium level in haemodialysis patients receiving sevelamer hydrochloride. *Int Urol Nephrol* 2005;**37**(2):321–8.
60. Oka T, Hamano T, Sakaguchi Y, et al. Proteinuria-associated renal magnesium wasting leads to hypomagnesemia: a common electrolyte abnormality in chronic kidney disease. *Nephrol Dial Transplant* 2018. https://doi.org/10.1093/ndt/gfy119 [Epub ahead of print].

61. Lameris AL, Monnens LA, Bindels RJ, Hoenderop JG. Drug-induced alterations in Mg2+ homoeostasis. *Clin Sci* 2012;**123**(1): 1−14.
62. Alexander RT, Dimke H. Effect of diuretics on renal tubular transport of calcium and magnesium. *Am J Physiol Renal Physiol* 2017; **312**(6):F998−1015.
63. Kurstjens S, de Baaij JH, Bouras H, Bindels RJ, Tack CJ, Hoenderop JG. Determinants of hypomagnesemia in patients with type 2 diabetes mellitus. *Eur J Endocrinol* 2017;**176**(1):11−9.
64. Kao WH, Folsom AR, Nieto FJ, Mo JP, Watson RL, Brancati FL. Serum and dietary magnesium and the risk for type 2 diabetes mellitus: the Atherosclerosis Risk in Communities Study. *Arch Intern Med* 1999;**159**(18):2151−9.
65. Sakaguchi Y, Iwatani H, Hamano T, et al. Magnesium modifies the association between serum phosphate and the risk of progression to end-stage kidney disease in patients with non-diabetic chronic kidney disease. *Kidney Int* 2015;**88**(4):833−42.
66. Sakaguchi Y, Hamano T, Matsui I, et al. Low magnesium diet aggravates phosphate-induced kidney injury. *Nephrol Dial Transplant* 2018. https://doi.org/10.1093/ndt/gfy358 [Epub ahead of print].
67. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; **32**(5 Suppl. 3):S112−119.
68. Nuss HB, Kaab S, Kass DA, Tomaselli GF, Marban E. Cellular basis of ventricular arrhythmias and abnormal automaticity in heart failure. *Am J Physiol* 1999;**277**(1):H80−91.
69. Bogin E, Massry SG, Harary I. Effect of parathyroid hormone on rat heart cells. *J Clin Investig* 1981;**67**(4):1215−27.
70. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol* 2001;**12**(10):2131−8.
71. Drueke T, Fauchet M, Fleury J, et al. Effect of parathyroidectomy on left-ventricular function in haemodialysis patients. *Lancet* 1980; **1**(8160):112−4.
72. Kestenbaum B, Sampson JN, Rudser KD, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 2005;**16**(2):520−8.
73. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998;**31**(4):607−17.
74. Hu MC, Shi M, Cho HJ, et al. Klotho and phosphate are modulators of pathologic uremic cardiac remodeling. *J Am Soc Nephrol* 2015;**26**(6):1290−302.
75. Xie J, Yoon J, An SW, Kuro-o M, Huang CL. Soluble klotho protects against uremic cardiomyopathy independently of fibroblast growth factor 23 and phosphate. *J Am Soc Nephrol* 2015;**26**(5): 1150−60.
76. Morishita K, Shirai A, Kubota M, et al. The progression of aging in klotho mutant mice can be modified by dietary phosphorus and zinc. *J Nutr* 2001;**131**(12):3182−8.
77. Hu MC, Shi M, Gillings N, et al. Recombinant alpha-Klotho may be prophylactic and therapeutic for acute to chronic kidney disease progression and uremic cardiomyopathy. *Kidney Int* 2017;**91**(5):1104−14.
78. Xie J, Cha SK, An SW, Kuro OM, Birnbaumer L, Huang CL. Cardioprotection by Klotho through downregulation of TRPC6 channels in the mouse heart. *Nat Commun* 2012;**3**:1238.
79. Kieboom BC, Niemeijer MN, Leening MJ, et al. Serum magnesium and the risk of death from coronary heart disease and sudden cardiac death. *J Am Heart Assoc* 2016;**5**(1).
80. Qu X, Jin F, Hao Y, et al. Magnesium and the risk of cardiovascular events: a meta-analysis of prospective cohort studies. *PLoS One* 2013;**8**(3):e57720.
81. Shanahan CM. Mechanisms of vascular calcification in CKD-evidence for premature ageing? *Nat Rev Nephrol* 2013;**9**(11): 661−70.
82. Chen TH, Kuro OM, Chen CH, et al. The secreted Klotho protein restores phosphate retention and suppresses accelerated aging in Klotho mutant mice. *Eur J Pharmacol* 2013;**698**(1−3):67−73.
83. Lau WL, Leaf EM, Hu MC, et al. Vitamin D receptor agonists increase klotho and osteopontin while decreasing aortic calcification in mice with chronic kidney disease fed a high phosphate diet. *Kidney Int* 2012;**82**(12):1261−70.
84. Masuda H, Chikuda H, Suga T, Kawaguchi H, Kuro-o M. Regulation of multiple ageing-like phenotypes by inducible klotho gene expression in klotho mutant mice. *Mech Ageing Dev* 2005;**126**(12): 1274−83.
85. Saito Y, Yamagishi T, Nakamura T, et al. Klotho protein protects against endothelial dysfunction. *Biochem Biophys Res Commun* 1998;**248**(2):324−9.
86. Hamano T, Matsui I, Mikami S, et al. Fetuin-mineral complex reflects extraosseous calcification stress in CKD. *J Am Soc Nephrol* 2010;**21**(11):1998−2007.
87. Pasch A, Farese S, Graber S, et al. Nanoparticle-based test measures overall propensity for calcification in serum. *J Am Soc Nephrol* 2012;**23**(10):1744−52.
88. Sage AP, Lu J, Tintut Y, Demer LL. Hyperphosphatemia-induced nanocrystals upregulate the expression of bone morphogenetic protein-2 and osteopontin genes in mouse smooth muscle cells in vitro. *Kidney Int* 2011;**79**(4):414−22.
89. Shuto E, Taketani Y, Tanaka R, et al. Dietary phosphorus acutely impairs endothelial function. *J Am Soc Nephrol* 2009;**20**(7): 1504−12.
90. Bostom A, Pasch A, Madsen T, et al. Serum calcification propensity and fetuin-A: biomarkers of cardiovascular disease in kidney transplant recipients. *Am J Nephrol* 2018;**48**(1):21−31.
91. Pasch A, Block GA, Bachtler M, et al. Blood calcification propensity, cardiovascular events, and survival in patients receiving hemodialysis in the EVOLVE trial. *Clin J Am Soc Nephrol* 2017;**12**(2): 315−22.
92. Ishimura E, Okuno S, Kitatani K, et al. Significant association between the presence of peripheral vascular calcification and lower serum magnesium in hemodialysis patients. *Clin Nephrol* 2007; **68**(4):222−7.
93. Sakaguchi Y, Hamano T, Nakano C, et al. Association between density of coronary artery calcification and serum magnesium levels among patients with chronic kidney disease. *PLoS One* 2016;**11**(9):e0163673.
94. Ter Braake AD, Shanahan CM, de Baaij JHF. Magnesium counteracts vascular calcification: passive interference or active modulation? *Arterioscler Thromb Vasc Biol* 2017;**37**(8):1431−45.
95. Ter Braake AD, Tinnemans PT, Shanahan CM, Hoenderop JGJ, de Baaij JHF. Magnesium prevents vascular calcification in vitro by inhibition of hydroxyapatite crystal formation. *Sci Rep* 2018;**8**(1):2069.
96. Bressendorff I, Hansen D, Schou M, Pasch A, Brandi L. The effect of increasing dialysate magnesium on serum calcification propensity in subjects with end stage kidney disease: a randomized, controlled clinical trial. *Clin J Am Soc Nephrol* 2018;**13**(9):1373−80.
97. Yenchek RH, Ix JH, Shlipak MG, et al. Bone mineral density and fracture risk in older individuals with CKD. *Clin J Am Soc Nephrol* 2012;**7**(7):1130−6.

98. Naylor KL, McArthur E, Leslie WD, et al. The three-year incidence of fracture in chronic kidney disease. *Kidney Int* 2014; **86**(4):810–8.
99. Moe S, Drueke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006;**69**(11):1945–53.
100. Frazao JM, Messa P, Mellotte GJ, et al. Cinacalcet reduces plasma intact parathyroid hormone, serum phosphate and calcium levels in patients with secondary hyperparathyroidism irrespective of its severity. *Clin Nephrol* 2011;**76**(3):233–43.
101. Goldsmith D, Ritz E, Covic A. Vascular calcification: a stiff challenge for the nephrologist: does preventing bone disease cause arterial disease? *Kidney Int* 2004;**66**(4):1315–33.
102. Sitara D, Kim S, Razzaque MS, et al. Genetic evidence of serum phosphate-independent functions of FGF-23 on bone. *PLoS Genet* 2008;**4**(8):e1000154.
103. Yuan Q, Jiang Y, Zhao X, et al. Increased osteopontin contributes to inhibition of bone mineralization in FGF23-deficient mice. *J Bone Miner Res* 2014;**29**(3):693–704.
104. Wang H, Yoshiko Y, Yamamoto R, et al. Overexpression of fibroblast growth factor 23 suppresses osteoblast differentiation and matrix mineralization in vitro. *J Bone Miner Res* 2008;**23**(6):939–48.
105. Allard L, Demoncheaux N, Machuca-Gayet I, et al. Biphasic effects of vitamin D and FGF-23 on human osteoclast biology. *Calcif Tissue Int* 2015;**97**(1):69–79.
106. Rhee Y, Bivi N, Farrow E, et al. Parathyroid hormone receptor signaling in osteocytes increases the expression of fibroblast growth factor-23 in vitro and in vivo. *Bone* 2011;**49**(4):636–43.
107. Komaba H, Kaludjerovic J, Hu DZ, et al. Klotho expression in osteocytes regulates bone metabolism and controls bone formation. *Kidney Int* 2017;**92**(3):599–611.
108. Alfrey AC, Miller NL. Bone magnesium pools in uremia. *J Clin Investig* 1973;**52**(12):3019–27.
109. Farsinejad-Marj M, Saneei P, Esmaillzadeh A. Dietary magnesium intake, bone mineral density and risk of fracture: a systematic review and meta-analysis. *Osteoporos Int* 2016;**27**(4):1389–99.
110. Brodowski J. Levels of ionized magnesium in women with various stages of postmenopausal osteoporosis progression evaluated on the basis of densitometric examinations. *Przegl Lek* 2000; **57**(12):714–6.
111. Huang JH, Cheng FC, Wu HC. Low magnesium exacerbates osteoporosis in chronic kidney disease patients with diabetes. *Int J Endocrinol* 2015;**2015**:380247.
112. Veronese N, Stubbs B, Solmi M, et al. Dietary magnesium intake and fracture risk: data from a large prospective study. *Br J Nutr* 2017;**117**(11):1570–6.
113. Kunutsor SK, Whitehouse MR, Blom AW, Laukkanen JA. Low serum magnesium levels are associated with increased risk of fractures: a long-term prospective cohort study. *Eur J Epidemiol* 2017;**32**(7):593–603.
114. Sakaguchi Y, Hamano T, Wada A, Hoshino J, Masakane I. Magnesium and risk of hip fracture among patients undergoing hemodialysis. *J Am Soc Nephrol* 2018;**29**(3):991–9.
115. Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO chronic kidney disease-mineral and bone disorder (CKD-MBD) guideline update: what's changed and why it matters. *Kidney Int* 2017;**92**(1):26–36.
116. Hollis BW. Assessment of vitamin D status and definition of a normal circulating range of 25-hydroxyvitamin D. *Curr Opin Endocrinol Diabetes Obes* 2008;**15**(6):489–94.
117. Parfitt AM. Bone and plasma calcium homeostasis. *Bone* 1987; **8**(Suppl. 1):S1–8.
118. Labriola L, Wallemacq P, Gulbis B, Jadoul M. The impact of the assay for measuring albumin on corrected ('adjusted') calcium concentrations. *Nephrol Dial Transplant* 2009;**24**(6):1834–8.
119. Portale AA, Halloran BP, Morris Jr RC. Dietary intake of phosphorus modulates the circadian rhythm in serum concentration of phosphorus. Implications for the renal production of 1,25-dihydroxyvitamin D. *J Clin Investig* 1987;**80**(4):1147–54.
120. Quamme GA. Laboratory evaluation of magnesium status. Renal function and free intracellular magnesium concentration. *Clin Lab Med* 1993;**13**(1):209–23.
121. Nadler JL, Rude RK. Disorders of magnesium metabolism. *Endocrinol Metab Clin N Am* 1995;**24**(3):623–41.
122. Alfrey AC, Miller NL, Butkus D. Evaluation of body magnesium stores. *J Lab Clin Med* 1974;**84**(2):153–62.
123. Fawcett WJ, Haxby EJ, Male DA. Magnesium: physiology and pharmacology. *Br J Anaesth* 1999;**83**(2):302–20.
124. Gao P, D'Amour P. Evolution of the parathyroid hormone (PTH) assay–importance of circulating PTH immunoheterogeneity and of its regulation. *Clin Lab* 2005;**51**(1–2):21–9.
125. Souberbielle JC, Friedlander G, Cormier C. Practical considerations in PTH testing. *Clin Chim Acta* 2006;**366**(1–2):81–9.
126. Coen G, Bonucci E, Ballanti P, et al. PTH 1-84 and PTH "7-84" in the noninvasive diagnosis of renal bone disease. *Am J Kidney Dis* 2002;**40**(2):348–54.
127. Dupuy AM, Bargnoux AS, Morena M, et al. Moving from the second to the third generation Roche PTH assays: what are the consequences for clinical practice? *Clin Chem Lab Med* 2018;**57**(2):244–9.
128. Joly D, Drueke TB, Alberti C, et al. Variation in serum and plasma PTH levels in second-generation assays in hemodialysis patients: a cross-sectional study. *Am J Kidney Dis* 2008;**51**(6): 987–95.
129. Ersfeld DL, Rao DS, Body JJ, et al. Analytical and clinical validation of the 25 OH vitamin D assay for the LIAISON automated analyzer. *Clin Biochem* 2004;**37**(10):867–74.
130. Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. *J Clin Endocrinol Metab* 2008;**93**(3): 677–81.
131. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2009;(113): S1–130.
132. Shimada T, Mizutani S, Muto T, et al. Cloning and characterization of FGF-23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci USA* 2001;**98**(11):6500–5.
133. Pereira RC, Juppner H, Azucena-Serrano CE, Yadin O, Salusky IB, Wesseling-Perry K. Patterns of FGF-23, DMP1, and MEPE expression in patients with chronic kidney disease. *Bone* 2009;**45**(6): 1161–8.
134. Azuma M, Koyama D, Kikuchi J, et al. Promoter methylation confers kidney-specific expression of the Klotho gene. *FASEB J* 2012; **26**(10):4264–74.
135. Pedersen L, Pedersen SM, Brasen CL, Rasmussen LM. Soluble serum Klotho levels in healthy subjects. Comparison of two different immunoassays. *Clin Biochem* 2013;**46**(12):1079–83.
136. West SL, Lok CE, Langsetmo L, et al. Bone mineral density predicts fractures in chronic kidney disease. *J Bone Miner Res* 2015; **30**(5):913–9.

137. Sprague SM, Bellorin-Font E, Jorgetti V, et al. Diagnostic accuracy of bone turnover markers and bone histology in patients with CKD treated by dialysis. *Am J Kidney Dis* 2016;**67**(4):559–66.
138. Braun J, Oldendorf M, Moshage W, Heidler R, Zeitler E, Luft FC. Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. *Am J Kidney Dis* 1996;**27**(3):394–401.
139. Ott SM. Review: osteoporosis drugs may improve BMD and reduce fractures in some patients with CKD. *Ann Intern Med* 2017;**167**(4):JC19.
140. Taksande SR, Worcester EM. Calcium supplementation in chronic kidney disease. *Expert Opin Drug Saf* 2014;**13**(9):1175–85.
141. Moe SM. Rationale to reduce calcium intake in adult patients with chronic kidney disease. *Curr Opin Nephrol Hypertens* 2018;**27**(4):251–7.
142. Kidney Disease: Improving Global Outcomes CKDMBDUWG. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl* 2017;**7**(1):1–59.
143. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int* 2007;**71**(5):438–41.
144. Block GA, Spiegel DM, Ehrlich J, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int* 2005;**68**(4):1815–24.
145. Shimada M, Shutto-Uchita Y, Yamabe H. Lack of awareness of dietary sources of phosphorus is a clinical concern. *In Vivo* 2019;**33**(1):11–6.
146. Ginsberg C, Ix JH. Nicotinamide and phosphate homeostasis in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2016;**25**(4):285–91.
147. Sabbagh Y, O'Brien SP, Song W, et al. Intestinal npt2b plays a major role in phosphate absorption and homeostasis. *J Am Soc Nephrol* 2009;**20**(11):2348–58.
148. Labonte ED, Carreras CW, Leadbetter MR, et al. Gastrointestinal inhibition of sodium-hydrogen exchanger 3 reduces phosphorus absorption and protects against vascular calcification in CKD. *J Am Soc Nephrol* 2015;**26**(5):1138–49.
149. Massy ZA, Nistor I, Apetrii M, et al. Magnesium-based interventions for normal kidney function and chronic kidney disease. *Magnes Res* 2016;**29**(4):126–40.

QUESTIONS AND ANSWERS

Question 1

Which of the following statements about bone examination in CKD is false?

A. Bone examination in patients with CKD stages ≥3 and evidence of CKD-MBD and/or risk factors for osteoporosis is recommended for diagnosis and prognosis
B. In patients with advanced CKD and low or normal PTH, DXA measures of BMD predict pathologic fracture risk
C. Noninvasive examination of bone disease yields high negative predictive values for differentiating low-turnover vs. nonlow-turnover
D. Noninvasive examination of bone disease yields low positive predictive values for differentiating high-turnover vs. nonhigh-turnover bone disease
E. Bone biopsy should be considered in patients with pathological fractures, suspicion of osteomalacia, and refractory hypercalcemia

Answer: C

Bone examination in patients with CKD stages 3 or above and evidence of CKD-MBD and/or risk factors for osteoporosis is now recommended for diagnosis and prognosis. DXA measures of BMD—specifically femoral neck and total hip—predict pathologic fracture risk in CKD patients with stages 3 or above, particularly when levels of PTH are low or normal. Noninvasive examination of bone disease is not fully informative for the classification of low, normal, and high bone turnover in some patients with CKD-MBD, yielding low negative predictive values and low positive predictive values for differentiating low-turnover vs. nonlow-turnover and high-turnover vs. non high-turnover bone disease, respectively. Although bone biopsy is not routinely performed for the evaluation of CKD-MBD, it is important to recognize that the ultimate pathologic diagnosis of ROD can only be achieved with a bone biopsy, the diagnostic gold standard. Bone biopsy should be strongly considered in patients with pathological fractures, suspicion of osteomalacia, refractory hypercalcemia, or erratic therapeutic response to standard CKD-MBD therapy.

Question 2

Which of the following statements about PTH secretion and measurement is false?

A. Extracellular Pi is a main determinant of secretion of PTH
B. Third-generation bioactive PTH assays truly detect the 1− 84-amino-acid, full-length PTH molecule
C. Earlier PTH assays measuring C-terminal fragments lacked accuracy due to impaired renal excretion of these inactive peptides in CKD
D. Second-generation PTH assays can detect active full-length PTH but can still detect accumulated large C-terminal fragments, particularly in patients with advanced CKD

Answer: A

PTH is stored in the parathyroid gland for pulsatile secretion and is cleaved at different sites (N-terminal, C-terminal, and mid-region fragments). The circulating 1−84 amino-acid protein has a half-life of 2−4 minutes. The extracellular ionized Ca^{2+} concentration is a main determinant of minute-to-minute secretion of PTH. There are multiple PTH assays. Earlier assays measured C-terminal fragments, lacking accuracy due to impaired renal excretion of these inactive peptides in CKD. N-terminal assays also detected inactive metabolites. Second generation PTH assays (two-site immunoradiometric capture at the amino- and carboxy-termini) can better detect active full-length PTH but can still pick up accumulated large C-terminal fragments, particularly in patients with advanced CKD. Third-generation bioactive PTH assays truly detect the 1− 84-amino-acid, full-length PTH molecule.

Question 3

CKD is often considered a state of accelerated aging associated with α-Klotho deficiency and phosphate retention. Based on current knowledge, which one of the following events has not been linked to α-Klotho deficiency in CKD:

A. Cardiac remodeling
B. Increase in blood FGF-23 levels
C. Renal magnesium wasting
D. Increase in parathyroid hormone levels

Answer: C

Both α-Klotho deficiency and low serum magnesium levels have been associated with adverse outcomes in CKD. However, the crosstalk between α-Klotho and magnesium homeostasis is not currently defined. The principal role of α-Klotho is to form the specific receptor complex with FGFR1 that is required for FGF-23 signaling. As α-Klotho levels decline progressively in CKD, FGF-23 resistance develops, causing a compensatory increase in blood FGF-23 levels, high parathyroid hormone and S[P] levels, and low $1,25(OH)_2D_3$ accompany these changes. Preclinical studies showed that α-Klotho deficiency plays a role in the pathogenesis of uremic cardiomyopathy independently of FGF-23 and S[P].

Question 4

Select the molecular events that do not contribute to medial vascular calcification in CKD:

A. Production of reactive oxygen species by endothelial cells
B. Increase in circulating fetuin A levels
C. Transdifferentiation of vascular smooth muscle cells
D. Increased formation of calcioprotein particles in the blood

Answer: B

Fetuin A is circulating inhibitor of ectopic calcification. CKD-MBD is characterized by a decrease, not an increase, in circulating fetuin A levels, an event that promotes blood calcification propensity, formation of pathological secondary calcioprotein particles, and vascular calcification. Endothelial cells damaged by the uremic milieu or high phosphate show an increase in reactive oxygen species together with impaired nitric oxide production, and release of proinflammatory, profibrotic, and proangiogenic factors. These events not only induce endothelial dysfunction but also stimulate vascular smooth muscle cells transdifferentiation and vascular calcification.

Question 5

Which of the following statements about phosphate management in CKD is true?

A. The use of enteric phosphate binder lowers S[P] levels, parathyroid hormone, soft tissue calcification, and mortality in patient with CKD
B. Phosphate absorption from the gut can be decreased by dietary modification, inhibition of transcellular, and paracellular intestinal absorption
C. S[P] is usually increased in most patient with CKD stage 3
D. Dietary phosphate can be sequestered by oral administration of monovalent, divalent, or trivalent metallic ions.

Answer: B

Although phosphate binders correct a number of biochemical abnormalities in CKD, therapy with phosphate binders has not been shown in randomized control trials to lower mortality. The available methods to decrease phosphate absorption include lowering phosphate intake, changing the form of phosphate ingested, sequestering phosphate in the gut lumen, or decreasing transcellular or paracellular absorption. Frank hyperphosphatemia can occur in stage 3 CKD, but it rather unusual. There are no effective monovalent cations that can bind phosphate in the gut lumen.

Question 6

Based on both preclinical and clinical data, which one of the following is not a potential beneficial effect of magnesium supplementation in CKD?

A. Lowers phosphate absorption in the intestine
B. Prevents formation of calcioprotein particles in the blood
C. Acts directly on blood vessels to ameliorate uremic vasculopathy
D. Prevents hyperkalemia

Answer: D

Magnesium chelates phosphate in the gut lumen in an insoluble form and is a well-known phosphate binder. In the blood, magnesium can form soluble complexes with phosphate and prevent the formation of calcium phosphate precipitates and calcioprotein particles. There are many cell culture and *ex vivo* vascular experiments that show magnesium may protect the vasculature. The clinical data, albeit showing only association and not causality, clearly demonstrate a beneficial effect of higher S[Mg], particularly in the presence of hyperphosphatemia. Magnesium deficiency promotes renal potassium wasting and hypokalemia.

CHAPTER

42

Acid/Base Metabolism in Chronic Kidney Disease

Lee Hamm

Tulane University, New Orleans, LA, United States

Abstract

Chronic kidney disease (CKD) frequently causes metabolic acidosis. By stage 4 CKD approximately 40% of patients have metabolic acidosis. This is usually a hyperchloremic acidosis with a near-normal anion gap and normal S[K]. When the glomerular filtration rate (GFR) is less than 20 mL/min, a classic high anion gap metabolic acidosis ensues. Although a variety of defects in acid–base regulation have been reported, the predominant defect causing acidosis is an inadequate increase in ammonium excretion in the urine.

A variety of complications are caused by this acidosis in conjunction with the other consequences of CKD: loss of muscle mass, loss of bone mineral, insulin resistance, and faster loss of GFR. Increased mortality is associated with the acidosis as well.

Treatment of the acidosis may be with sodium bicarbonate, citrate, or diets high in fruits and vegetables. A few single-center trials have suggested that treatment of acidosis improves the progression of chronic kidney disease (CKD) and improves muscle function. Similar treatments have been evaluated in a few studies in patients with normal systemic pH and serum bicarbonate concentration. The rationale for such studies is based on some evidence of retained acid in selected patients with CKD.

SCOPE OF THE PROBLEM/PUBLIC HEALTH IMPLICATIONS

Metabolic acidosis is a common problem in patients with CKD, particularly as the CKD progresses beyond the earliest stages. Usually the acidosis is hyperchloremic with a normal anion gap when the glomerular filtration rate (GFR) is between 20 and 50 mL/min. As the GFR falls further below 20 mL/min, the acidosis frequently changes to a high anion gap type. Using a plasma bicarbonate concentration (HCO_3^-) of <22 mEq/L as the definition of acidosis, 2–13% of patients with stage 3 CKD and 19–37% of patients with stage 4 CKD have overt acidosis[1–3] (Figure 42.1).

This acidosis is not only a cause of a variety of complications but is likely also associated with further progression of the fall in GFR (Figure 42.2).

In addition to overt clinical acidosis reflected by a low plasma HCO_3^- or arterial pH, intrarenal (interstitial) acidosis or retained acid in CKD patients may be present when overt acidosis is not apparent.[4,5] This acid retention has been identified by administering boluses of bicarbonate and measuring the change in plasma HCO_3^-. Less than a normal increase in plasma HCO_3^- is assumed to represent retained acid.[4,5] Because this phenomenon of retained acid may be common,[5] even in early CKD, this may be an important target for future treatment. This retained acid may cause progressive renal damage, just as systemic acidosis does.

PATHOPHYSIOLOGY

Mechanisms of Metabolic Acidosis in CKD

Metabolic acidosis in CKD usually results from failure of the kidneys to adequately excrete the normal nonvolatile, endogenous acid load derived from typical diets and metabolism.[6] The acid load from a typical Western diet is normally 40–70 mEq per day in adults, with a vegetarian diet leading to lesser acid loads. This is usually reported as about 1 mEq/kg body weight in adults and 2–3 mEq/kg in children. The kidneys normally excrete this entire acid load with about 1/3 as titratable acid and 2/3 as ammonium excretion. Titratable acid excretion is the acid excreted along the nephron, lowering urine pH, and titrated by urinary buffers, predominantly phosphate moieties. Normally

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00042-5

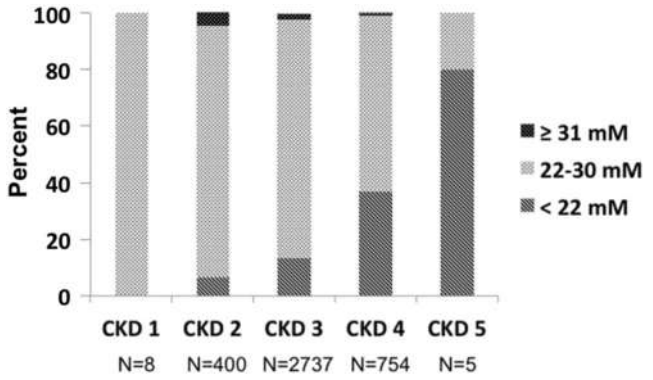


FIGURE 42.1 Prevalence of serum bicarbonate abnormalities by stage of chronic kidney disease (CKD) in the CRIC (Chronic Renal Insufficiency Cohort) study.[1]

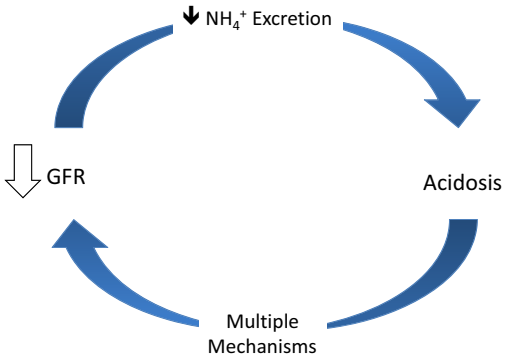


FIGURE 42.2 Schematic of the relationship of CKD and reduced glomerular filtration rate (GFR) and acidosis. Reduced GFR, particularly at levels below 30 mL/min is often associated with and causes metabolic acidosis. This is attributable predominantly to inadequate excretion of ammonium (NH_4^+). In recent years numerous studies have suggested that acidosis leads to further worsening of GFR.

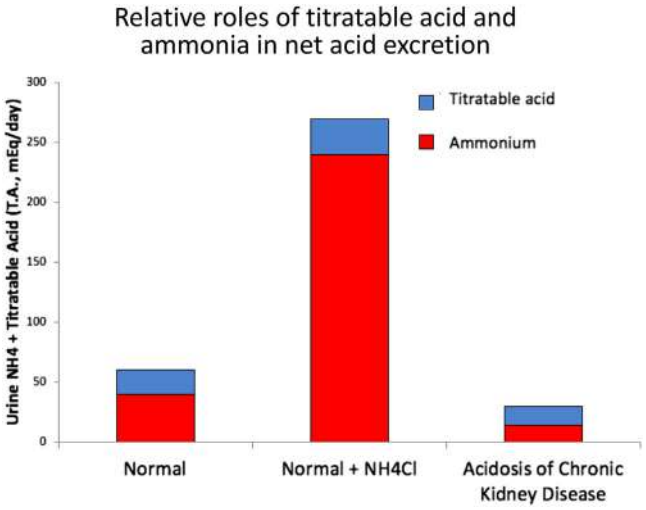


FIGURE 42.3 Acid excretion in normal individuals, normal individuals with an acid load induced with NH_4Cl (average plasma HCO_3^- 20 mEq/L), and individuals with acidosis accompanying CKD (average GFR 20 mL/min, average plasma HCO_3^- 17 mEq/L). In normal participants, increases in NH_4^+ excretion account for the predominant compensatory response to acidosis. In advanced CKD, NH_4^+ excretion fails to adequately increase with resultant acidosis. Abbreviations: *CKD*, chronic kidney disease; *GFR*, glomerular filtration rate; *T.A.*, urine titratable acidity. *Adapted with permission from reference 7.*

if daily acid load is higher, the predominant adaptation to excrete this acid load is an increase in ammonium excretion in the urine (Figure 42.3). The increased ammonium excretion occurs *via* both increased ammoniagenesis and increased transport of the produced ammonium into the tubular lumen and final urine.[8] With the acidosis of CKD, both increased titratable acid and increased urinary ammonium are observed (Figure 42.3), but the increases particularly in ammonium excretion are often inadequate to prevent or correct the acidosis. If one factors the increased acid excretion for the number of remaining nephrons, both titratable acid and ammonium excretion per nephron (or per mL of GFR) increase. The amount of increase, particularly in ammonium excretion, however, usually is insufficient to adequately compensate for the loss of nephrons or GFR.[7] Titratable acid excretion in CKD is aided by increased phosphate excretion per nephron, because of secondary hyperparathyroidism and increases in serum phosphate concentration as GFR declines.[6] Decreased protein intake and use of phosphate binders will usually lessen urinary phosphate excretion. There is evidence that there is some defect in outer medullary ammonium accumulation and trapping.[9] Most patients with CKD can appropriately lower the urine pH, and titratable acid excretion is relatively well preserved.[9] In some CKD patients, hyperkalemia may also suppress ammoniagenesis and ammonium excretion.[10]

Bone buffering may account for much of the relative stability of plasma HCO_3^-.[11] Retained acid, however, even in the absence of a decreased plasma HCO_3^- can also be detected in the renal interstitium and muscles of experimental animals with reduced renal mass.[12–14] The same retention of acid, even in the absence of a reduced plasma HCO_3^-, is postulated to occur in at least some patients with CKD.[4,5] In humans, this acid retention has been assessed using the response of plasma HCO_3^- 2 hours after giving 0.5 mEq/kg body weight oral $NaHCO_3$[5] (Figure 42.4).

CONSEQUENCES OF METABOLIC ACIDOSIS IN CKD

Metabolic acidosis in CKD causes or contributes to many secondary deleterious complications (Table 42.1). As delineated below, the acidosis worsens bone demineralization, contributes to loss of muscle function and

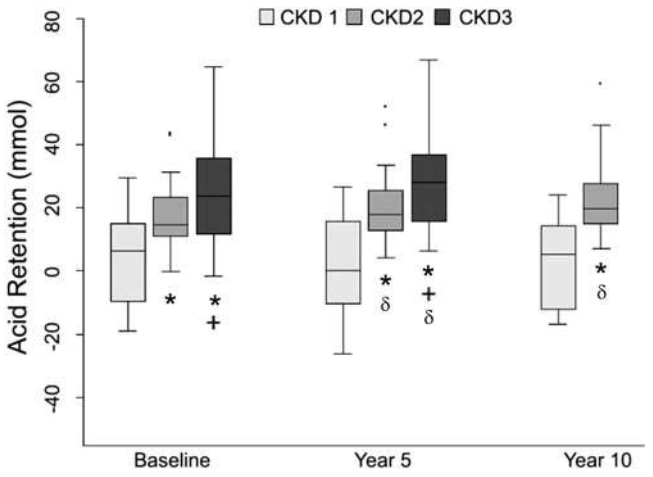


FIGURE 42.4 Acid retention for CKD stages 1, 2, and 3 calculated from the increment in plasma HCO_3^- after oral HCO_3^- loads. The figure displays boxplots showing acid (H+) retention for individuals with stage CKD 1, CKD 2, and CKD 3 at baseline (*year 0*), *year 5*, and *year 10* of follow-up. *$p < 0.05$ vs. respective CKD 1; $^{+}p < 0.05$ vs. respective CKD 2; $^{\delta}p < 0.05$ vs. respective baseline value. *From reference 5; see reference for details of methods.*

TABLE 42.1 Consequences of Acidosis of CKD

Worsening bone disease
Impaired growth in children
Increased protein catabolism, decreased synthesis with decreased muscle mass, and decreased plasma albumin concentration
Impaired glucose tolerance and insulin resistance
Increased inflammation
Progression of renal disease
Increased mortality

mass, causes hypoalbuminemia, and is associated with glucose intolerance. In addition, over the past decade, many studies have associated acidosis or acid retention with progression of CKD. Most importantly, acidosis in CKD is associated with increased mortality.[15–18]

CKD is associated with loss of muscle mass,[19] and metabolic acidosis in CKD decreases muscle mass, lessening activity, and therefore probably contributes to increasing morbidity and mortality.[20–24] The mechanisms involve interactions with cortisol, inflammatory cytokines, activation of the ubiquitin–proteasome pathway, impaired insulin/IGF-1 signaling, and activation of caspase-3 proteolysis.[20–22,24,25] There is some evidence of improvement of muscle strength and mass with treatment of acidosis with bicarbonate.[26–28] Similarly, acidosis in CKD is associated with lower serum albumin concentration, which improves with treatment.[2,27]

Metabolic acidosis, including that associated with CKD, causes bone demineralization.[11,24,29] Although hyperparathyroidism and vitamin D abnormalities are the main factors in the bone and mineral disease with CKD, acidosis contributes. Acidosis increases the activity of osteoclasts and decreases that of osteoblasts.[30] Clinically, bone disease is worse in CKD patients with acidosis.[24,31] The interactions of acidosis with other factors (such as PTH, 1,25-dihydroxyvitamin D, and fibroblast growth factor 23) contributing to bone disease in CKD are complex.[24] In children, acidosis is associated with impaired growth.

Metabolic acidosis in CKD can worsen glucose tolerance and increase insulin resistance. Both states improve with treatment of the acidosis.[32–36] Metabolic acidosis is also associated with abnormalities in the growth hormone-IGF-1 axis, decreased leptin levels, and reduced T4 levels,[24,37] but the clinical impact of these is not yet known with certainty. There is also some evidence that cognitive function is worse in patients with acidosis.[38]

Several studies have shown an association between acidosis in CKD and faster progression of CKD.[18,39–44] Is this causation or just association? The experimental and clinical studies, which demonstrate that treatment of acidosis slows the deterioration of GFR, are the most compelling evidence of a causal relationship between acidosis and further declines in GFR. Experimental animal studies have demonstrated that acid loads or a more acidic or higher protein diet accelerate GFR decline and that alkali loads prevent this decline.[12–14,45,46]

Mechanisms for CKD Progression

The mechanisms that account for acidosis or retained acid causing progressive kidney injury and further reduction in GFR are not completely established (Figure 42.1) but have been investigated to some extent (Table 42.2). Early studies suggested that acidosis, by inducing medullary accumulation of ammonia, activates complement and subsequently increases interstitial fibrosis.[47] More recent studies have shown increased interstitial endothelin, angiotensin II, and

TABLE 42.2 Proposed Mechanisms of Acidosis Causing Progressive Renal Damage

Ammonium activation of complement leading to fibrosis
Increased proinflammatory cytokines
Increased endothelin
Increased angiotensin II, aldosterone

aldosterone are major factors underlying this pathophysiology.[12–14,45,46] These hormones may be part of the mechanisms whereby a homeostatic increase in acid excretion occurs in response to systemic acidosis. The renal damage is an unfortunate side effect of the increase in these hormones.

DIAGNOSIS

Metabolic acidosis is recognized by a reduced arterial pH as a consequence of a decreased plasma HCO_3^-. Respiratory compensation lowers the pCO_2. In the setting of known CKD of appropriate magnitude (sufficiently reduced GFR), an arterial blood gas is not usually necessary to establish a diagnosis. A reduced venous plasma HCO_3^- or total CO_2 is sufficient to make the diagnosis of metabolic acidosis secondary to CKD (assuming nothing else to suggest another cause, such as respiratory alkalosis).

Metabolic acidosis in CKD patients often begins with a hyperchloremic, normal anion gap acidosis. As the CKD gets more severe, a high anion gap metabolic acidosis ensues. Retention of phosphate, sulfate, urate, and other anions accounts for the elevation in anion gap. The increase in anion gap may be seen earlier when the anion gap is fully adjusted for albumin.[48] A higher anion gap independent of the plasma HCO_3^- may correlate with progression of CKD.[44]

Some patients with CKD do not have overt metabolic acidosis (reduced plasma HCO_3^-) but have apparent retained acid or an acidotic renal interstitium and a normal plasma HCO_3^- and arterial pH. This has been referred to as subclinical acidosis, preclinical acidosis, or eubicarbonatemic acidosis and may be present in patients with CKD.[29,49,50] For research purposes in humans, this acid retention has been identified using the response of plasma HCO_3^- after giving oral $NaHCO_3$.[5] Reduced urine citrate excretion may also indicate retained acid.[51] Urinary citrate excretion is regulated predominantly by acid–base status, as urinary citrate decreases significantly with acid loads or acidosis.[52] Reduced urinary citrate excretion is associated with increased incidence of calcium kidney stones, as citrate is among the most important inhibitors of calcium stone formation.[53]

In contrast to the typical acidosis of CKD, some patients with CKD may have an early hyperchloremic, hyperkalemic acidosis that is disproportionate to the degree of decrement in GFR. This is often called type 4 renal tubular acidosis or hyporeninemic, hypoaldosteronism, associated with diabetes, obstructive uropathy, sickle cell disease, or other interstitial kidney diseases. Often in these patients the hyperkalemia is actually more pronounced than the acidosis. In fact, the hyperkalemia contributes to the acidosis. Hyperkalemia suppresses ammoniagenesis and ammonium secretion, and it is an important contributor to the acidosis in these patients.[10] This hyperkalemia contrasts with the usual acidosis of CKD, which is typically normokalemic, due to adaptations in both renal collecting duct and colonic K+ secretion as GFR declines.[9]

TREATMENT

The clinical evidence that treatment of acidosis in CKD slows the progression of GFR decline has been recently summarized[29,54] (Figure 42.5). Several single-center studies strongly suggest that treating acidosis slows progression of CKD.[26,27,54,55,57] These studies have used sodium bicarbonate (0.3–0.5 mEq/kg per day), sodium citrate, or a diet high in fruits and vegetables to treat acidosis. Another positive study used a keto-analog-supplemented low-protein vegetarian diet to treat CKD and the associated acidosis.[56] A low-protein diet has been shown to raise plasma HCO_3^-.[58] Although most of these studies have addressed patients with reduced plasma HCO_3^-, some studies used patients with normal plasma HCO_3^- levels.[59] Other studies are underway.[29] There are limited data regarding whether treatment of acidosis in CKD improves mortality.[60]

Current guidelines for therapy of the acidosis of CKD by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative and others is to monitor total CO_2 (or HCO_3^-) and maintain plasma HCO_3^- above 22 mEq/L.[61,62] Many now question whether this is sufficient, or whether others with higher plasma HCO_3^- should be treated. A so-called subclinical acidosis, preclinical acidosis, or eubicarbonatemic acidosis may be present in many patients with CKD.[29,49,50] At the present time, there are no large randomized trials that address this question.[54] Which

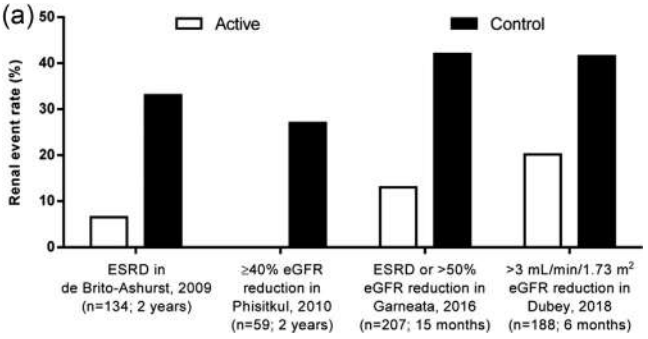


FIGURE 42.5 Renal event rate in some of the trials of treating acidosis of CKD. Active refers to treatment with (from left to right) sodium bicarbonate,[27] sodium citrate,[55] very low protein diet with ketoanalogue supplementation,[56] or sodium bicarbonate,[26] respectively. *From reference 54.*

patients with normal acid–base status should be treated has not been defined. Lower urinary ammonium excretion, possibly indicating inability to adequately excrete acid, has been associated with worse outcomes in some populations.[63–65] However, lower urinary ammonium could also result from a low dietary and metabolic endogenous acid load, which may be beneficial.[66]

Reduced urinary citrate excretion may indicate those patients who have retained acid, and those that may therefore benefit from alkali treatment or other means of treating acidosis or retained acid.[51] Urinary citrate is regulated predominantly by acid–base status of individuals, such that urinary citrate excretion declines remarkably with even modest acid loads.

Alkali or HCO_3^- can be given as Shohl's solution (Citric Acid—Sodium Citrate), other forms of citrate, or sodium bicarbonate tablets. The dose can initially exceed the daily endogenous and dietary acid load (typically 40–70 mEq/kg body weight per day). New therapies with a H^+ binding agent are under development.[67,68] Neither alkali supplementation or adding fruits and vegetables in the diet require dietary protein restriction, but this may have added benefit. Alkali therapy not only slows progression of CKD but also improves bone and skeletal muscle effects of CKD.[69] Citrate (such as Shohl's solution) has been shown to enhance the absorption of aluminum from the gastrointestinal tract and therefore should be used with caution or not at all in patients receiving aluminum-containing antacids, because of the risk of aluminum intoxication.[70]

Potential negative side effects of treating acidosis have been raised[29,71] but do not seem significant with the present data.[72] Hypertension with sodium loads has not occurred during most studies with sodium bicarbonate. There is some association of higher serum HCO_3^- with congestive heart failure, but this is not necessarily the result of treatment of acidosis[73] and has not been consistently found.[74] There is a theoretical risk of worsened vascular calcification with treatment of acidosis, but this has also not been clinically confirmed.[29]

CONCLUSIONS

Metabolic acidosis in CKD is very common, particularly as GFR declines and patients reach stage 4 CKD. The acidosis results predominantly from inadequate ammonium excretion. This acidosis clearly contributes to several complications, including loss of muscle mass and bone mineral, accelerated decline in GFR, and increased mortality. There is also some evidence that some patients with CKD and normal plasma HCO_3^- have retained acid, particularly in the renal interstitium, and that this contributes to progressive GFR decline. Although there have not been any large randomized trials, several single center trials of moderate size suggest that treatment of acidosis slows the progression of CKD. Treatment of acidosis in patients with CKD may be with sodium bicarbonate, citrate, or diets high in fruits and vegetables.

References

1. Raphael KL, Zhang Y, Ying J, Greene T. Prevalence of and risk factors for reduced serum bicarbonate in chronic kidney disease. *Nephrology* 2014;**19**(10):648–54.
2. Eustace JA, Astor B, Muntner PM, Ikizler TA, Coresh J. Prevalence of acidosis and inflammation and their association with low serum albumin in chronic kidney disease. *Kidney Int* 2004;**65**(3):1031–40.
3. Moranne O, Froissart M, Rossert J, Gauci C, Boffa JJ, Haymann JP, et al. Timing of onset of CKD-related metabolic complications. *J Am Soc Nephrol* 2009;**20**(1):164–71.
4. Wesson DE, Simoni J, Broglio K, Sheather S. Acid retention accompanies reduced GFR in humans and increases plasma levels of endothelin and aldosterone. *Am J Physiol Renal Physiol* 2011; **300**(4):F830–7.
5. Goraya N, Simoni J, Sager LN, Pruszynski J, Wesson DE. Acid retention in chronic kidney disease is inversely related to GFR. *Am J Physiol Renal Physiol* 2018;**314**(5):F985–91.
6. Nagami GT, Hamm LL. Regulation of acid-base balance in chronic kidney disease. *Adv Chron Kidney Dis* 2017;**24**(5):274–9.
7. Gauthier P, Simon EE, Lemann Jr J. Acidosis of chronic renal failure. In: DuBose TD, Hamm LL, editors. *Acid-base and electrolyte disorders*. Saunders; 2002. p. 207–16.
8. Hamm LL, Nakhoul N, Hering-Smith KS. Acid-base homeostasis. *Clin J Am Soc Nephrol* 2015;**10**(12):2232–42.
9. Kraut JA, Kurtz I. Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment. *Am J Kidney Dis* 2005;**45**(6):978–93.
10. Hamm LL, Hering-Smith KS, Nakhoul NL. Acid-base and potassium homeostasis. *Semin Nephrol* 2013;**33**(3):257–64.
11. Lemann Jr J, Bushinsky DA, Hamm LL. Bone buffering of acid and base in humans. *Am J Physiol Renal Physiol* 2003;**285**(5):F811–32.
12. Wesson DE, Simoni J. Acid retention during kidney failure induces endothelin and aldosterone production which lead to progressive GFR decline, a situation ameliorated by alkali diet. *Kidney Int* 2010;**78**(11):1128–35.
13. Wesson DE, Simoni J. Increased tissue acid mediates a progressive decline in the glomerular filtration rate of animals with reduced nephron mass. *Kidney Int* 2009;**75**(9):929–35.
14. Wesson DE, Jo CH, Simoni J. Angiotensin II receptors mediate increased distal nephron acidification caused by acid retention. *Kidney Int* 2012;**82**(11):1184–94.
15. Raphael KL, Zhang Y, Wei G, Greene T, Cheung AK, Beddhu S. Serum bicarbonate and mortality in adults in NHANES III. *Nephrol Dial Transplant* 2013;**28**(5):1207–13.
16. Navaneethan SD, Schold JD, Arrigain S, Jolly SE, Wehbe E, Raina R, et al. Serum bicarbonate and mortality in stage 3 and stage 4 chronic kidney disease. *Clin J Am Soc Nephrol* 2011;**6**(10):2395–402.
17. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD. *Nephrol Dial Transplant* 2009;**24**(4): 1232–7.
18. Menon V, Tighiouart H, Vaughn NS, Beck GJ, Kusek JW, Collins AJ, et al. Serum bicarbonate and long-term outcomes in CKD. *Am J Kidney Dis* 2010;**56**(5):907–14.
19. Foley RN, Wang C, Ishani A, Collins AJ, Murray AM. Kidney function and sarcopenia in the United States general population: NHANES III. *Am J Nephrol* 2007;**27**(3):279–86.

20. Fahal IH. Uraemic sarcopenia: aetiology and implications. *Nephrol Dial Transplant* 2014;**29**(9):1655–65.
21. Pickering WP, Price SR, Bircher G, Marinovic AC, Mitch WE, Walls J. Nutrition in CAPD: serum bicarbonate and the ubiquitin-proteasome system in muscle. *Kidney Int* 2002;**61**(4): 1286–92.
22. Workeneh BT, Mitch WE. Review of muscle wasting associated with chronic kidney disease. *Am J Clin Nutr* 2010;**91**(4): 1128S–32S.
23. Abramowitz MK, Hostetter TH, Melamed ML. Association of serum bicarbonate levels with gait speed and quadriceps strength in older adults. *Am J Kidney Dis* 2011;**58**(1):29–38.
24. Kraut JA, Madias NE. Adverse effects of the metabolic acidosis of chronic kidney disease. *Adv Chron Kidney Dis* 2017;**24**(5):289–97.
25. Wang XH, Mitch WE. Mechanisms of muscle wasting in chronic kidney disease. *Nat Rev Nephrol* 2014;**10**(9):504–16.
26. Dubey AK, Sahoo J, Vairappan B, Haridasan S, Parameswaran S, Priyamvada PS. Correction of metabolic acidosis improves muscle mass and renal function in chronic kidney disease stages 3 and 4: a randomized controlled trial. *Nephrol Dial Transplant* 2018:1–9.
27. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol* 2009;**20**(9):2075–84.
28. Abramowitz MK, Melamed ML, Bauer C, Raff AC, Hostetter TH. Effects of oral sodium bicarbonate in patients with CKD. *Clin J Am Soc Nephrol* 2013;**8**(5):714–20.
29. Raphael KL. Metabolic acidosis and subclinical metabolic acidosis in CKD. *J Am Soc Nephrol* 2018;**29**(2):376–82.
30. Krieger NS, Sessler NE, Bushinsky DA. Acidosis inhibits osteoblastic and stimulates osteoclastic activity in vitro. *Am J Physiol* 1992;**262**(3 Pt 2):F442–8.
31. Coen G, Mazzaferro S, Ballanti P, Sardella D, Chicca S, Manni M, et al. Renal bone disease in 76 patients with varying degrees of predialysis chronic renal failure: a cross-sectional study. *Nephrol Dial Transplant* 1996;**11**(5):813–9.
32. Garibotto G, Sofia A, Russo R, Paoletti E, Bonanni A, Parodi EL, et al. Insulin sensitivity of muscle protein metabolism is altered in patients with chronic kidney disease and metabolic acidosis. *Kidney Int* 2015;**88**(6):1419–26.
33. Mak RH. Effect of metabolic acidosis on insulin action and secretion in uremia. *Kidney Int* 1998;**54**(2):603–7.
34. Kobayashi S, Maesato K, Moriya H, Ohtake T, Ikeda T. Insulin resistance in patients with chronic kidney disease. *Am J Kidney Dis* 2005;**45**(2):275–80.
35. Khairallah P, Scialla JJ. Role of acid-base homeostasis in diabetic kidney disease. *Curr Diabetes Rep* 2017;**17**(4):28.
36. Bellasi A, Di Micco L, Santoro D, Marzocco S, De Simone E, Cozzolino M, et al. Correction of metabolic acidosis improves insulin resistance in chronic kidney disease. *BMC Nephrol* 2016;**17**(1): 158.
37. Zheng F, Qiu X, Yin S, Li Y. Changes in serum leptin levels in chronic renal failure patients with metabolic acidosis. *J Ren Nutr* 2001;**11**(4):207–11.
38. Dobre M, Gaussoin SA, Bates JT, Chonchol MB, Cohen DL, Hostetter TH, et al. Serum bicarbonate concentration and cognitive function in hypertensive adults. *Clin J Am Soc Nephrol* 2018;**13**(4): 596–603.
39. Shah SN, Abramowitz M, Hostetter TH, Melamed ML. Serum bicarbonate levels and the progression of kidney disease: a cohort study. *Am J Kidney Dis* 2009;**54**(2):270–7.
40. Dobre M, Yang W, Chen J, Drawz P, Hamm LL, Horwitz E, et al. Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: a report from the chronic renal insufficiency cohort (CRIC) study. *Am J Kidney Dis* 2013;(13):10.
41. Raphael KL, Wei G, Baird BC, Greene T, Beddhu S. Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans. *Kidney Int* 2011;**79**(3):356–62.
42. Tangri N, Stevens LA, Griffith J, Tighiouart H, Djurdjev O, Naimark D, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA* 2011;**305**(15):1553–9.
43. Harambat J, Kunzmann K, Azukaitis K, Bayazit AK, Canpolat N, Doyon A, et al. Metabolic acidosis is common and associates with disease progression in children with chronic kidney disease. *Kidney Int* 2017;**92**(6):1507–14.
44. Banerjee T, Crews D, Wesson DE, McCulloch C, Johansen K, Saydah S, et al. Elevated serum anion gap in adults with moderate chronic kidney disease increases risk for progression to end stage renal disease. *Am J Physiol Renal Physiol* 2019;**316**(6):F1244–53.
45. Phisitkul S, Hacker C, Simoni J, Tran RM, Wesson DE. Dietary protein causes a decline in the glomerular filtration rate of the remnant kidney mediated by metabolic acidosis and endothelin receptors. *Kidney Int* 2008;**73**(2):192–9.
46. Wesson DE, Nathan T, Rose T, Simoni J, Tran RM. Dietary protein induces endothelin-mediated kidney injury through enhanced intrinsic acid production. *Kidney Int* 2007;**71**(3):210–7.
47. Nath KA, Hostetter MK, Hostetter TH. Pathophysiology of chronic tubulo-interstitial disease in rats. Interactions of dietary acid load, ammonia, and complement component C3. *J Clin Invest* 1985;**76**(2): 667–75.
48. Abramowitz MK, Hostetter TH, Melamed ML. The serum anion gap is altered in early kidney disease and associates with mortality. *Kidney Int* 2012;**82**(6):701–9.
49. Alpern RJ, Sakhaee K. The clinical spectrum of chronic metabolic acidosis: homeostatic mechanisms produce significant morbidity. *Am J Kidney Dis* 1997;**29**(2):291–302.
50. DuBose Jr TD. Urine ammonium and preclinical acidosis in CKD. *J Am Soc Nephrol* 2017;**28**:2258–60.
51. Goraya N, Simoni J, Sager LN, Madias NE, Wesson DE. Urine citrate excretion as a marker of acid retention in patients with chronic kidney disease without overt metabolic acidosis. *Kidney Int* 2019; **95**(5):1190–6.
52. Hering-Smith KS, Hamm LL. Acidosis and citrate: provocative interactions. *Ann Transl Med* 2018;**6**:374.
53. Hering-Smith KS, Hamm LL, Moe OW. Renal citrate metabolism and transport: physiology and pathophysiology. In: Coe F, Worcester E, Lingeman JE, Evan AP, editors. *Kidney stones: medical and surgical management*. 2nd ed. 2017.
54. Goraya N, Wesson DE. Clinical evidence that treatment of metabolic acidosis slows the progression of chronic kidney disease. *Curr Opin Nephrol Hypertens* 2019;**28**(3):267–77.
55. Phisitkul S, Khanna A, Simoni J, Broglio K, Sheather S, Rajab MH, et al. Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR. *Kidney Int* 2010;**77**(7):617–23.
56. Garneata L, Stancu A, Dragomir D, Stefan G, Mircescu G. Ketoanalogue-supplemented vegetarian very low-protein diet and CKD progression. *J Am Soc Nephrol* 2016;**27**(7):2164–76.
57. Goraya N, Simoni J, Jo CH, Wesson DE. A comparison of treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with fruits and vegetables or sodium bicarbonate. *Clin J Am Soc Nephrol* 2013;**8**(3):371–81.
58. Gennari FJ, Hood VL, Greene T, Wang X, Levey AS. Effect of dietary protein intake on serum total CO2 concentration in chronic kidney disease: modification of Diet in Renal Disease study findings. *Clin J Am Soc Nephrol* 2006;**1**(1):52–7.
59. Mahajan A, Simoni J, Sheather SJ, Broglio KR, Rajab MH, Wesson DE. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. *Kidney Int* 2010;**78**(3):303–9.
60. Caravaca F, Alvarado R, Garcia-Pino G, Martinez-Gallardo R, Luna E. During the pre-dialysis stage of chronic kidney disease,

which treatment is associated with better survival in dialysis? *Nefrologia* 2014;**34**(4):469−76.
61. Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. *Am J Kidney Dis* 2000; **35**(6 Suppl. 2):S1−140.
62. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Work G. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013; (Suppl. 3):1−150.
63. Raphael KL, Carroll DJ, Murray J, Greene T, Beddhu S. Urine ammonium predicts clinical outcomes in hypertensive kidney disease. *J Am Soc Nephrol* 2017;**28**(8):2483−90.
64. Vallet M, Metzger M, Haymann JP, Flamant M, Gauci C, Thervet E, et al. Urinary ammonia and long-term outcomes in chronic kidney disease. *Kidney Int* 2015;**88**(1):137−45.
65. Scialla JJ, Asplin J, Dobre M, Chang AR, Lash J, Hsu CY, et al. Higher net acid excretion is associated with a lower risk of kidney disease progression in patients with diabetes. *Kidney Int* 2017;**91**(1): 204−15.
66. Scialla JJ, Appel LJ, Astor BC, Miller III ER, Beddhu S, Woodward M, et al. Net endogenous acid production is associated with a faster decline in GFR in African Americans. *Kidney Int* 2012; **82**(1):106−12.
67. Bushinsky DA, Hostetter T, Klaerner G, Stasiv Y, Lockey C, McNulty S, et al. Randomized, controlled trial of TRC101 to increase serum bicarbonate in patients with CKD. *Clin J Am Soc Nephrol* 2018;**13**(1):26−35.
68. Wesson DE, Mathur V, Tangri N, Stasiv Y, Parsell D, Li E, et al. Veverimer versus placebo in patients with metabolic acidosis associated with chronic kidney disease: a multicentre, randomised, double-blind, controlled, phase 3 trial. *Lancet* 2019;**393**(10179): 1417−27.
69. Loniewski I, Wesson DE. Bicarbonate therapy for prevention of chronic kidney disease progression. *Kidney Int* 2014;**85**(3):529−35.
70. Froment DP, Molitoris BA, Buddington B, Miller N, Alfrey AC. Site and mechanism of enhanced gastrointestinal absorption of aluminum by citrate. *Kidney Int* 1989;**36**(6):978−84.
71. Kraut JA, Madias NE. Metabolic acidosis of CKD: an update. *Am J Kidney Dis* 2016;**67**(2):307−17.
72. Susantitaphong P, Sewaralthahab K, Balk EM, Jaber BL, Madias NE. Short- and long-term effects of alkali therapy in chronic kidney disease: a systematic review. *Am J Nephrol* 2012; **35**(6):540−7.
73. Dobre M, Yang W, Pan Q, Appel L, Bellovich K, Chen J, et al. Persistent high serum bicarbonate and the risk of heart failure in patients with chronic kidney disease (CKD): a report from the Chronic Renal Insufficiency Cohort (CRIC) study. *J Am Heart Assoc* 2015;**4**(4).
74. Schutte E, Lambers Heerspink HJ, Lutgers HL, Bakker SJ, Vart P, Wolffenbuttel BH, et al. Serum bicarbonate and kidney disease progression and cardiovascular outcome in patients with diabetic nephropathy: a post hoc analysis of the RENAAL (reduction of end points in non-insulin-dependent diabetes with the angiotensin II antagonist losartan) study and IDNT (irbesartan diabetic nephropathy trial). *Am J Kidney Dis* 2015;**66**(3):450−8.

QUESTIONS AND ANSWERS

Question 1

What is the main cause of metabolic acidosis in CKD?

A. Inability to acidify the urine
B. Decreased HCO_3^- reabsorption in the distal nephron
C. Inadequate HCO_3^- reabsorption in the proximal tubule
D. Decreased titratable acid excretion
E. Inadequate NH_4^+ excretion

Answer: E

Although many defects in acid–base metabolism are present in kidney disease, the main factor causing acidosis is inadequate NH_4^+ excretion.

Question 2

Which of the following is not usually a complication of acidosis in CKD?

A. Loss of bone mineral
B. Cardiomyopathy
C. Hypoalbuminemia
D. Progression of CKD
E. Insulin resistance

Answer: B

Cardiomyopathy is not a specific complication of the acidosis of CKD. Although a significant spectrum of complications has been found, cardiomyopathy is not included. Increased muscle catabolism and loss of skeletal muscle mass is a known complication. The other complications, such as loss of bone mineral, progression of CKD, hypoalbuminemia, and insulin resistance are known.

Question 3

Which type of acidosis is most common in early CKD?

A. Hyperchloremic normal anion gap metabolic acidosis
B. Respiratory acidosis
C. High anion gap metabolic acidosis
D. Mixed high anion gap and hyperchloremic acidosis
E. Hyperkalemic hyperchloremic metabolic acidosis

Answer: A

Although other patterns can be seen, particularly in later stages of CKD, a hyperchloremic acidosis (with normal serum potassium concentration [S[K]]) is the most common, if overt acidosis is present.

Question 4

What is the potassium level in most early CKD?

A. Low
B. Normal
C. High

Answer: B

Potassium levels are usually normal until very late in CKD due to a number of adaptations. Some patients, particularly with diabetic nephropathy, are hyperkalemic and have hyporeninemic hypoaldosteronism.

Question 5

Which approaches to treatment of metabolic acidosis have been studied and reported to improve progression of CKD?

A. Citrate
B. Sodium bicarbonate
C. Diet high in fruits and vegetables
D. A and B
E. A, B, and C

Answer: E

All of the approaches above have been reported to improve the progression of CKD.

Question 6

What is the most typical pattern of electrolytes for a patient with an estimated glomerular filtration rate of 65 mL/min/1.73m^2 ? The kidney disease is from hypertension with minimal proteinuria.

A. Na 140, Cl 105, K 4.0, HCO_3^- 17
B. Na 140, Cl 107, K 5.5, HCO_3^- 22
C. Na 140, Cl 105, K 4.0, HCO_3^- 25
D. Na 140, Cl 100, K 3.0, HCO_3^- 30
E. Na 140, Cl 108, K 4.0, HCO_3^- 22

Answer: C

Normal electrolytes including a normal HCO_3^- is statistically the most likely electrolyte pattern in patients with stage 2 CKD. If an acidosis were present, it would most likely be hyperchloremic (e) with normal S[K]. Other patterns are not typical for relatively mild CKD: (a) high anion gap; (b) hyperkalemic hyperchloremic metabolic acidosis, and (d) likely metabolic alkalosis.

CHAPTER

43

Uric Acid Metabolism and the Kidney

Duk-Hee Kang[a], *Richard J. Johnson*[b]

[a]Division of Nephrology, Department of Internal Medicine, Ewha Women's University School of Medicine, Seoul, South Korea; [b]Division of Renal Diseases and Hypertension, University of Colorado Anschutz Medical Campus, Aurora, CO, United States

Abstract

Hyperuricemia and gout are common in chronic kidney disease (CKD) patients. This relationship has been noted since the 1800s. Over the years there has been great controversy over the biologic significance of hyperuricemia, with some individuals arguing it is a major cause of CKD, and others viewing the rise in serum urate concentration (S[Ur]) as strictly an epiphenomenon. During the last 10–15 years, interest in uric acid has reawakened with the realization that an elevated S[Ur] can predict the development of CKD and by experimental studies that document a causal role for uric acid in both the development and progression of CKD. Today there is great interest in the potential that uric acid may represent a remediable risk factor for CKD. We provide an update on uric acid and the kidney, focusing both on uric acid metabolism and a critical evaluation of the current evidence base for uric acid as a risk factor for CKD.

INTRODUCTION

Hyperuricemia and gout are common in chronic kidney disease (CKD) patients. This relationship has been noted since the 1800s.[1] Over the years there has been great controversy over the biologic significance of hyperuricemia. Some argue hyperuricemia is one of the major causes of CKD,[2] whereas others view the rise in serum urate concentration (S[Ur]) as strictly an epiphenomenon.[3] During the last 10–15 years, interest in uric acid has reawakened with the realization that an elevated S[Ur] can predict the development of CKD,[4,5] and by experimental studies that document a causal role for uric acid in both the development and progression of CKD.[6–9] Today there is great interest in the potential that uric acid may represent a remediable risk factor for CKD. We provide an update on uric acid and the kidney, focusing both on uric acid metabolism and a critical evaluation of the current evidence for uric acid as a risk factor for kidney disease.

URIC ACID METABOLISM

Generation of Uric Acid

Uric acid is generated from metabolic conversion of either exogenous (dietary) or endogenous purines, primarily in the liver and intestine. The immediate precursor of uric acid is xanthine, which is metabolized to uric acid by either xanthine oxidase or by its isoform, xanthine dehydrogenase. Approximately two-thirds of total body urate is produced endogenously, while the remaining one-third is accounted for by dietary purines.[10] Purine-rich foods include beer, meat, poultry, seafood, mushrooms, spinach, asparagus, and cauliflower.[11] Uric acid can also be generated by fructose, which is produced both from nucleotide turnover and from increased synthesis from amino acid precursors.[12,13] Alcohol can also increase uric acid levels from increased nucleotide turnover and reduced urinary excretion.[14,15] In healthy men, the urate pool averages about 1200 mg with a mean turnover rate of 700 mg/day.[16]

In humans, uric acid represents the final enzymatic degradation product in purine metabolism. In most mammals a liver enzyme, uricase, degrades uric acid to 5-hydroxyisourate and eventually allantoin.[17] However, in humans, and great and lesser apes, uricase was mutated approximately 10–15 million years ago, and as such, serum urate levels are higher in these species compared to other mammals.[18,19] Nevertheless, much of uric acid is still metabolized in humans. First, uric acid is an antioxidant and can react with a variety of substances, resulting in the formation of allantoin

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00043-7

(from superoxide), triuret (from reaction with peroxynitrite), or 6-aminouracil (from reaction with nitric oxide).[20,21] These products account for less than 1% of uric acid metabolism, but it can be elevated in patients with CKD and those treated with maintenance dialysis. However, as much as one-third of uric acid enters the gut *via* transporters (ABCG2 and SLC2A9) where it is metabolized by gut bacteria and can be excreted in the stool as uric acid or downstream products.

Excretion of Uric Acid

One-third of the total uric acid excreted is *via* bacterial metabolism in the gut, with two-thirds excreted by the kidneys. Normal urinary urate excretion ranges between 250 and 750 mg a day. Urate, the form of uric acid in the circulation, is freely filtered at the glomerulus, followed by both reabsorption and secretion in the proximal tubule. The fractional urate excretion is 8–10% in the healthy adult. Some adaptation occurs in people with impaired renal function, in whom the fractional excretion increases to the range of 10–20%[22] along with an increased intestinal excretion of uric acid. An increase in the gut transporter ATP-binding cassette superfamily G member 2 (ABCG2) mRNA expression in an animal model of CKD has also been reported, consistent with a compensatory increase in uric acid elimination from the intestine.[23]

During the last decade there have been great advances in our understanding of urate transport by the kidney, largely due to the characterization and isolation of transporters mainly or exclusively restricted to urate transport. Membrane vesicle studies have suggested the existence of two major mechanisms modulating urate reabsorption and secretion, consisting of a voltage-sensitive pathway and a urate–organic anion exchanger.[24,25] Several of these transporters/channels have been identified (Figure 43.1).[26] Organic anion transporters 1–10 (OAT1–10) and the urate transporter-1 (URAT-1) belong to the SLC22A gene family, which facilitate the movement of a variety of chemically unrelated endogenous and exogenous organic anions including uric acid.[27] URAT-1, which is encoded by SLC22A12, is the major organic anion exchanger for uric acid on the apical (luminal brush border) side of the proximal tubular cell.[28] In the human kidney, urate is transported *via* URAT-1 across the apical membrane of proximal tubular cells, in exchange for anions being transported back into the tubular lumen to maintain electrical balance. URAT-1 has a high affinity for urate together with lactate, ketones, α-ketoglutarate, and related compounds. Pyrazinamide, probenecid, losartan, and benzbromarone all inhibit urate uptake in exchange for chloride at the luminal side of the cell by

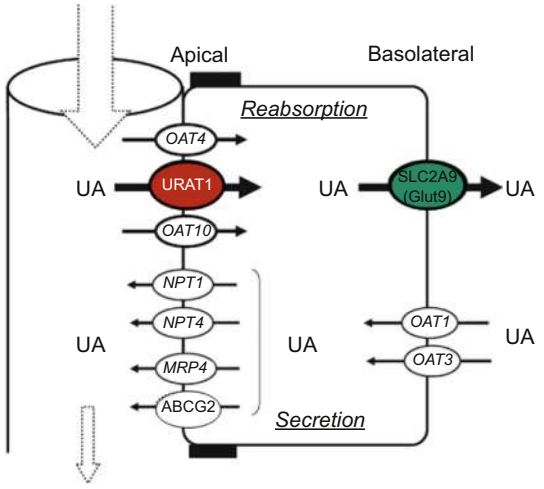


FIGURE 43.1 Renal urate transport. Renal urate transport is thought to occur primarily, if not exclusively, in the proximal tubule. The two most important transporters involved in reabsorption are URAT1 (on the apical membrane) and SLC2A9 (on the basolateral membrane). Important transporters for urate secretion include ABCG2, MRP4, and others. *Adapted from reference 26.*

competition with the urate exchanger. OAT-4 exhibits 53% amino acid homology with URAT1. After uptake into cells, urate then moves across the basolateral membrane into the blood by other organic anion transporters, of which the most important is SLC2A9 (also known as GLUT9).[29,30] SLC2A9 is highly expressed in the kidney, gut and liver. Individuals with mutations in either URAT1 or SLC2A9 have severe hypouricemia with marked uricosuria.[31,32]

Urate secretion appears to be mediated principally by a voltage-sensitive urate transporter, which is expressed ubiquitously and localizes to the apical side of the proximal tubule.[33] One candidate is MRP4, which is a novel human renal apical organic anion efflux transporter. MRP4 is a member of the ATP-binding cassette transporter family. MRP4 mediates secretion of urate and other organic anions such as cAMP, cGMP, and methotrexate across the apical membrane of human renal proximal tubular cells.[34] Another important voltage-sensitive transporter for uric acid is ABCG2. ABCG2 is expressed in both the proximal tubule and gut and appears to have a critical role in the movement of uric acid into the gut.[35]

Another protein involved in renal transport of urate is Tamm–Horsfall protein (THP), also known as uromodulin. THP is exclusively expressed and secreted by epithelial cells of the thick ascending limb.[36] THP has antibacterial effects. THP also colocalizes with the Na, K, 2Cl transporter in lipid rafts in the apical cell membrane, suggesting a functional interaction.[37] Mutations in the human uromodulin gene have been identified in people with type 2 medullary cystic kidney disease and familial juvenile hyperuricemic nephropathy.[38,39]

THP polymorphisms have also been associated with hyperuricemia,[40] which is inconsistent with the conventional wisdom that uric acid handling is restricted to the proximal tubule. However, there is some evidence that some urate secretion in the rat can occur distal to the proximal tubule. Furthermore, the THP mutation may lead to sodium wasting and diuresis,[41] possibly resulting in stimulation of urate reabsorption proximally.

CAUSES OF HYPERURICEMIA AND HYPOURICEMIA

Hyperuricemia

Hyperuricemia is arbitrarily defined as a S[Ur] greater than 7.0 mg/dL in men and greater than 6.5 mg/dL in women.[42] S[Ur] levels in the population appear to be increasing throughout the last century, likely as a consequence of changes in diet.[43] Uric acid levels tend to be higher in certain populations (such as African Americans and Pacific Islanders), with certain phenotypes (such as obesity and metabolic syndrome) and with special diets. Uric acid also has a circadian variation, with the highest levels in the early morning.[44]

The S[Ur] is determined by the balance between urate production and elimination. Hyperuricemia may occur from excessive production of urate (overproduction) or decreased elimination (underexcretion). Frequently a combination of both processes occurs in the same patient. Furthermore, uric acid levels may vary in the same individual by as much as 1−2 mg/dL during the course of a day, due to the effects of diet, hydration, and exercise.

Genetic mechanisms mediating hyperuricemia include overproduction due to a lack of hypoxanthine−guanine phosphoribosyltransferase (HGPRT) or overactivation of phosphoribosyl pyrophosphate synthetase. People with Lesch−Nyhan syndrome (due to a mutation of HGPRT on the X chromosome) present with neurologic manifestations (mental retardation, choreoathetosis, and dystonia) in childhood and have an increased risk for nephrolithiasis, renal failure, and gout. A partial deficiency of HGPRT may manifest later in life as recurrent gout and/or nephrolithiasis (Kelley−Seegmiller syndrome).[45] Other genetic mechanisms include people with the uromodulin mutation, who develop hyperuricemia (due to underexcretion) with early and progressive renal disease. Certain populations such as indigenous peoples living in Oceania also have higher uric acid levels than Caucasian populations.[46] Finally, African Americans also have higher uric acid levels, and a twofold higher incidence of gout compared to Caucasian or Asian populations.[47] However, this could reflect diets higher in fructose-containing sugars rather than genetic mechanisms.[48]

Hyperuricemia may also result from diets high in purines, ethanol, or fructose. The effect of alcohol is in part related to increased urate synthesis, which is due to enhanced turnover of ATP during the conversion of acetate to acetyl-CoA as part of the metabolism of ethanol.[14] In addition, acute alcohol consumption causes increased lactate production. Because lactate is an antiuricosuric agent, it reduces renal urate excretion and exacerbates hyperuricemia.[15] Fructose (a simple sugar present in sucrose, table sugar, high fructose corn syrup, honey, and fruits) can also induce a rapid rise in S[Ur], due in part to its rapid phosphorylation in hepatocytes with ATP consumption, intracellular phosphate depletion, and the stimulation of AMP deaminase with the generation of uric acid.[49] Chronic fructose consumption also stimulates the synthesis of uric acid from amino acid precursors. The marked increase in fructose intake may have a role in the rising levels of S[Ur] and obesity worldwide.[50]

In addition, uric acid levels may be affected by exercise, with moderate exercise reducing urate levels (probably by increasing renal blood flow) and severe exercise causing a rise in S[Ur] (probably due to ATP consumption with adenosine and xanthine formation). Urate levels vary between genders. Premenopausal women have lower S[Ur] than men due to the uricosuric effect of estrogen.[51] S[Ur] tends to increase in the setting of low blood volume and/or low salt diet due to its increased reabsorption in proximal tubules. Hyperuricemia is particularly common in patients with obesity and/or metabolic syndrome (thought to be secondary to the effect of insulin to stimulate uric acid reabsorption) and in those with untreated hypertension (in association with reduced renal blood flow). Thiazides also increase uric acid reabsorption in the proximal tubule by decreasing blood volume and *via* a direct interaction with the organic anion exchanger.

Other drugs, such as cyclosporine, pyrazinamide, and low-dose aspirin increase S[Ur], primarily by interfering with renal urate excretion. In addition, the generation of organic anions by lactate or β-hydroxybutyrate may interfere with urate secretion in the proximal tubule and cause a rise in serum urate levels. Chronic lead ingestion can also cause hyperuricemia by reducing urate excretion. In contrast, acute toxicity with extremely high lead concentrations may cause hypouricemia, due to proximal tubular injury and the induction of a Fanconi syndrome.[52,53]

Uric acid production is also increased in the setting of tissue hypoxia or with cell turnover. With tissue hypoxia, ATP is consumed and the isoform, xanthine oxidase, is induced, resulting in increased local uric acid concentrations. Circulating uric acid levels are thus high in

subjects with congestive heart failure, acute and chronic high altitude hypoxia, congenital cyanotic heart disease, and with obstructive sleep apnea.[54,55] Uric acid levels are commonly elevated with certain malignancies, especially leukemia and lymphoma, and levels may sharply rise following chemotherapy. Finally, S[Ur] has a tendency to be elevated in patients with polycythemia vera and other myeloproliferative disorders.

In the setting of reduced renal function, the fractional excretion of urate increases, but not enough to fully compensate for the reduction in GFR. As a consequence serum urate levels rise in CKD patients. In an animal model of CKD, the expression of URAT1, GLU9, ABCG2, and NPT4 in proximal tubules uniformly decreased possibly due to tubular injury.[23] Therefore, the mechanism for an elevation of uric acid in CKD is not clear yet, and simply may be because of the decreased GFR. In CKD, uric acid excretion by the gastrointestinal tract is also enhanced.[56] Therefore serum urate levels tend to be only mildly elevated in patients with CKD, and gout is relatively rare. However, by the time dialysis is initiated, half of CKD patients are hyperuricemic.[57,58]

Hypouricemia

Low uric acid levels (levels less than 2.0 mg/dL) can occur *via* a variety of mechanisms, including with liver disease (due to decreased production), Fanconi syndrome (due to impaired reabsorption by the proximal tubule) and diabetic glucosuria (which causes uricosuria). There is also a hereditary renal hypouricemia syndrome, particularly common in East Asia, due to a mutation in the URAT-1 gene.[59] A similar hypouricemia syndrome has also been observed with mutations in SLC2A9.[31] Patients carrying these mutations are particularly prone to develop acute kidney injury (AKI) following vigorous exercise.[32]

Drugs such as probenecid, high-dose salicylates, sulfinpyrazone, benziodarone, benzbromarone, the new class of glifozin SGLT2 inhibitors, and losartan are uricosuric. Allopurinol, febuxostat, and oxypurinol lower S[Ur] by blocking xanthine oxidase. Some statins also lower S[Ur].[60] Recombinant uricase (rasburicase) can markedly reduce S[Ur] and is approved for use in patients with tumor lysis syndrome. Pegloticase is a recombinant uricase that has polyethylene glycol attached to increase the circulating half-life and is used to treat refractory gout.[61]

URIC ACID AND RENAL DISEASE

There are two types of renal disease induced by uric acid. One is mediated by urate crystal deposition, and the other is unrelated to crystals, but is mediated by soluble uric acid, which causes or aggravates renal disease. Acute uric acid nephropathy, chronic urate nephropathy, and uric acid nephrolithiasis are the diseases induced by urate crystals. Among them, the identity of chronic urate nephropathy as a disease entity fell into question due to the focal nature of urate crystal deposition, the presence of intrarenal crystalline deposition in patients without renal disease, and because the kidney disease could often be attributed to coexisting risk factors such as hypertension and vascular disease in gout patients. We focus on the kidney disease associated with an elevation of soluble uric acid levels.

Hyperuricemia as a Primary Cause of CKD

Hyperuricemia is common in CKD patients. Although in some cases the hyperuricemia is due to specific disease entities, uric acid excretion is impaired in patients with reduced GFR. Therefore, in many cases the rise in S[Ur] may be simply secondary to CKD, although this does not rule out the possibility that uric acid may still have a role in modifying progression of renal disease.[62]

Gout was considered a cause of CKD, dating back to the mid-19th century. Natural history studies prior to the availability of uric acid–lowering drugs reported that as many as 25% of gouty patients developed proteinuria, 50% developed renal insufficiency, and 10–25% developed ESRD.[2] Renal histologic changes in patients with gout include arteriolosclerosis, glomerulosclerosis, and tubulointerstitial fibrosis, often with focal deposition of monosodium urate in interstitial areas, especially the outer medulla.[63] This led to the supposition that the disease "gouty nephropathy" or "chronic urate nephropathy" might be due to urate crystal deposition in the kidney. However, studies in the late 1970s challenged this hypothesis, as the intrarenal crystal deposition was focal and could not explain the diffuse disease that was commonly observed. In addition, the renal lesions observed in gout were similar to the findings one observes in patients with hypertensive renal disease (nephrosclerosis) or with aging, suggesting these latter conditions might be responsible for the diffuse renal scarring.[3] Studies using uric acid–lowering therapy to improve renal function in gout patients also showed variable results, leading to skepticism regarding whether the disease truly exists.[3,64]

New Insights Regarding the Entity of Primary Hyperuricemic Nephropathy

Renewed interest in the role of gout and/or asymptomatic hyperuricemia in the pathogenesis of CKD

began when it was realized that it was inappropriate to ascribe hypertension to explain every case of renal insufficiency in the gouty patient, because most subjects with essential hypertension have relatively preserved renal function.[65] Another implicit assumption was that gouty nephropathy had to be due to crystal deposition, and the possibility that uric acid might mediate effects through crystal-independent mechanisms was not considered.[65] Furthermore, the analysis also assumed that the presence of hypertension was a separate cause of renal disease and that it had to be independent of the uric acid.[66] This led to a proposal to reinvestigate the role of uric acid in CKD.

Subsequently numerous epidemiological studies have shown that serum urate is an independent risk factor for developing CKD (Table 43.1).[62] Most observational studies suggested hyperuricemia as an independent risk factor for new onset CKD or progression to end-stage renal disease (ESRD). In one Japanese study, hyperuricemia conferred a 10.8-fold increased risk in women and a 3.8-fold increased risk in men for the development of CKD, compared to those with normal uric acid levels. This higher relative risk in subjects with hyperuricemia was independent of age, body mass index, systolic blood pressure, total cholesterol, serum albumin, glucose, history of smoking, alcohol use, exercise habits, hematuria, and even proteinuria. An elevated S[Ur] was also independently associated with a markedly increased risk of ESRD in another study of more than 49,000 male railroad workers.[67] Meta-analysis of 13 observational studies including 190,718 patients demonstrated that an increase in S[Ur] was an independent risk factor for newly diagnosed CKD.[68] The association was stronger in Western countries compared to that in Asian populations. The population with longer follow-up was associated with the greater risk of CKD, indicating that hyperuricemia may aggravate the progression of renal injury over the long term. In addition, a GLUT9 polymorphism, which determines level of S[Ur] in healthy populations with normal kidney function, predicted the progression of CKD in a cohort of 755 CKD patients.[69] However, not all studies showed

TABLE 43.1 Elevated Serum Urate Predicts Development of Chronic Kidney disease (CKD)

Location	Population	Follow-up	Type	Independent	Author, Year
Japan	6403 adults	2 yrs	CKD	Yes	Iseki, 2001
Japan	48,177 adults	10 yrs	ESRD	Women	Iseki, 2004
Thailand	3499 adults	12 yrs	CKD	Yes	Domrongkitchaiporn, 2005
USA	5808 adults	5 yrs	CKD	No	Chonchol, 2007
Austria	21,457 adults	7 yrs	CKD	Yes	Obermayr, 2008
USA	13,338 adults	8.5 yrs	CKD	Yes	Weiner, 2008
Austria	17,375 adults	7 yrs	CKD	Yes	Obermayr, 2008
USA	177,500 adults	25 yrs	ESRD	Yes	Hsu, 2009
USA	355 type 1 diabetes*	6 yrs	CKD	Yes	Ficociello, 2010
Italy	900 adults	5 yrs	CKD	Yes	Bellomo, 2010
Japan	7078 adults	5 yrs	CKD	Yes	Sonoda, 2011
Taiwan	94,422 adults	3.5 yrs	CKD	Men	Wang, 2011
Israel	2449 adults	26 yrs	ESRD	Yes	Ben-Dov, 2011
Japan	14,399 adults	5 yrs	CKD	Yes	Yamada, 2011
USA	488 renal transplants	1 yr	Graft loss	Yes	Haririan, 2011
China	1410 adults	4 yrs	CKD	Yes	Zhang, 2012
Korea	14,939 adults	10.2 yrs	CKD	Men	Mok, 2012
Italy	1449 type 2 diabetics	5 yrs	CKD	Yes	Zoppini, 2012
Korea	18,778 men	4 yrs	CKD	Men	Ryoo, 2013

** Subjects with albuminuria.*

Source: From Johnson RJ, Nakagawa T, Jalal D, Sanchez-Lozada LG, Kang DH, Ritz E. Uric acid and chronic kidney disease: which is chasing which? Nephrol Dial Transplant *2013; 28(9):2221–8. Reproduced with permission.*

a significant association of hyperuricemia with kidney disease. *Post hoc* analysis of the Modification of Diet in Renal Disease study, enrolling 838 patients with stage 3 and 4 CKD showed that hyperuricemia was associated with mortality and cardiovascular disease, but not with renal progression.[70]

A second insight came from experimental studies in which chronic mild hyperuricemia was induced in rats, which developed hypertension and progressive renal disease without intrarenal crystal deposition.[6,8] The primary mechanism appeared to be due to the ability of increased levels of S[Ur] to induce glomerular hypertension and renal vasoconstriction.[71] Early in the course the rats developed arteriolar thickening and rarely hyalinosis of the preglomerular arterioles, often accompanied by glomerular hypertrophy.[7] Proteinuria appeared subsequently with the development of worsening vascular disease, glomerulosclerosis, and interstitial fibrosis. The lesion was identical to that observed with nephrosclerosis of hypertension, with aging-associated glomerulosclerosis, and with gouty nephropathy, except for the absence of crystal deposition that had been observed in the latter condition.[6–9] This finding suggests that chronic hyperuricemia may cause renal disease and hypertension *via* a crystal-independent pathway (Figure 43.2).

Further studies showed that uric acid was able to induce endothelial dysfunction *in vitro*. Several mechanisms appear to be operative, including the ability of uric acid to block uptake of the substrate (L-arginine) for nitric oxide, increased degradation of intracellular L-arginine, and a scavenging of nitric oxide by uric acid or uric acid-induced oxidants.[72–75] Indeed, uric acid inhibits endothelial release of nitric oxide, blocks endothelial cell proliferation, and induces senescence *via* activation of the local renin–angiotensin system and induction of oxidative stress.[72,76,77] Uric acid also stimulates vascular smooth muscle cell proliferation *in vitro via* uptake of urate into the cell with activation of MAP kinases, nuclear transcription factors (including NF-κB and AP-1), and inflammatory mediators (including monocyte chemoattractant protein-1 and C-reactive protein).[9,78–80] Uric acid also inhibits tubular cell proliferation and induces epithelial-to-mesenchymal phenotype transition of renal tubular cells with the production of extracellular matrix.[81] Hyperuricemic rats displayed evidence of endothelial dysfunction (with low serum nitrites reflecting low NO) and increased intrarenal renin expression.[8,72] The *in vivo* renal changes could be reversed by lowering circulating uric acid levels with uric acid–lowering drugs such as allopurinol and febuxostat.[6,9,82–84] In addition, micropuncture

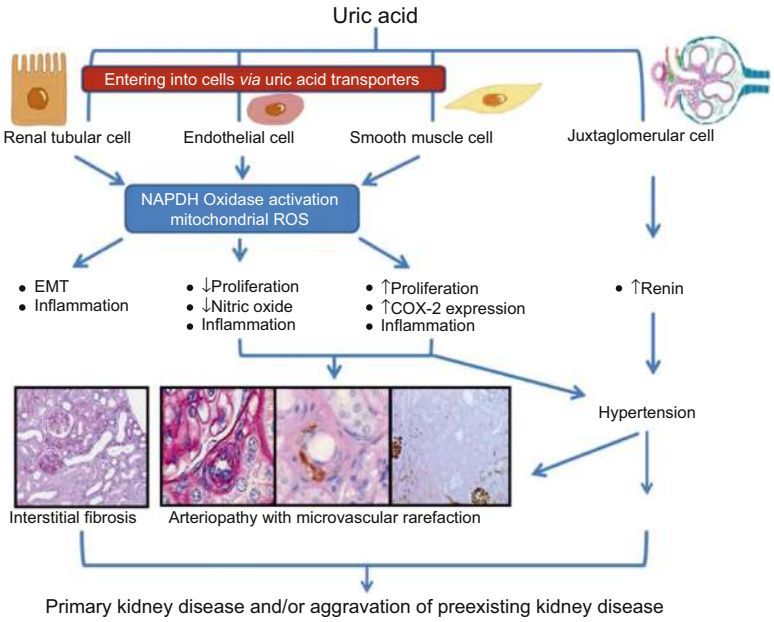


FIGURE 43.2 Proposed mechanism for uric acid–induced renal disease. Uric acid can have direct effects on cells and may also induce hemodynamic changes in the kidney. Some of the effects include the stimulation of oxidative stress in the cell, including stimulation of NADPH oxidase and oxidative stress in mitochondria. The oxidative stress is associated with tubular changes (epithelial mesenchymal transition, EMT). Endothelial cells show impaired nitric oxide bioavailability and reduced proliferation. Vascular smooth muscle cells produce growth factors, thromboxane, and inflammatory mediators. Renin is also stimulated. Glomerular hypertension and reduced renal blood flow result, and over time vascular changes (arteriolosclerosis), glomerulosclerosis, and tubulointerstitial fibrosis develop. *COX*, cyclooxygenase; *ROS*, reactive oxygen species.

studies performed on the hyperuricemic rats demonstrated glomerular hypertension with a reduction in renal plasma flow. All these mechanisms can lead to renal injury.

One of the key mechanisms by which uric acid appears to work is by inducing intracellular oxidative stress and inflammation.[77,85–88] (Figure 43.2) This is paradoxical, in that uric acid is an antioxidant that can bind and inactivate superoxide and peroxynitrite, and some studies suggest that uric acid may represent one of the more important antioxidants in the circulatory system.[89,90] However, the binding of uric acid with peroxynitrite generates radicals (aminocarbonyl radical and triuretcarbonyl radical) as the peroxynitrite is inactivated, and the urate–peroxynitrite reaction also generates alkylating species.[20,91] In addition, when uric acid enters cells it stimulates NADPH oxidase, leading to both intracellular and mitochondrial oxidative stress. Indeed, uric acid induces oxidative stress in a large variety of cell types, including vascular endothelial and smooth muscle cells, renal tubular epithelial cells, hepatocytes, islet cells, and adipocytes.[77,85–88] Taken together, uric acid may induce primary kidney disease or accelerate the progression of CKD by effects on the renal microvasculature, renal tubules, and interstitium.

Clinical Manifestations of Hyperuricemic Nephropathy

Most patients with longstanding gout have asymptomatic renal involvement with either normal or only mild renal insufficiency.[2,92] The majority have hypertension.[93] Renal blood flow is usually disproportionately low for the degree of decrement in renal function.[94] Fractional excretion of uric acid is usually less than 10%. Proteinuria occurs in the minority of cases, and, when present, is usually in the nonnephrotic range. The urinary sediment is also usually benign. However, hypertension is frequent, occurring in 50–60% of patients, and increasing in prevalence as renal function worsens. Renal biopsy shows chronic changes indistinguishable from chronic hypertensive nephropathy, with chronic glomerulosclerosis, tubulointerstitial fibrosis, and renal microvascular disease.[2] Intrarenal crystals may occasionally be observed, but their presence or absence does not rule out a role for uric acid in the pathogenesis of the kidney disease.[65] Nonetheless, a disproportionately elevated S[Ur] in relation to impaired renal function (such as S[Ur] greater than 9 mg/dL for a S[Cr] of less than 1.5 mg/dL, S[Ur] greater than 10 mg/dL for a S[Cr] of 1.5–2.0 mg/dL, and S[Ur] greater than 12 mg/dL when S[Cr] is greater than 2.0 mg/dL) would suggest there is a primary process raising S[Ur] besides reduction in GFR.

Role of Hyperuricemia in Progression of CKD

Although there is extensive epidemiological evidence that an elevated S[Ur] is an independent risk factor for the development of CKD (Table 43.1), it remains controversial whether an elevated S[Ur] is a risk factor for progression of kidney disease in patients with preexisting CKD. This is because patients with CKD may have elevated S[Ur] simply due to the reduction in urate excretion that accompanies reduced GFR. For example, neither the Modification of Diet in Renal Disease Study nor the Mild to Moderate Kidney Disease Study could show S[Ur] to be an independent risk factor for progression in patients with preexisting CKD.[70,95] A study in middle-aged and old Taiwanese subjects found an elevated S[Ur] increased the risk of renal disease, after adjustment for other metabolic risk factors such as gender, BMI, cholesterol, triglyceride, blood pressure, and blood sugar. An interesting finding from this study was that S[Ur] was independently associated with estimated glomerular filtration rate (eGFR) only in stage 3 CKD but not in stage 4 or 5 CKD patients.[96]

There may be a variety of reasons why an elevated S[Ur] may not predict CKD in subjects with established CKD. One potential explanation is that factors associated with reduced GFR itself may have major effects on driving renal progression that dwarf the biological mechanisms by which uric acid may cause renal disease. Thus, impaired renal function results in hypertension from impaired salt excretion, causes endothelial dysfunction, and is associated with inflammation.[97] Many people with severe CKD also suffer from malnutrition, and these patients may have low S[Ur] due to a reduction in food intake (because uric acid levels are driven in part by diet). It is also possible that in the setting of a prooxidant state such as CKD, the antioxidant benefits of uric acid may outweigh its proinflammatory and prooxidant effects. More studies need to be performed to better understand the complexity of uric acid and its potential pathogenic role in established CKD.

Role of Uric Acid–Lowering Therapy in CKD

Allopurinol

There have been a limited number of studies to examine the effect of uric acid–lowering in the development or progression of CKD. Kanbay et al. reported that treatment of healthy subjects with asymptomatic hyperuricemia improved renal function.[98] Siu et al. also reported that the treatment of asymptomatic hyperuricemia delayed disease progression, with a lesser increase in blood pressure following a 12-month treatment of allopurinol in patients with stage 3 CKD.[99] Shi et al. evaluated the effects of allopurinol in subjects with

IgA nephropathy and mild CKD, but because the control group did not progress, it was not possible to judge whether allopurinol was protective or not.[100] In another prospective study of 113 patients with stable CKD with eGFR less than 60 mL/min/1.73 m^2, Goicoechea et al. demonstrated that 100 mg/day allopurinol significantly slowed the progression of renal disease after 23.4 ± 7.8 months of treatment compared to controls, although the relative benefit was mild (difference in GFR of 4.6 mL/min/1.73 m^2).[101] However, follow-up with an extension study over 7 years confirmed a significant benefit of allopurinol treatment on renal survival.[102] One recent meta-analysis of eight randomized controlled trials (RCTs) reported that allopurinol did not improve renal survival compared to controls in five trials (n = 346), but did slow renal progression in three trials (n = 130).[103] However, a problem with the negative studies in this analysis was that there was no change in eGFR in the control group, and hence it was not possible to assess if allopurinol was protective because renal function remained stable. In another meta-analysis of 19 RCTs including 992 stage 3−5 CKD patients, allopurinol reduced S[Ur] and blood pressure with a preserved eGFR compared to control groups.[104] One problem with meta-analysis is the substantial heterogeneity among the trials regarding study design, populations enrolled, duration of follow-up, and level of baseline renal function.

Although early studies suggest some potential benefit of lowering S[Ur] on renal function, one of the more striking benefits appears to be on heart disease. In the study by Goicoechea et al., there was a significant reduction in cardiovascular events in patients with CKD.[101] Terawaki et al. also noted a nearly 50% reduction in cardiovascular events by allopurinol in people with hypertensive nephrosclerosis.[105] Furthermore, Kao et al. noted that allopurinol could improve left ventricular mass and endothelial dysfunction in CKD patients.[106] These studies suggest that lowering uric acid may be of benefit to reduce cardiovascular events in CKD.

Febuxostat

Febuxostat is a potent nonpurine-selective inhibitor of xanthine oxidase, which is metabolized in the liver, with only 1−6% of the dose being excreted through the kidneys. Hence, impaired renal function has little impact on the pharmacokinetic profile of febuxostat, allowing its safe administration to CKD patients.[107] In one RCT enrolling 93 stage 3 and 4 CKD patients, febuxostat slowed the decline in eGFR compared to placebo.[108] The mean eGFR in the febuxostat group showed a nonsignificant increase from a baseline of 31.5 ± 13.6 to 34.7 ± 18.1 mL/min/1.73 m^2 at 6 months. With placebo, mean eGFR decreased from 32.6 ± 11.6 to 28.2 ± 11.5 mL/min/1.73 m^2 (p = 0.003). Of the 45 (38%) participants in the febuxostat group, 17 had >10% decline in eGFR over baseline, compared with 26 of 48 (54%) from the placebo group (p < 0.004). A recent RCT including 467 stage 3 CKD patients with asymptomatic hyperuricemia demonstrated that febuxostat did not slow renal progression.[109] However, a problem with this study was that the control group only progressed 0.5 mL/min/1.73 m^2, making it difficult to show that the treatment arm was protective. However, subgroup analysis showed a benefit of febuxostat treatment in patients without proteinuria or with S[Cr] lower than the median.

Uric Acid and ESRD

In subjects with normal renal function, an elevated S[Ur] is almost always associated with increased cardiovascular risk, and a smaller rise in cardiovascular risk occurs in subjects with low S[Ur] levels ("J curve" of mortality).[110] However, in ESRD patients, the high risk for mortality is generally in those subjects with the lowest S[Ur] (reverse J curve).[57,58] The reason for this finding is unknown, but it is important to note that the lower quartile for S[Ur] in the ESRD population is still quite high compared to normal subjects. One potential explanation for the association of lower S[Ur] with increased mortality in dialysis patients may relate to the fact that subjects in the lowest S[Ur] category are those with the poorest nutrition, such as subjects who are bedridden or suffering from stroke.[58] A cohort study in 4298 incident HD patients showed an increased mortality risk of low S[Ur] (<5.0 mg/dL) among patients with low normalized protein catabolic rate (nPCR) (<0.9 g/kg/day; HR 1.73, 95% CI 1.42−2.10) but not with high nPCR (≥0.9 g/kg/day; HR 0.99, 95% CI 0.74−1.33).[111] It is also possible that S[Ur] might act similarly to obesity or hypertension as a risk factor associated with improved survival in ESRD patients. Further studies are necessary to better understand this complex relationship.

Hyperuricemia, Hypertension, and Metabolic Syndrome

Hyperuricemia is commonly associated with other conditions, including obesity, metabolic syndrome, fatty liver, and hypertension. For decades the increase in S[Ur] in these conditions has been thought to be secondary, and due to effects of hyperinsulinemia or obesity to alter uric acid excretion or metabolism. However, more recent studies have raised the exciting possibility that uric acid may have a causal role in these conditions.[112] For example, experimentally induced hyperuricemia has been shown to result in hypertension.[6] In various

models of metabolic syndrome and fatty liver, lowering uric acid with allopurinol has been reported to be protective.[113,114] Epidemiological studies demonstrate that an elevated S[Ur] is a consistent independent risk factor for hypertension, metabolic syndrome, diabetes, fatty liver, and obesity.[112,115] Pilot clinical interventional studies also report some benefit of lowering S[Ur] on blood pressure, insulin resistance, and systemic inflammation.[116–118] Clearly more studies need to be performed, but there is increasing evidence that uric acid may be a true risk factor not only for CKD but also for metabolic syndrome, hypertension, and fatty liver.

Challenges to the Uric Acid Hypothesis

The uric acid hypothesis is not without controversy. For example, some continue to argue that uric acid is actually a pure antioxidant and that the benefits of lowering serum urate with allopurinol are due to the ability of xanthine oxidase inhibitors to also block oxidants generated during the production of uric acid from xanthine. In support of this hypothesis, it has been repeatedly observed that allopurinol therapy improves endothelial dysfunction in humans, yet treatment with a uricosuric agent was reported to have no effect.[119,120] However, the mechanism by which uric acid causes cardiovascular disease appears to be due to the intracellular effects of uric acid, so treatments that block uric acid synthesis (such as allopurinol) would likely be more effective than uricosuric agents. Furthermore, in some cell culture studies the benefit of allopurinol can be prevented if uric acid is added to the media,[121] suggesting it is the uric acid that is responsible for the effect. In addition, in a recent clinical trial, both allopurinol and probenecid (a uricosuric drug) lowered blood pressure significantly in obese prehypertensive adolescents.[117]

The other major challenge is that genome wide association studies have found several polymorphisms in urate transport that predict hyperuricemia and gout, but they do not appear to predict hypertension or diabetes.[122,123] This has been interpreted as meaning that it is unlikely that S[Ur] is a true risk factor for these conditions. However, the polymorphisms alter the transport of uric acid in and out of cells, so it is unclear how these polymorphisms affect intracellular uric acid levels where the uric acid is working. We need more studies on this complex topic before any conclusions can be made firmly.

Should People with CKD and Hyperuricemia Be Treated?

Hyperuricemia is common in CKD patients, but it remains unclear if lowering uric acid is beneficial. Certainly the experimental, epidemiological, and pilot clinical studies raise the possibility that lowering S[Ur] may benefit both renal function and the cardiovascular risk in these patients, but we need larger, randomized trials before such therapy should be routinely embraced. We must also remember that allopurinol can induce a Stevens–Johnson syndrome, and rarely AKI. Although the serious reactions from allopurinol may be minimized by testing the HLA status of patients and excluding treatment in those who are HLA-B58 positive,[124] we still need to be careful to do no harm. We have another option in the use of febuxostat. The US FDA, however, issued a warning about the increased risk for mortality with febuxostat compared to allopurinol. Although it was not confirmed in many clinical trials using febuxostat, one study showed an increased cardiovascular and all-cause mortality in patients treated with febuxostat.[125] As such, we recommend treatment only for those patients with severe hyperuricemia (S[Ur] greater than 10 mg/dL in men and greater than 9 mg/dL in women), and only after discussing the pros and cons of such therapy with the patient.

CONCLUSIONS

Serum urate levels are determined by the balance of uric acid generation and excretion by the kidney. Decreased GFR and altered expression/function of uric acid transporters in renal tubules and the gastrointestinal tract can lead to elevations of S[Ur]. Hyperuricemia is epidemiologically associated with increased risk for kidney disease, and experimental studies suggest uric acid may have a contributory role. There is also accumulating evidence supporting hyperuricemia as a true risk factor for CKD, based on recent epidemiologic, clinical, and experimental observations. Nonetheless, there are still controversies regarding the causative role of uric acid in kidney disease. As such, we recommend a large randomized clinical trial be conducted to determine if uric acid–lowering therapy provides benefit in hyperuricemic subjects with CKD before routine lowering of uric acid levels is recommended.

References

1. Johnson SG. *On the diseases of the kidney.* John W Parker and Son; 1852.
2. Talbott JH, Terplan KL. The kidney in gout. *Medicine* 1960;**39**: 405–67.
3. Beck LH. Requiem for gouty nephropathy. *Kidney Int* 1986;**30**: 280–7.
4. Iseki K, et al. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. *Am J Kidney Dis* 2004;**44**: 642–50.
5. Iseki K, et al. Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. *Hypertens Res* 2001; **24**:691–7.

6. Mazzali M, et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension* 2001; **38**:1101–6.
7. Mazzali M, et al. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol* 2002;**282**:F991–997.
8. Nakagawa T, et al. Hyperuricemia causes glomerular hypertrophy in the rat. *Am J Nephrol* 2003;**23**:2–7.
9. Kang D-H, et al. A role for uric acid in the progression of renal disease. *J Am Soc Nephrol* 2002;**13**:2888–97.
10. Schumacher Jr HR. The pathogenesis of gout. *Clevel Clin J Med* 2008;**75**(Suppl. 5):S2–4.
11. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med* 2004;**350**:1093–103.
12. Raivio KO, et al. Stimulation of human purine synthesis de novo by fructose infusion. *Metabolism* 1975;**24**:861–9.
13. Emmerson BT. Effect of oral fructose on urate production. *Ann Rheum Dis* 1974;**33**:276–80.
14. Faller J, Fox IH. Ethanol-induced hyperuricemia: evidence for increased urate production by activation of adenine nucleotide turnover. *N Engl J Med* 1982;**307**:1598–602.
15. Lieber CS, Jones DP, Losowsky MS, Davidson CS. Interrelation of uric acid and ethanol metabolism in man. *J Clin Investig* 1962;**41**: 1863–70.
16. Scott JT, Holloway VP, Glass HI, Arnot RN. Studies of uric acid pool size and turnover rate. *Ann Rheum Dis* 1969;**28**:366–73.
17. Kahn K, Serfozo P, Tipton PA. Identification of the true product of the urate oxidase reaction. *J Am Chem Soc* 1997;**119**:5435–42.
18. Oda M, Satta Y, Takenaka O, Takahata N. Loss of urate oxidase activity in hominoids and its evolutionary implications. *Mol Biol Evol* 2002;**19**:640–53.
19. Keebaugh AC, Thomas JW. The evolutionary fate of the genes encoding the purine catabolic enzymes in hominoids, birds, and reptiles. *Mol Biol Evol* 2010;**27**:1359–69.
20. Gersch C, et al. Reactions of peroxynitrite with uric acid: formation of reactive intermediates, alkylated products and triuret, and in vivo production of triuret under conditions of oxidative stress. *Nucleos Nucleot Nucleic Acids* 2009;**28**:118–49.
21. Gersch C, et al. Inactivation of nitric oxide by uric acid. *Nucleos Nucleot Nucleic Acids* 2008;**27**:967–78.
22. Maesaka JK, Fishbane S. Regulation of renal urate excretion: a critical review. *Am J Kidney Dis* 1998;**32**:917–33.
23. Nagura M, Tamura Y, Kumagai T, Hosoyamada M, Uchida S. Uric acid metabolism of kidney and intestine in a rat model of chronic kidney disease. *Nucleos Nucleot Nucleic Acids* 2016;**35**:550–8.
24. Roch-Ramel F, Guisan B, Diezi J. Effects of uricosuric and antiuricosuric agents on urate transport in human brush-border membrane vesicles. *J Pharmacol Exp Ther* 1997;**280**:839–45.
25. Roch-Ramel F, Werner D, Guisan B. Urate transport in brush-border membrane of human kidney. *Am J Physiol* 1994;**266**: F797–805.
26. Anzai N, Jutabha P, Amonpatumrat-Takahashi S, Sakurai H. Recent advances in renal urate transport: characterization of candidate transporters indicated by genome-wide association studies. *Clin Exp Nephrol* 2012;**16**:89–95.
27. Hediger MA, Johnson RJ, Miyazaki H, Endou H. Molecular physiology of urate transport. *Physiology* 2005;**20**:125–33.
28. Enomoto A, et al. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. *Nature* 2002;**417**: 447–52.
29. Anzai N, et al. Plasma urate level is directly regulated by a voltage-driven urate efflux transporter URATv1 (SLC2A9) in humans. *J Biol Chem* 2008;**283**:26834–8.
30. Bibert S, et al. Mouse GLUT9: evidences for a urate uniporter. *Am J Physiol Renal Physiol* 2009;**297**:F612–9.
31. Dinour D, et al. Homozygous SLC2A9 mutations cause severe renal hypouricemia. *J Am Soc Nephrol* 2010;**21**:64–72.
32. Ichida K, et al. Clinical and molecular analysis of patients with renal hypouricemia in Japan-influence of URAT1 gene on urinary urate excretion. *J Am Soc Nephrol* 2004;**15**:164–73.
33. Lipkowitz MS, Leal-Pinto E, Rappoport JZ, Najfeld V, Abramson RG. Functional reconstitution, membrane targeting, genomic structure, and chromosomal localization of a human urate transporter. *J Clin Investig* 2001;**107**:1103–15.
34. Van Aubel RAMH, Smeets PHE, van den Heuvel JJMW, Russel FGM. Human organic anion transporter MRP4 (ABCC4) is an efflux pump for the purine end metabolite urate with multiple allosteric substrate binding sites. *Am J Physiol Renal Physiol* 2005;**288**:F327–33.
35. Ichida K, et al. Decreased extra-renal urate excretion is a common cause of hyperuricemia. *Nat Commun* 2012;**3**:764.
36. Scolari F, et al. Uromodulin storage diseases: clinical aspects and mechanisms. *Am J Kidney Dis* 2004;**44**:987–99.
37. Bachmann S, et al. Renal effects of Tamm-Horsfall protein (uromodulin) deficiency in mice. *Am J Physiol Renal Physiol* 2005;**288**: F559–67.
38. Hart TC, et al. Mutations of the UMOD gene are responsible for medullary cystic kidney disease 2 and familial juvenile hyperuricaemic nephropathy. *J Med Genet* 2002;**39**:882–92.
39. Turner JJO, et al. UROMODULIN mutations cause familial juvenile hyperuricemic nephropathy. *J Clin Endocrinol Metab* 2003;**88**: 1398–401.
40. Han J, et al. Common genetic variants of the human uromodulin gene regulate transcription and predict plasma uric acid levels. *Kidney Int* 2013;**83**:733–40.
41. Gersch MS, et al. Does Tamm-Horsfall protein-uric acid binding play a significant role in urate homeostasis? *Nephrol Dial Transplant* 2006;**21**:2938–42.
42. Terkeltaub RA. Gout. *N Engl J Med* 2003;**349**:1647–55.
43. Johnson RJ, Titte S, Cade JR, Rideout BA, Oliver WJ. Uric acid, evolution and primitive cultures. *Semin Nephrol* 2005;**25**:3–8.
44. Kanabrocki EL, et al. Circadian relationship of serum uric acid and nitric oxide. *J Am Med Assoc* 2000;**283**:2240–1.
45. Augoustides-Savvopoulou P, et al. Partial hypoxanthine-Guanine phosphoribosyltransferase deficiency as the unsuspected cause of renal disease spanning three generations: a cautionary tale. *Pediatrics* 2002;**109**:E17.
46. Merriman TR, Dalbeth N. The genetic basis of hyperuricaemia and gout. *Joint Bone Spine* 2011;**78**:35–40.
47. Alderman MH, Cohen H, Madhavan S, Kivlighn S. Serum uric acid and cardiovascular events in successfully treated hypertensive patients. *Hypertension* 1999;**34**:144–50.
48. Johnson RJ, et al. Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. *Am J Clin Nutr* 2007; **86**:899–906.
49. Van den Berghe G. Fructose: metabolism and short-term effects on carbohydrate and purine metabolic pathways. *Prog Biochem Pharmacol* 1986;**21**:1–32.
50. Johnson RJ, et al. Hypothesis: could excessive fructose intake and uric acid cause type 2 diabetes? *Endocr Rev* 2009;**30**:96–116.
51. Nicholls A, Snaith ML, Scott JT. Effect of oestrogen therapy on plasma and urinary levels of uric acid. *Br Med J* 1973;**1**:449–51.
52. Wilson VK, Thomson ML, Dent CE. Amino-aciduria in lead poisoning; a case in childhood. *Lancet* 1953;**265**:66–8.
53. Inglis JA, Henderson DA, Emmerson BT. The pathology and pathogenesis of chronic lead nephropathy occurring in Queensland. *J Pathol* 1978;**124**:65–76.
54. Jefferson JA, et al. Hyperuricemia, hypertension, and proteinuria associated with high-altitude polycythemia. *Am J Kidney Dis* 2002; **39**:1135–42.

55. Hare JM, Johnson RJ. Uric acid predicts clinical outcomes in heart failure: insights regarding the role of xanthine oxidase and uric acid in disease pathophysiology. *Circulation* 2003;**107**:1951–3.
56. Sorensen LB. Role of the intestinal tract in the elimination of uric acid. *Arthritis Rheum* 1965;**8**:694–706.
57. Suliman ME, et al. J-shaped mortality relationship for uric acid in CKD. *Am J Kidney Dis* 2006;**48**:761–71.
58. Lee SMK, et al. Low serum uric acid level is a risk factor for death in incident hemodialysis patients. *Am J Nephrol* 2009;**29**:79–85.
59. Athyros VG, et al. Effect of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: a subgroup analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Am J Kidney Dis* 2004;**43**:589–99.
60. Iwai N, et al. A high prevalence of renal hypouricemia caused by inactive SLC22A12 in Japanese. *Kidney Int* 2004;**66**:935–44.
61. Guttmann A, Krasnokutsky S, Pillinger MH, Berhanu A. Pegloticase in gout treatment – safety issues, latest evidence and clinical considerations. *Ther Adv Drug Saf* 2017;**8**:379–88.
62. Johnson RJ, et al. Uric acid and chronic kidney disease: which is chasing which? *Nephrol Dial Transplant* 2013;**28**:2221–8.
63. Bluestone R, Waisman J, Klinenberg JR. The gouty kidney. *Semin Arthritis Rheum* 1977;**7**:97–113.
64. Nickeleit V, Mihatsch MJ. Uric acid nephropathy and end-stage renal disease–review of a non-disease. *Nephrol Dial Transplant* 1997;**12**:1832–8.
65. Johnson RJ, Kivlighn SD, Kim YG, Suga S, Fogo AB. Reappraisal of the pathogenesis and consequences of hyperuricemia in hypertension, cardiovascular disease, and renal disease. *Am J Kidney Dis* 1999;**33**:225–34.
66. Johnson RJ, Tuttle KR. Much ado about nothing, or much to do about something? The continuing controversy over the role of uric acid in cardiovascular disease. *Hypertension* 2000;**35**:E10.
67. Tomita M, et al. Does hyperuricemia affect mortality? A prospective cohort study of Japanese male workers. *J Epidemiol* 2000;**10**:403–9.
68. Li L, et al. Is hyperuricemia an independent risk factor for new-onset chronic kidney disease?: a systematic review and meta-analysis based on observational cohort studies. *BMC Nephrol* 2014;**15**:122.
69. Testa A, et al. Association of a polymorphism in a gene encoding a urate transporter with CKD progression. *Clin J Am Soc Nephrol* 2014;**9**:1059–65.
70. Madero M, et al. Uric acid and long-term outcomes in CKD. *Am J Kidney Dis* 2009;**53**:796–803.
71. Sánchez-Lozada LG, Tapia E, Rodríguez-Iturbe B, Johnson RJ, Herrera-Acosta J. Hemodynamics of hyperuricemia. *Semin Nephrol* 2005;**25**:19–24.
72. Khosla UM, et al. Hyperuricemia induces endothelial dysfunction. *Kidney Int* 2005;**67**:1739–42.
73. Park J-H, et al. Uric acid attenuates nitric oxide production by decreasing the interaction between endothelial nitric oxide synthase and calmodulin in human umbilical vein endothelial cells: a mechanism for uric acid-induced cardiovascular disease development. *Nitric Oxide* 2013;**32**:36–42.
74. Zharikov S, et al. Uric acid decreases NO production and increases arginase activity in cultured pulmonary artery endothelial cells. *Am J Physiol Cell Physiol* 2008;**295**:C1183–90.
75. Schwartz IF, et al. Hyperuricemia attenuates aortic nitric oxide generation, through inhibition of arginine transport, in rats. *J Vasc Res* 2011;**48**:252–60.
76. Kang D-H, Park S-K, Lee I-K, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. *J Am Soc Nephrol* 2005;**16**:3553–62.
77. Yu M-A, Sánchez-Lozada LG, Johnson RJ, Kang D-H. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. *J Hypertens* 2010;**28**:1234–42.
78. Kang D-H, et al. Uric acid causes vascular smooth muscle cell proliferation by entering cells via a functional urate transporter. *Am J Nephrol* 2005;**25**:425–33.
79. Watanabe S, et al. Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. *Hypertension* 2002;**40**:355–60.
80. Kanellis J, et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. *Hypertension* 2003;**41**:1287–93.
81. Ryu E-S, et al. Uric acid-induced phenotypic transition of renal tubular cells as a novel mechanism of chronic kidney disease. *Am J Physiol Renal Physiol* 2013;**304**:F471–80.
82. Sánchez-Lozada LG, et al. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. *Kidney Int* 2005;**67**:237–47.
83. Sánchez-Lozada LG, et al. Effect of febuxostat on the progression of renal disease in 5/6 nephrectomy rats with and without hyperuricemia. *Nephron Physiol* 2008;**108**:69–78.
84. Sánchez-Lozada LG, et al. Treatment with the xanthine oxidase inhibitor febuxostat lowers uric acid and alleviates systemic and glomerular hypertension in experimental hyperuricaemia. *Nephrol Dial Transplant* 2008;**23**:1179–85.
85. Sautin YY, Nakagawa T, Zharikov S, Johnson RJ. Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. *Am J Physiol Cell Physiol* 2007;**293**:C584–96.
86. Corry DB, et al. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. *J Hypertens* 2008;**26**:269–75.
87. Roncal-Jimenez CA, et al. Sucrose induces fatty liver and pancreatic inflammation in male breeder rats independent of excess energy intake. *Metabolism* 2011;**60**:1259–70.
88. Lanaspa MA, et al. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in fructose-dependent and -independent fatty liver. *J Biol Chem* 2012;**287**:40732–44.
89. Nieto FJ, Iribarren C, Gross MD, Comstock GW, Cutler RG. Uric acid and serum antioxidant capacity: a reaction to atherosclerosis? *Atherosclerosis* 2000;**148**:131–9.
90. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. *Proc Natl Acad Sci USA* 1981;**78**:6858–62.
91. Imaram W, et al. Radicals in the reaction between peroxynitrite and uric acid identified by electron spin resonance spectroscopy and liquid chromatography mass spectrometry. *Free Radic Biol Med* 2010;**49**:275–81.
92. Yü TF, Berger L. Impaired renal function gout: its association with hypertensive vascular disease and intrinsic renal disease. *Am J Med* 1982;**72**:95–100.
93. Wallace SL. Gout and hypertension. *Arthritis Rheum* 1975;**18**:721–4.
94. Yü TF, Berger L, Dorph DJ, Smith H. Renal function in gout. V. Factors influencing the renal hemodynamics. *Am J Med* 1979;**67**:766–71.
95. Sturm G, Kollerits B, Neyer U, Ritz E, Kronenberg F. Uric acid as a risk factor for progression of non-diabetic chronic kidney disease? The Mild to Moderate Kidney Disease (MMKD) Study. *Exp Gerontol* 2008;**43**:347–52.

96. Chang H-Y, et al. Hyperuricemia as an independent risk factor of chronic kidney disease in middle-aged and elderly population. *Am J Med Sci* 2010;**339**:509–15.
97. Stenvinkel P, et al. IL-10, IL-6, and TNF-alpha: central factors in the altered cytokine network of uremia–the good, the bad, and the ugly. *Kidney Int* 2005;**67**:1216–33.
98. Kanbay M, et al. A randomized study of allopurinol on endothelial function and estimated glomular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. *Clin J Am Soc Nephrol* 2011;**6**:1887–94.
99. Siu Y-P, Leung K-T, Tong MK-H, Kwan T-H. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *Am J Kidney Dis* 2006;**47**:51–9.
100. Shi Y, et al. Clinical outcome of hyperuricemia in IgA nephropathy: a retrospective cohort study and randomized controlled trial. *Kidney Blood Press Res* 2012;**35**:153–60.
101. Goicoechea M, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *Clin J Am Soc Nephrol* 2010;**5**:1388–93.
102. Goicoechea M, et al. Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial. *Am J Kidney Dis* 2015;**65**:543–9.
103. Bose B, et al. Effects of uric acid-lowering therapy on renal outcomes: a systematic review and meta-analysis. *Nephrol Dial Transplant* 2014;**29**:406–13.
104. Kanji T, Gandhi M, Clase CM, Yang R. Urate lowering therapy to improve renal outcomes in patients with chronic kidney disease: systematic review and meta-analysis. *BMC Nephrol* 2015; **16**:58.
105. Terawaki H, et al. Effect of allopurinol on cardiovascular incidence among hypertensive nephropathy patients: the Gonryo study. *Clin Exp Nephrol* 2013;**17**:549–53.
106. Kao MP, et al. Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease. *J Am Soc Nephrol* 2011;**22**:1382–9.
107. Hoshide S, et al. PK/PD and safety of a single dose of TMX-67 (febuxostat) in subjects with mild and moderate renal impairment. *Nucleos Nucleot Nucleic Acids* 2004;**23**:1117–8.
108. Sircar D, et al. Efficacy of febuxostat for slowing the GFR decline in patients with CKD and asymptomatic hyperuricemia: a 6-month, double-blind, randomized, placebo-controlled trial. *Am J Kidney Dis* 2015;**66**:945–50.
109. Kimura K, et al. Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: a randomized trial. *Am J Kidney Dis* 2018. https://doi.org/10.1053/j.ajkd.2018.06.028.
110. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999;**131**:7–13.
111. Park C, et al. Serum uric acid, protein intake and mortality in hemodialysis patients. *Nephrol Dial Transplant* 2017;**32**:1750–7.
112. Johnson RJ, et al. Sugar, uric acid, and the etiology of diabetes and obesity. *Diabetes* 2013;**62**:3307–15.
113. Baldwin W, et al. Hyperuricemia as a mediator of the proinflammatory endocrine imbalance in the adipose tissue in a murine model of the metabolic syndrome. *Diabetes* 2011;**60**:1258–69.
114. Nakagawa T, et al. A causal role for uric acid in fructose-induced metabolic syndrome. *Am J Physiol Renal Physiol* 2006;**290**: F625–631.
115. Feig DI, Madero M, Jalal DI, Sanchez-Lozada LG, Johnson RJ. Uric acid and the origins of hypertension. *J Pediatr* 2013;**162**: 896–902.
116. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *J Am Med Assoc* 2008;**300**:924–32.
117. Soletsky B, Feig DI. Uric acid reduction rectifies prehypertension in obese adolescents. Novelty and significance. *Hypertension* 2012; **60**:1148–56.
118. Ogino K, et al. Uric acid-lowering treatment with benzbromarone in patients with heart failure: a double-blind placebo-controlled crossover preliminary study. *Circ Heart Fail* 2010;**3**:73–81.
119. George J, Carr E, Davies J, Belch JJF, Struthers A. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. *Circulation* 2006;**114**:2508–16.
120. Borgi L, et al. Effect of uric acid-lowering agents on endothelial function: a randomized, double-blind, placebo-controlled trial. *Hypertension* 2017;**69**:243–8.
121. Lanaspa MA, et al. Uric acid stimulates fructokinase and accelerates fructose metabolism in the development of fatty liver. *PLoS One* 2012;**7**:e47948.
122. Yang Q, et al. Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. *Circ Cardiovasc Genet* 2010;**3**:523–30.
123. Caulfield MJ, et al. SLC2A9 is a high-capacity urate transporter in humans. *PLoS Med* 2008;**5**:e197.
124. Jung J-W, et al. HLA-B58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency. *Nephrol Dial Transplant* 2011;**26**:3567–72.
125. White WB, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med* 2018;**378**:1200–10.

QUESTIONS AND ANSWERS

Question 1

A 22-year-old medical student presents to the emergency room with nausea and vomiting. He has a BUN 24 mg/dL, S[Cr] 2.4 mg/dL. S[Ur] was 1.4 mg/dL. He states he ran a 10K race yesterday. The most likely diagnosis is:

A. Rhabdomyolysis. The patient needs a CPK evaluation
B. Cocaine-induced AKI. This is common in medical students
C. Acute renal failure associated with SLC2A9 mutation
D. Dehydration-induced prerenal azotemia

Answer: C
A, B, and C are associated with a high S[Ur]. SLC2A9 mutation causes uricosuria and is associated with increased risk for exercise-induced AKI.

Question 2

Which of the following is not associated with hyperuricemia?

A. Hiking in the Andes
B. Jogging around the park
C. Pyrazinamide therapy in a patient with tuberculosis
D. Medullary Cystic Kidney Disease

Answer: B
Hyperuricemia can be observed with the hypoxia at high altitude, with pyrazinamide therapy and in medullary cystic disease. Moderate exercise tends to lower S [Ur], not raise it.

Question 3

Current Drugs used to Lower S[Ur] include all of the following except:

A. Febuxostat
B. Pegloticase
C. Losartan
D. Probenecid
E. Enalapril

Answer: E
Enalapril does not reliably lower S[Ur]. All other compounds do—losartan acts by directly inhibiting urate transport in the renal tubule independent of its angiotensin receptor blocking activity.

Question 4

All are true regarding CKD patients except:

A. An elevation in S[Ur] may be secondary to the renal disease
B. An elevated S[Ur] correlates with increased risk for cardiovascular events
C. S[Ur] is a better predictor for the progression of CKD than for the development of CKD
D. Pilot studies have shown benefit of lowering uric acid on cardiovascular events in subjects with CKD

Answer: C
Uric acid is better at predicting development of CKD, not progression. All other statements are true.

Question 5

All of the following are Risk Factors for Hyperuricemia Except:

A. Calcineurin inhibitor use
B. Thiazide use
C. Low-dose aspirin
D. Furosemide
E. Atorvastatin

Answer: E
Atorvastatin use is associated with lower S[Ur] levels. All other statements are true.

Question 6

All are true regarding the entity "Gouty Nephropathy" except

A. "Gouty Nephropathy" is observed in people with longstanding gout, who often have tophi
B. A primary finding in "Gouty Nephropathy" is a greater reduction in renal blood flow compared to GFR
C. "Gouty Nephropathy" is strongly associated with hypertension
D. "Gouty Nephropathy" is characterized by diffuse deposition of urate crystals in the renal medulla and cortex
E. "Gouty Nephropathy" results in ESRD in about 25% of patients untreated with Allopurinol

Answer: D
Renal histologic findings in patients with "Gouty Nephropathy" do not typically demonstrate focal deposition of urate crystals in the renal medulla. All other statements are true.

CHAPTER

44

Trace Elements in Chronic Kidney Disease

Andrew Davenport

UCL Centre for Nephrology, University College London, Royal Free Hospital, London, United Kingdom

Abstract

Essential trace elements play a vital role in cellular metabolism and the maintenance of homeostasis, by acting as key cofactors for enzymes. Their intracellular and plasma concentrations are regulated by gastrointestinal absorption and renal and gastrointestinal excretion to prevent deficiency and toxicity. Patients with chronic kidney disease (CKD) are potentially at risk of both essential trace element deficiencies and toxicity due to the failure to excrete other nonessential elements, leading to accumulation within the kidney which may cause chronic kidney damage, resulting in hypertension, proteinuria, and progression of kidney disease. Environmental exposure to chemical elements varies throughout the world due to differences in the composition of topsoil and surface water. Epidemiologic studies suggest possible linkages between environmental contaminations and increased local populations.

INTRODUCTION

Both a deficiency of essential trace elements and conversely an excess of trace elements are well recognized to cause harm in the general population.[1,2] The patient with chronic kidney disease (CKD) may be at greater risk of both deficiencies, due to the combination of dietary restrictions and increased urinary losses (in particular loss of binding proteins associated with heavy proteinuria), and, on the other hand, accumulation due to failure of renal excretion.

Exposure to trace elements varies from geographic region to region, due to differences in the chemical composition of topsoil. Minerals and other elements are washed from topsoil into rivers, and so can potentially enter the drinking water system. Similarly, plants take up nutrients and elements from the topsoil, allowing them to enter the normal human food chain. In industrialized areas, patients are exposed to airborne sources of chemicals, and contamination of land by industrial waste, with subsequent leaching into water tables and potentially into the domestic water supply. Although water companies aim to "purify" domestic water supplies, this is not universal worldwide. In addition, most systems are designed to remove low-level contaminants and not large industrial waste spills. Historically, lead piping was used to transport domestic water, allowing lead to leach into the water. Water companies also add chemicals to domestic water, not only to prevent bacterial growth but also precipitate small particles, so improving the clarity of drinking water. In some countries, fluoride is added to reduce dental decay as part of a public health policy.

TRACE METALS AND CHRONIC KIDNEY DISEASE

Not every element in the periodic table is vital to sustain human life. Exposure to some elements may result in pathology. As the kidney is one of the main routes of excretion, the kidney may become a target organ for damage by nonessential metals, including mercury, lead, cadmium, chromium, and platinum and metalloids such as arsenic. Depending on the level of acute or chronic exposure, and how the metal is handled within the kidney, a spectrum of renal pathologies ranging from acute kidney injury (AKI) to Fanconi-like proximal tubular syndromes, chronic interstitial fibrosis, and CKD may ensue. Patients with preexisting CKD may be more susceptible to toxicity. Environmental or other exposure to these elements may lead to progressive CKD.

RENAL TRANSPORT OF CATIONIC METALS

The biologically important divalent metals, zinc, copper, and iron, operate at micromolar levels and are carefully regulated by gastrointestinal absorption and renal

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00044-9

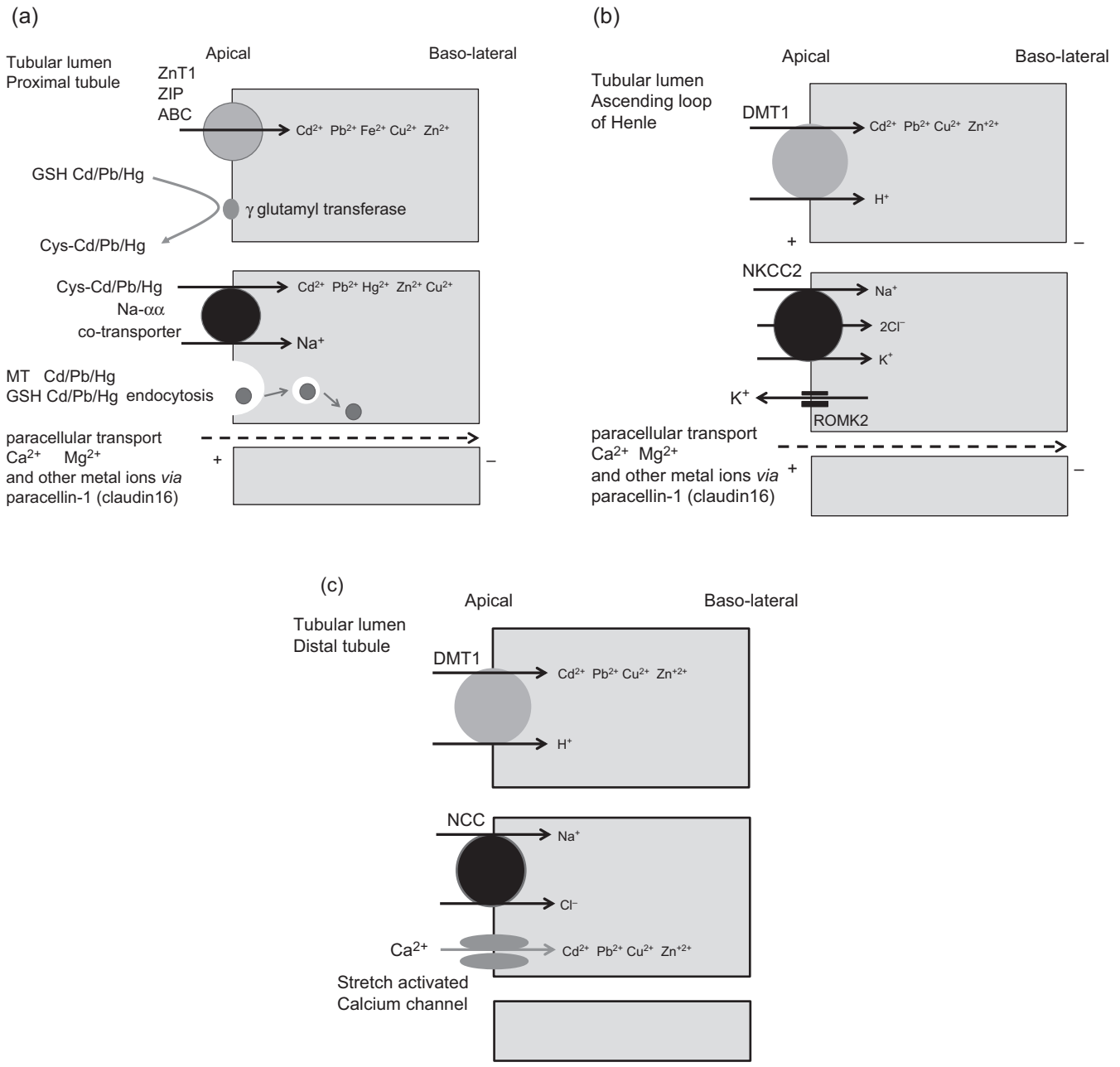


FIGURE 44.1 Ionized metal reabsorption in the proximal tubule (a), ascending loop of Henle (b), and distal tubule (c). (a) A variety of ionized metal transporters are present in the proximal tubule in addition to the DMT1, including zinc transporter 1 (Znt1), Zrt/Irt-like protein (ZIP), and ATP-binding cassette transporters (ABC). Metals which can bind glutathione can be cleaved by apical brush boarder γ-glutamyl transferase to cysteine bound metals which can then be reabsorbed by sodium-amino acid (αα) cotransporters. In addition, ionized metals can also be reabsorbed by endocytosis of metallothionein (MT) and glutathione (GSH) complexes, along with some paracellular transport. (b) In the ascending loop of Henle, reabsorption of metal ions takes place by DMT1 and paracellular transport. Paracellular transport is greater due to the electrical gradients generated by the sodium potassium 2 chloride transporter (NKCC2) and inwardly rectifying potassium channel (ROMK2). (c) In the distal tubule, ionized metals can be reabsorbed by the DMT1 transporter and also through stretch-activated cation channels. Sodium potassium cotransporter (NCC).

and gastrointestinal elimination, to tightly control intracellular and body fluid concentrations. Pathology may equally occur due to either low or high intracellular concentrations.

Although the normal renal handling of divalent cations has not been fully elucidated, approximately 70% of the transport occurs within the proximal tubule,[3] *via* the endosomal divalent cation transporter (DMT1) (Figure 44.1), which is also present in the gastrointestinal tract. DMT1 is also involved in the transport of highly toxic divalent cations, including cadmium, lead, cobalt, nickel, and platinum. Competition for DMT1

transporter can lead to both uptake of the toxic cation into the renal tubular cell and failure to reabsorb essential divalent metals. DMT1 is not the only reabsorption pathway for renal divalent cations, as zinc can be taken up into proximal tubules complexed with cysteine or histidine *via* sodium-amino acid cotransporters.[4] Toxic metals, particularly mercury and cadmium, which form cysteine conjugates, may potentially compete with zinc by binding these amino acids.

Toxic or essential plasma heavy metals exist either as nondiffusible protein-bound or diffusible complexed and ionized forms. Accidental intoxications usually result in gastrointestinal absorption, with the majority of the divalent metal ions absorbed binding to circulating plasma proteins, predominantly albumin, with only a relatively small amount (<10%) of the free ionized metal remaining in plasma water. As some plasma albumin is filtered by the glomerulus, the filtrate entering the proximal tubule may contain both the divalent metal bound to albumin and other protein transporters and the ionized form. Thus, proximal tubular uptake following acute intoxication is a combination of both the albumin-bound and free forms of the metal. Chronic low-level intoxication leads to a compensatory increase in circulating metal-binding plasma proteins, and metallothionein and glutathione in the liver and kidney. These latter compounds protect against heavy metal toxicity by forming conjugates which trap the metal inside.[5]

In vivo animal experimental studies suggest 99% of filtered divalent metal ions in free ionized form are taken up by tubular absorbption.[6] However, there are then differences regarding how divalent metals are transported out across the basolateral membrane. There is relatively rapid transport of essential metals, such as iron, zinc, and copper, whereas mercury, lead, and cadmium accumulate in the proximal tubular cell, with less than 10% transported out of the cell, due to slower basolateral transport.[5]

A series of heavy metal ion transporters, besides DMT1, have been isolated, including zinc transporter 1 (ionized zinc, iron, copper, cadmium), and ATP-binding cassette transporters (nickel, manganese, iron, molybdenum). Stretch-activated cation channels may also be involved. The binding affinities for ionized metals differ between transporters. The relative role of these transporters and channels has yet to be fully elucidated.

Although the majority of metal cations are reabsorbed in the proximal part of the tubule, reabsorption also occurs in the loop of Henle, distal tubule, and collecting duct through DMT1. During passage through the loop of Henle, local electrical gradients generated also allow paracellular reabsorption of cations. Additional metal ion transporters may be present in the distal tubule and collecting duct.

Cations bound to proteins are reabsorbed in the proximal tubule by the luminal multiligand receptor complex megalin:cubilin:amnionless. These include metalloproteins, such as iron bound to transferrin and cadmium bound to metallothionein. Many of the iron-binding proteins, such as transferrin, neutrophil gelatinase-associated lipocaclin (NGAL)/24p3/lipocalin-2, lactoferrin, albumin, hemoglobin, myoglobin, and hepcidin are filtered by the glomerulus, yet normally there is little or no iron lost in the urine. The proximal tubule megalin:cubilin:amnionless is important for transferrin and albumin reabsorption. Transferrin is also reabsorbed by the transferrin receptor, located in the proximal tubule and collecting duct. Other iron-containing proteins are reabsorbed *via* the NGAL/24p3/lipocalin-2 receptor (distal tubule, collecting duct), ferroportin (proximal tubule), the Zrt, Irt-related proteins ZIP 4 and 14 (proximal tubule), the epithelial Ca2+ channel 1 (TRPV5 Ca2+ channel) (distal tubule), and transient opening type Ca2+ channel $Ca_v3,1$ (distal tubule). Cadmium can compete with iron for all of these transporters. Similarly, these transporters will transport calcium, barium, strontium, and manganese and are inhibited by several di- and trivalent cations. In cases of iron deficiency, the renal tubule reabsorbs more of these divalent metals. In cases of metal toxicity, such as cadmium poisoning, cadmium competes with iron for reabsorption, leading to renal iron losses, and losses of other divalent cations.[7] Thus, toxicity with one metal or divalent cation can be exacerbated by losses of another metal.

In cases of chronic exposure to toxic cations, liver damage releases metals bound to metal-metallothionein and glutathione. These complexes are filtered by the glomerulus. In animal experimental models, around 50% is reabsorbed in the proximal tubule by endocytosis.[8] Enzymatic cleavage can occur, releasing Cys-metal conjugates which can then be reabsorbed by sodium-amino acid cotransporters.

RENAL TOXICITY OF CATIONIC METALS

Albumin and protein-bound and conjugated cationic metals are not directly toxic to the kidney, but when released in ionized forms, they can cause renal tubular epithelial pathology. The actual pathological injury will depend on the individual metal, the amount delivered to the kidney, and whether exposure is acute or chronic. For example, a single exposure to cadmium may simply cause calciuria and polyuria. More extensive proximal tubular necrosis may lead to an acquired Fanconi-like

syndrome. A single exposure to lead or mercury in an animal model can lead to reduced glomerular filtration rate, glycosuria, proteinuria, and tubular obstruction due to sloughing of tubular cells.

Typically, chronic exposure to toxic metal ions will result in an acquired Fanconi syndrome, with reduced glomerular filtration rate, increased urinary flow, proteinuria, glycosuria, and amino aciduria. In addition, because of competition for metal ion reabsorption systems within the tubules, patients may have increased urinary loss of essential metals such as iron, copper, and zinc.

TRACE METALS AND CHRONIC KIDNEY DISEASE

Zinc

Zinc is an essential micronutrient, incorporated into many metalloenzymes and proteins which are involved in cell metabolism, production of neurotransmitters, and regulatory pathways controlling oxidative stress.[1] Zinc deficiency has been reported to be a major cause of disease in developing countries.[9] Zinc deficiency is associated with delayed wound healing[10] and an immune deficiency characterized by defective phagocytosis and abnormal lymphocyte function,[10,11] which may contribute to suboptimal response to vaccinations reported in CKD patients.[12] Zinc deficiency may also cause or contribute to a number of relatively nonspecific conditions including dysgeusia and anorexia and may exacerbate anemia.[13]

Dietary sources of zinc are widespread, as zinc is present in meats, whole grains, legumes, and shell fish. However, zinc may bind to phytates and oxalate within the gut, leading to the formation of insoluble complexes, preventing absorption.[14] Zinc can also potentially bind to ion exchange resins prescribed to the CKD patient as phosphate binders. As zinc is mainly excreted in feces, urinary losses usually have little impact on zinc balance. In patients with severe nephrotic syndrome, plasma zinc concentrations may appear to be low, due to the associated hypoalbuminemia, as zinc is predominantly transported by albumin. Plasma zinc levels reflect current zinc status, whereas zinc in red blood cells and hair provide an estimate of longer-term zinc nutritional status. Competition for divalent transporters in the renal tubule, for example, by chronic cadmium toxicity, can lead to urinary loss of zinc.[15]

Generally, plasma zinc levels are normal or slightly reduced in CKD patients,[16] although reports suggest that as CKD progresses, patients are more likely to have lower levels of plasma zinc.[17] Whether this relates to a reduction in red meat consumption remains to be determined. As zinc is predominantly excreted by the gastrointestinal tract, CKD patients are at no greater risk of zinc toxicity than the general population. Zinc toxicity has been reported with zinc-denture adhesives and can lead to a neuropathy with bone marrow failure, especially in the presence of reduced serum copper concentration.[18] As several of the serine proteases in the clotting cascade are zinc dependent, there have been reports of increased risk of thrombosis with high levels of zinc. Conversely, increased risk of bleeding with platelet dysfunction has been reported with zinc deficiency.[19]

Copper

Copper is also an essential micronutrient, incorporated into many metalloenzymes and proteins involved in cell metabolism, and regulatory pathways controlling oxidative stress.[20] Because of its ubiquitous distribution among food sources and low daily requirement, acquired copper deficiency is rare in humans. Copper is predominantly excreted into the bile, so patients with CKD are not at increased risk of copper-related disorders.[21,22] Copper mainly binds not only to circulating ceruloplasmin but also to albumin. Therefore, increased urinary copper losses in patients with nephrotic syndrome and heavy proteinuria can occur. Children with Fanconi syndrome, particularly secondary to cystinosis, may also become copper deplete when treated with cysteamine.[23] Acquired copper deficiency may occur after bariatric surgery, typically presenting with a progressive myelopathy with spastic paraparesis, paraesthesias, and ataxic gait,[113] similar to that observed in subacute combined degeneration, as in cases of Vitamin B_{12} deficiency. Rarely, central nervous system demyelination, optic neuritis, and neuropathies have been reported.[23]

Acute release of copper, as in Wilson disease, or acute copper toxicity, can lead to met-hemoglobinemia, and red cell hemolysis with hemoglobinuria, resulting in AKI. Chronic copper toxicity can lead to renal proximal tubular damage, as copper is taken up by proximal tubular cells *via* the Ctr1 transporter.[24,25]

Manganese

Manganese is an essential cofactor for the metalloenzyme superoxide dismutase, and enzyme activity is decreased in manganese-deficient animals.[26] Whether subtle manganese deficiency contributes to the increased oxidative stress remains unknown.

Manganese is present in meat, fish, nuts, and dried fruit, but less than 5% is absorbed in the small bowel. Absorption can be reduced by concurrent high dietary intake of fiber, calcium, and phosphate. Manganese is stored primarily in the skeleton and mitochondria.[26] Most reports suggest patients with CKD have normal or low manganese levels.[16,22]

Manganese toxicity is typically secondary to water contamination and industrial exposure. Manganese toxicity causes neurological damage resulting in memory loss, ataxia, and a Parkinsonian-like neurological disturbance.[27] In cases of chronic toxicity, both serum and urine often show high levels of manganese, but there are no reports of kidney damage. In patients with CKD, manganese accumulation can contribute to anemia.[28]

Cadmium

Cadmium can be ingested by eating shell fish, liver, and kidney meats, and fish that live in cadmium-exposed water. However, most cadmium toxicity occurs from industrial exposure. Smokers have around twice as much cadmium in their body as nonsmokers, due to traces of cadmium in tobacco plants. Cadmium can compete with calcium for gastrointestinal absorption and is then taken up by the liver and kidney. Cadmium can be released by the liver during episodes of acute liver failure, possibly contributing to acute renal tubular damage.[29] Chronic cadmium exposure results in renal tubular toxicity, and proximal tubular cell necrosis, initially affecting the pars convoluta of the proximal tubule, then progressing to more distal regions of the tubule leading to chronic renal tubulointerstitial fibrosis with glomerular drop out,[30] and progressive CKD with hypertension.[15,31]

Cobalt

Cobalt is a key component of vitamin B_{12} and is required for the synthesis of hemoglobin. Food sources rich in cobalt include fish, nuts, leafy green vegetables, such as broccoli and spinach, and cereals, including oats.

Dietary deficiency is unusual, but more recently concerns have arisen over cobalt toxicity due to cobalt release from metal on artificial hips, resulting in neurological (hand tremor, incoordination, cognitive decline, depression, vertigo, hearing loss, and visual changes), cardiac (arrhythmias and cardiomyopathy), and endocrine (hypothyroidism) symptoms. Cobalt is strongly bound to albumin and readily excreted in the urine. It has been suggested that patients with CKD may be at greater risk of arthroprosthetic cobaltism and toxicity from cobalt containing coronary artery stents.[32,33]

Gadolinium

Gadolinium is used as a contrast agent for magnetic resonance imaging techniques. Gadolinium is filtered by the glomerulus and initially taken up into proximal renal tubular cells, stored, and then resecreted, similar to aluminum. Early clinical studies reported that high dosages could cause kidney damage.[34] Much lower gadolinium dosages are now used in clinical practice. However, of greater concern is the risk of nephrogenic systemic fibrosis[35] for patients with CKD stages 4 and 5 (glomerular filtration rate <30 mL/min/1.73 m^2) and renal dysfunction due to the hepatorenal syndrome or in the perioperative liver transplantation period, where the risk applies to any severity of renal dysfunction.[36,37] Although the majority of reports have been linked with linear gadolinium chelates, these contrast agents were introduced into clinical practice some time before the newer cyclical chelates. It is currently unclear whether the different forms of gadolinium contrast media have different risks for the development of nephrogenic systemic fibrosis.[38]

Strontium

Strontium is not recognized as being essential for life. The majority of strontium absorbed from the gastrointestinal tract is eliminated by the kidney. However, in patients with CKD, strontium can accumulate and be deposited in bone, causing osteomalcia. This has been reported in CKD patients living in areas with strontium in the drinking water and topsoil,[39] as well as those prescribed strontium supplements for the treatment of osteoporosis. Strontium supplements should be avoided or dosages must be reduced in elderly patients with CKD.[40]

Platinum

Platinum-based drugs are used in the treatment of several solid organ malignancies, including testicular and ovarian cancer, transitional cell bladder cancer, and small cell lung cancer.[41] Besides the acute side effects of cisplatin, gastrointestinal toxicity, and moderate myelosuppression, reduction in glomerular filtration rate occurs in 20%–30% of patients, despite prophylactic-intensive hydration and forced diuresis. Such changes in glomerular function are essentially irreversible.[42] Persistent effects on tubular renal function occur less commonly, but classically hypomagnesemia due to hypermagnesiuria is often seen due to distal tubular toxicity.[43] The risk of renal tubular injury is increased by concomitant prescription of nonsteroidal antiinflammatory drugs, diuretics, and inadequate hydration, coupled with administration of high dose cisplatinum.[44] Neurotoxicity, mainly sensory peripheral neuropathy, may occur during treatment, but typically disappears in the majority of patients after completion of the chemotherapy course. Persistent paresthesias are reported in 20%–60% of patients. Bilateral loss of

hearing at 4–8 kHz is seen in around 50% of patients. Several studies have reported a direct correlation between the cumulative cisplatin dose administered and the frequency of both neuro- and nephrotoxicity.[43] Chemotherapy schedules using single-day infusions have also been associated with increased neural and renal toxicity, possibly due to the higher peak plasma levels of cisplatin achieved. Renal toxicity potentially becomes cumulative with the increasing number of chemotherapy cycles.

Uranium

Uranium-induced AKI in animal models is typically associated with a reduction in outer renal cortical blood flow and glomerular perfusion.[45] Decreased glomerular perfusion may occur without decreased renal plasma flow, perhaps consequent on increased tubular hydraulic pressure secondary to impaired tubular solute and fluid reabsorption or tubular blockage due to cellular debris. In animal models of acute uranium nephrotoxicity, glomerular endothelial damage may also be marked. However, in man, chronic exposure leads to renal tubular damage, typically affecting the ascending limb and the proximal tubule. Renal injury is cumulative and related to chronic uranium exposure in mine and quarry workers. Proteinuria typically develops with tubular damage, but cannot reliably be used as a marker of renal damage. Low levels of uranium in drinking water do not appear to lead to clinically significant renal damage.[46]

Nickel

Industrial contamination with nickel typically leads to inhalation of nickel particles. Nickel settles in the topsoil and contaminates plants and water sources. Drinking water contaminated with nickel has been reported to cause hemolysis, hemoglobinuria, and kidney damage.[47] Patients with CKD have been reported to have elevated serum nickel concentrations.[22] Whether this is consequent to CKD or a cause of progressive renal damage or both is unclear.[48]

Thallium

Thallium is used as a rodenticide and has been included in some herbal remedies for skin conditions. Although thallium is mainly excreted *via* the fecal route, around 35% is renally excreted. Thallium poisoning typically presents with abdominal pain, nausea, and vomiting occurring within a few hours of an acute exposure. A few days later, alopecia often develops, along with a painful sensory neuropathy, typically involving the soles and palms, which may be followed by leg weakness, ataxia, confusion, psychosis, convulsions, and even coma. Liver function is often abnormal and patients may develop AKI.[49] Chronic low-level exposure may lead to CKD.

Thallium is used as an isotope for myocardial perfusion scans, and thallium cardiac washout times are prolonged in patients with CKD.[50]

Lanthanum

Lanthanum is prescribed to patients with CKD as a phosphate binder. Although lanthanum is predominantly excreted by the biliary system, it has been reported to be taken up into bone, and more recently into the gastric mucosa and upper gastrointestinal tract in both animal experimental models and patients with CKD.[51]

Bismuth

Besides industrial uses, bismuth containing compounds are used in surgical dressings, cosmetics, and for the treatment of gastric and duodenal ulcers, and some cancers. In cases of acute toxicity due to ingestion of bismuth salts, such as tripotassium dicitrato bismuthate (DeNol liquid), patients present with nausea, vomiting, and abdominal pain, and then may develop AKI and neurotoxicity. Patients chronically exposed to bismuth typically present with encephalopathy which has progressed from incoordination, loss of memory, and psychiatric symptoms. Other manifestations of chronic bismuth toxicity include CKD, thrombocytopenia, spontaneous fractures of the thoracic vertebra, and a paralytic ileus-like syndrome. Bismuth binds to sulfhydryl detoxification sites, inactivates enzymes, and affects methylation, leading to proximal tubular cell death by destabilizing the cell membrane.[52]

TOXICITY DUE TO METALS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Lead

Lead is the 19th most common element in the earth's surface, but has no essential biological role in man. Although lead has been recognized to cause toxicity for many centuries, lead piping has been used for domestic water supplies until relatively recently. Legislation was only recently introduced to curb lead emissions from gasoline-powered cars. Even so, current exposure generally occurs from air pollution or occupational exposure. Around 40% of inorganic lead inspired is absorbed through the lungs. Only 10–15% is absorbed

via the gastrointestinal tract, although the exact proportion depends on the presence of competition from other divalent cations. Organic lead from gasoline can also be absorbed through the skin. Lead workers are not the only group at risk of lead toxicity, as toxicity has also been reported in automobile mechanics.[53] Whereas many other cation metals bind to plasma proteins and albumin, lead and aluminum are predominantly transported in red blood cells. Ionized lead is filtered by the glomerulus and reabsorbed in the proximal tubule. Lead tends to be retained in the proximal tubular cell due to reduced basolateral secretion and thus accumulates causing renal tubular cell damage by free radical production, resulting in cell death.

Chronic exposure to lead leads to minor elevations in whole blood lead levels, resulting in impaired cognitive function, anemia (as lead competes for σ-aminolevulinic acid dehydratase and heme synthase, so reducing heme synthesis), and ultimately hypertension and CKD.[54,55] There is debate regarding whether lead accumulation is a consequence of CKD or whether lead exacerbates and accelerates the progression of CKD.[56–60] This may depend on the amount of lead exposure. There is clearer evidence for a role of lead in the progression of CKD from geographical areas with greater lead exposure.[59] In addition to renal damage, lead accumulation also affects the nervous and cardiovascular systems. Acute or acute and chronic exposure may result in colicky abdominal pain and general nonspecific symptoms of nausea, constipation, arthralgia and myalgia, headaches, and difficulty concentrating may occur. Lead may cause a peripheral motor neuropathy, classically causing wrist drop. Hypertension may increase the risk of stroke.[60]

There have been concerns that even low-level exposure to lead, especially in children, may result in developmental delay and brain damage, as well as anemia in infants and young children.[61]

As lead is carried in red blood cells, lead levels should be corrected for hematocrit. Whole blood lead levels may markedly underestimate total body lead stores.[62] To prevent industrial overexposure to lead, industrial workers often undergo provocation tests designed to mobilize tissue stores, and urine lead is measured in a timed urine collection. Newer alternatives to screening include X-Ray fluorescence techniques.[63,64]

Mercury

Toxicity from mercury may be caused by exposure to elemental, organic, and inorganic compounds. Organic mercury poisoning may result from industrial exposure to methyl and ethyl mercury compounds. Although inorganic mercury poisoning may be associated with occupational exposure, it has also been reported with medicinal products, including teething powders, skin whitening creams, and laxatives. Elemental mercury causes toxicity by releasing a mercury vapor which is inhaled.

Mercury is highly reactive with selenium, which is a key element in a series of intracellular enzymes. Selenium-containing enzymes prevent and reverse oxidative damage,[65] and these enzymes are irreversibly inhibited by mercury. For example, mercury inhibits thioredoxin reductase, the key enzyme which restores vitamins C and E, as well as a number of other important antioxidant molecules, back to their reduced forms, enabling them to counteract oxidative damage within cells. The proximal renal tubular epithelial cells have a high energy requirement and are vulnerable to mercury toxicity. Historically, mercury was used as a diuretic, as its toxic effects reduced renal tubular sodium reabsorption. In addition, mercury inactivates catecholaminei-o-methyltransferase, which increases serum and urinary epinephrine, norepinephrine, and dopamine, resulting in the development or worsening of hypertension.[66]

Organic mercury intoxication typically presents with a progressive neurologic illness, characterized by mental deterioration, leading progressively to paresthesia, ataxia, spasticity, deafness, and finally coma and death.[67] Inorganic mercury poisoning more often presents insidiously, sometimes only after many years of exposure, with chronic kidney damage, gastroenteritis, dermatitis, and in the latter stages dementia and tremor.[68–70]

Although mercury toxicity typically affects the renal tubular epithelium, resulting in cell death and chronic interstitial fibrosis, acquired Fanconi syndrome is rarely reported.[71] Mercury has also been reported to cause a number of glomerular pathologies, including nephrotic syndrome due to minimal change,[72] membranous[73] and possibly focal segmental sclerosis.[74] However, as with lead, mercury accumulates in patients with CKD,[22] but clinical studies failed to prove causation with progressive CKD.[75]

Aluminum

Aluminum is the third most common element in the earth's crust, yet it has no biological function in humans. Aluminum filtered by the glomerulus is taken up into the proximal tubule cells and accumulates due to slower basolateral transport. Aluminum can generate free radical oxygen species,[76] but does not appear to cause direct renal toxicity. Aluminum accumulates in patients with CKD due to reduced renal clearance. Other than aluminum-containing antacids and buffered aspirin, food is the primary source of exposure for most healthy people. Systemic uptake of aluminum after ingestion of

the monomeric salts is somewhat greater from drinking water (0.28%) than from food (0.1%). Aluminum exposure may result from contamination of domestic water due to treatment with aluminum salts, used to precipitate particulate matter to improve water clarity and appearance,[77] and from leaching from aluminum-coated cooking utensils.[78] In addition, some patients with CKD may be prescribed aluminum-containing medicines, not only as phosphate binders but also as antacids.

Aluminum accumulation leads to aluminum deposition in bone, resulting in reduced bone mineralization and osteomalacia.[79] Rarely, occupational aluminum exposure has been reported to cause multifocal osteonecrosis.[80] Aluminum can compete for key enzymes (delta aminolevulinic acid dehydratase and heme synthase), involved in the synthesis of hemoglobin, resulting in the development of anemia.[81,82] In severe cases of aluminum toxicity, patients can present with memory loss, a pseudo-Parkinsonian gait, tremor, which may progress to seizures, dementia, and death.[83] Aluminum is taken up into macrophages and leukocytes and has been suggested to affect immune function in CKD patients.[84–86]

METALLOIDS IN CHRONIC KIDNEY DISEASE

Arsenic

Arsenic contamination of groundwater is a problem that affects millions of people across the world. Other sources of arsenic include occupational industrial exposure and traditional medicines.[87] Arsenic poisoning usually causes headaches, confusion, severe diarrhea, and drowsiness and can progress to convulsions. Chronic poisoning leads to leukonychia and pigmentation of the hands. Acute arsenic poisoning is associated with abdominal pain, vomiting, and diarrhea, hematuria, myalgia, hair loss, convulsions, and ultimately death.[88]

Arsenic disrupts cell energy production by inhibiting the pyruvate dehydrogenase (PDH) complex in the Kreb cycle, resulting in apoptosis. Chronic low-level exposure inactivates endothelial nitric oxide synthase, leading to reduction in the generation and bioavailability of nitric oxide, and increases free radical production, with resultant increased oxidative stress. In addition, chronic arsenic exposure induces high oxidative stress, which may affect the structure and function of the cardiovascular system. Moreover, arsenic exposure may cause arrhythmias by altering voltage-gated potassium channels, increasing the QT interval and accelerating intracellular calcium overload.[89]

Low levels of arsenic exposure are associated with hypertension and peripheral vascular disease.[90] Population studies report an association between increased blood and urine arsenic levels and hypertension,[91] but whether chronic arsenic exposure *per se* leads to hypertension remains debatable, as there is no clear correlation between increasing arsenic levels and systolic hypertension.[92] However, chronic exposure to arsenic does result in chronic kidney damage and proteinuria,[92,93] and hypertension may be a consequence of chronic kidney damage. Occasionally arsenic can cause AKI.[94]

Polonium

Polonium is a radioactive metalloid which causes AKI and multiple organ failure when ingested.[95] Whether low-dose exposure results in CKD similar to uranium remains unknown.

Other Trace Elements in CKD

Other trace elements which have been implicated in causing CKD secondary to tubular damage include boron,[96] chromium,[97] and inhalation of silica dust.[98] One study in hemodialysis patients from Canada reported that tungsten and beryllium concentrations were commonly reduced, whereas vanadium, barium,

TABLE 44.1 Suggested Daily Intake of Trace Elements for Normal Adults

Element	Dietary Intake
Bismuth	25–50 μg
Chromium	Men 30 μg, women 20 μg
Cobalt	0.006′μg
Copper	0.9 mg
Fluoride	Men 4 mg, women 3 mg
Iodine	0.1–0.15 μg
Magnesium	Men 300 mg, women 270 mg
Manganese	≤4 mg but older subjects ≤0.5 mg
Molybdenum	45 μg
Nickel	0.4–0.6 mg
Selenium	Men 0.075, women 0.06 mg
Silicon	<700 mg
Strontium	Not determined
Sulfur	Not determined
Zinc	Men 5.6–9.5 mg, women 4–7 mg

antimony, molybdenum, and chromium concentrations were increased.[22] Whether these results are generalizable to other countries remains to be determined, as they may reflect the specific composition of local soil and water and exposure to industrial pollution.

Fluoride

Fluoride is a chemical element that is found most frequently in groundwater and has become one of the most important toxicologic environmental hazards globally.[99] Although when ingested in small quantities fluoride helps prevent dental caries, at higher concentrations (>1.5 mg/L) fluorosis may develop. It has been questioned whether increased fluoride exposure in parts of Sri Lanka is linked to the high rate of CKD reported in these areas,[100] as fluoride exposure has been linked to a chronic tubular interstitial nephritis.[101] Studies have reported that fluoride has direct toxic effects on the renal tubule, leading to apoptosis.[114]

Fluoride exposure from anesthetic gases including methoxyfluorane has been reported to reduce renal urate excretion.[102] In some parts of the world, fluoride is added to domestic water to reduce dental caries. Patients with CKD are more likely to retain fluoride[103] and be at risk of fluorosis.[104]

TABLE 44.2 Suggested Adult Reference Levels for Monitoring Deficiency of Essential Trace Elements and Toxicity of Nonessential Elements[1]

Element	Sample	SI Unit	Conventional Unit
Aluminum	Serum	<0.3 μmol/L	<8 μg/L
		Toxic[1] >7.4 μmol/L	Toxic[1] >200 μg/L
Arsenic	Whole blood[2]	0.03–0.08 μmol/L	0.2–6.2 μg/dL
	24-hr urine	Toxic >0.67 μmol/L	Toxic >50 μg/L
Bromide	Serum	≤0.15 mmol/L	<11 mg/L
		Toxic >20 mmol/L	Toxic >1500 mg/L
Cadmium	Whole blood	2.7–10.7 mmol/L[3]	0.3–1.2 μg/L[3]
		5.6–37 mmol/L[4]	0.6–3.9 μg/L[4]
Chromium	Serum	<10 nmol/L	<0.25 μg/L
Cobalt	Serum	1.7–6.8 nmol/L	0.1–0.4 μg/L
Copper	Plasma	11–22 μmol/L	72–164 μg/dL
Fluoride	Serum	0.3–2.2 μmol/L	0.57–4.2 μg/dL
Gadolinium	Serum	<1.0 nmol/L	<0.5 μg/L
Lanthanum	Serum	<10 nmol/L	<1.0 μg/L
Lead	Whole blood	<0.98 μmol/L	<20 μg/dL
		>2.4 μmol/L[5]	>50 μg/dL[5]
Manganese	Serum	9–24 nmol/L	0.5–1.3 μg/dL
Mercury	Whole blood	<20 nmol/L	<4 μg/L
		Toxic >500 nmol/L	Toxic >100 μg/L
Selenium	Plasma	0.89–1.65 μmol/L	70–130 μg/L
Silver	Whole blood	<0.28 nmol/L	<0.3 μg/L
Thallium	Whole blood	<5 nmol/L	<1 μg/L
Uranium	Serum	<10 nmol/L	<20 ng/L
Zinc	Serum	11–24 μmol/L	0.7–1.6 μg/L

Some samples must be taken into specially prepared specimen tubes to prevent environmental contamination.
[1]*Serum and whole blood samples do not readily correlate with tissue stores. As such, provocation testing should be considered in cases of suspected toxicity, for example, desferioxamine testing in cases of suspected aluminum toxicity.*
[2]*Whole blood taken in EDTA.*
[3]*Nonsmoker.*
[4]*Smoker.*
[5]*Industrial workers to be removed from occupational exposure.*

Selenium

Although the biological significance of low blood selenium concentrations in patients with CKD[105,106] is less clear, severe selenium deficiency is associated with sudden death and cardiomyopathy in the general population.[107–110] Selenium is vital for the function of a series of selenomethionine enzymes, which regulate immunity, redox state, and inflammation, including glutathione peroxidase, thioredoxin reductase, and selenoprotein P. Selenium deficiency leads to increased free radical activity and cell damage. The effect of mercury is to produce a selenium deficiency state. Therefore, some of the toxicity of mercury is due to selenium deficiency.[111] Lower levels of serum selenium without severe deficiency have been associated with hypertension,[106] heart failure,[107] and coronary artery disease[108] in the general population, and with cardiomyopathy among dialysis patients.[106] Although selenium is a vital micronutrient, too much selenium from contaminated soil or water can be toxic resulting in hair loss, sloughing of nails, neurodegenerative diseases, increased cancer risk, and death.[112]

SUMMARY

CKD patients are more susceptible to the consequences of trace element deficiencies and toxicity. The intracellular and plasma concentrations of trace elements are carefully regulated by the gastrointestinal tract and kidney to maintain homeostasis. Loss of regulation by the kidney typically leads to deficiency of key biological trace elements, including zinc and selenium, but accumulation and potential toxicity of elements with no normal physiological role, such as lead and arsenic. Exposure to trace elements varies throughout the world due to differences in the chemical composition of topsoil and drinking water. However, in industrial societies, mining and manufacturing processes not only potentially increase the risk of exposure to workers but also release of contaminated water and gases into the environment also exposes those living in neighboring areas to toxicity (Tables 44.1 and 44.2).

References

1. Prasad AS. Zinc in growth and development and spectrum of human zinc deficiency. *J Am Coll Nutr* 1988;**7**:377–84.
2. Moon K, Guallar E, Navas-Acien A. Arsenic exposure and cardiovascular disease: an updated systematic review. *Curr Atheroscler Rep* 2012;**14**(6):542–55.
3. Leazer TM, Liu Y, Klaassen CD. Cadmium absorption and its relationship to divalent metal transporter-1 in the pregnant rat. *Toxicol Appl Pharmacol* 2002;**185**:18–24.
4. Gachot B, Tauc M, Morat L, Poujeol P. Zinc uptake by proximal cells isolated from rabbit kidney: effects of cysteine and histidine. *Pflügers Arch* 1991;**419**:583–7.
5. Zalups RK. Molecular interactions with mercury in the kidney. *Pharmacol Rev* 2000;**52**:113–43.
6. Barbier O, Jacquillet G, Tauc M, Poujeol P, Cougnon M. Acute study of interaction between cadmium, calcium and zinc transport along the rat nephron in vivo. *Am J Physiol Renal Physiol* 2004;**287**:F1067–75.
7. Thevenod F, Wolf NA. Iron transport in the kidney: implications for physiology and cadmium nephrotoxicity. *Metallomics* 2016;**8**:17–42.
8. Hayashi T, Terui J, Sudo J. Clearance study for the estimation of glomerular filtration of Cd following the intravenous bolus of CdCl2 and Cd saturated metallothionein-II in rats. *Biol Pharm Bull* 1994;**17**:557–8.
9. Shrimpton R, Gross R, Hill I, Young M. Zinc deficiency: what are the most appropriate interventions? *BMJ* 2005;**330**:347–9.
10. Rink L, Gabriel P. Zinc and the immune system. *Proc Nutr Soc* 2000;**59**:541–52.
11. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. *Am J Clin Nutr* 1998; **68**(Suppl. 2):447S–63S.
12. Neu AM. Immunizations in children with chronic kidney disease. *Pediatr Nephrol* 2012;**27**(8):1257–63.
13. Foote JW, Hinks LJ. Zinc absorption in haemodialysis patients. *Ann Clin Biochem* 1988;**25**:398–402.
14. Saaka M. Combined iron and zinc supplementation improves hematologic status of pregnant women in upper west region of Ghana. *Ghana Med J* 2012;**46**(4):225–33.
15. Satarug S. Dietary cadmium intake and its effects on kidneys. *Toxics* 2018;**6**(1). https://doi.org/10.3390/toxics6010015. pii: E15.
16. Lin CC, Shih CT, Lee CH, Huang YL. Changes in trace elements during early stages of chronic kidney disease in type 2 diabetic patients. *Biol Trace Elem Res* 2018. https://doi.org/10.1007/s12011-018-1314-1. PMID: 29589268.
17. Kung WJ, Shih CT, Lee CH, Lin CC. The divalent elements changes in early stages of chronic kidney disease. *Biol Trace Elem Res* 2017. https://doi.org/10.1007/s12011-017-1228-3. PMID: 29285723.
18. Crown LA, May JA. Zinc toxicity: denture adhesives, bone marrow failure and polyneuropathy. *Tenn Med* 2012;**105**(2):39–40.
19. Tubek S, Grzanka P, Tubek I. Role of zinc in hemostasis: a review. *Biol Trace Elem Res* 2008;**121**(1):1–8.
20. Bulcke F, Dringen R, Scheiber IF. Neurotoxicity of copper. *Adv Neurobiol* 2017;**18**:313–43. https://doi.org/10.1007/978-3-319-60189-2_16.
21. Tapiero H, Townsend DM, Tew KD. Trace elements in human physiology and pathology. *Copper Biomed Pharmacother* 2003;**57**: 321–5.
22. Tonelli M, Wiebe N, Bello A, Field CJ, Gill JS, Hemmelgarn BR, Holmes DT, Jindal K, Klarenbach SW, Manns BJ, Thadhani R, Kinniburgh D, Alberta Kidney Disease Network. Concentrations of trace elements in hemodialysis patients: a prospective cohort study. *Am J Kidney Dis* 2017;**70**(5):696–704.
23. Besouw MT, Schneider J, Janssen MC, Greco M, Emma F, Cornelissen EA, et al. Copper deficiency in patients with cystinosis with cysteamine toxicity. *J Pediatr* 2013;**163**(3):754–60.
24. Wang H, Zhou Z, Hu J, Han Y, Wang X, Cheng N, Wu Y, Yang R. Renal impairment in different phenotypes of Wilson disease. *Neurol Sci* 2015;**36**(11):2111–5.
25. EL-Safty IA, Gadallah M, Shouman AE. Effect of silica exposure on urinary excretion of copper and zinc. *Am J Med Sci* 2003; **326**(3):122–7.

26. Horsburgh MJ, Wharton SJ, Karavolos M, Foster SJ. Manganese: elemental defence for a life with oxygen. *Trends Microbiol* 2002; **10**:496–501.
27. Koksal A, Baybas S, Sozmen V, Koksal NS, Altunkaynak Y, Dirican A, et al. Chronic manganese toxicity due to substance abuse in Turkish patients. *Neurol India* 2012;**60**(2):224–7.
28. Kim M, Koh ES, Chung S, Chang YS, Shin SJ. Altered metabolism of blood manganese is associated with low levels of hemoglobin in patients with chronic kidney disease. *Nutrients* 2017;**9**(11). https://doi.org/10.3390/nu9111177. pii: E1177.
29. Hoet P, Haufroid V, Deumer G, Dumont X, Lison D, Hantson P. Acute kidney injury following acute liver failure: potential role of systemic cadmium mobilization? *Intensive Care Med* 2012; **38**(3):467–73.
30. Barbier O, Jacquillet G, Tauc M, Cougnon M, Poujeol P. Effect of heavy metals on, and handling by, the kidney. *Nephron Physiol* 2005;**99**(4):105–10.
31. Kim Y, Lee BK. Associations of blood lead, cadmium, and mercury with estimated glomerular filtration rate in the Korean general population: analysis of 2008-2010 Korean National Health and Nutrition Examination Survey data. *Environ Res* 2012;**118**: 124–9.
32. Paustenbach DJ, Tvermoes BE, Unice KM, Finley BL, Kerger BD. A review of the health hazards posed by cobalt. *Crit Rev Toxicol* 2013;**43**(4):316–62.
33. Zywiel MG, Cherian JJ, Banerjee S, Cheung AC, Wong F, Butany J, Gilbert C, Overgaard C, Syed K, Jacobs JJ, Mont MA. *Bone Joint J* 2016;**98-B**(1):14–20.
34. Giozzet M, Cavagna E, De Dea M, Tarroni G, Casol D, DeSilvestro L, et al. Gadolinium for DSA in two patients with azotemia: images of suitable quality and risk of acute renal failure. *G Ital Nefrol* 2003;**20**(3):298–301.
35. Haley TJ, Raymond K, Komesu N, Upham HC. Toxicological and pharmacological effects of gadolinium and samarium chlorides. *Br J Pharmacol Chemother* 1961;**17**:526–32.
36. Grobner T. Gadolinium–a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006;**21**(4):1104–8.
37. Ramalho M, Ramalho J, Burke LM, Semelka RC. Gadolinium retention and toxicity-an update. *Adv Chron Kidney Dis* 2017; **24**(3):138–46.
38. Thomsen HS, Morcos SK, Almén T, Bellin MF, Bertolotto M, Bongartz G, ESUR Contrast Medium Safety Committee. Nephrogenic systemic fibrosis and gadolinium-based contrast media: updated ESUR Contrast Medium Safety Committee guidelines. *Eur Radiol* 2013;**23**(2):307–18.
39. Cohen-Solal M. Strontium overload and toxicity; impact on renal osteodystrophy. *Nephrol Dial Transplant* 2002;**17**(Suppl. 2):30–4.
40. Khanal A, Peterson GM, Castelino RL, Jose MD. Potentially inappropriate prescribing of renally cleared drugs in elderly patients in community and aged care settings. *Drugs Aging* 2015;**32**(5): 391–400.
41. Skinner R. Nephrotoxicity–what do we know and what don't we know? *J Pediatr Hematol Oncol* 2011;**33**(2):128–34.
42. Hartmann JT, Kollmannsberger C, Kanz L, Bokemeyer C. Platinum organ toxicity and possible prevention in patients with testicular cancer. *Int J Cancer* 1999;**83**(6):866–9.
43. Salas S, Mercier C, Ciccolini J, Pourroy B, Fanciullino R, Tranchand B, et al. Therapeutic drug monitoring for dose individualization of Cisplatin in testicular cancer patients based upon total platinum measurement in plasma. *Ther Drug Monit* 2006; **28**(4):532–9.
44. Bunel V, Tournay Y, Baudoux T, De Prez E, Marchand M, Mekinda Z, Maréchal R, Roumeguère T, Antoine MH, Nortier JL. Early detection of acute cisplatin nephrotoxicity: interest of urinary monitoring of proximal tubular biomarkers. *Clin Kidney J* 2017;**10**(5):639–47.
45. Diamond GL, Zalups RK. Understanding renal toxicity of heavy metals. *Toxicol Pathol* 1998;**26**:92–103.
46. Banning A, Benfer M. Drinking water uranium and potential health effects in the German federal state of Bavaria. *Int J Environ Res Public Health* 2017;**14**(8). https://doi.org/10.3390/ijerph1408092. pii: E927.
47. U.S. Department of Health and Human Services. *Public health service agency for toxic substances and disease registry.* Nickel; 1993.
48. Drazniowsky M, Parkinson IS, Ward MK, Channon SM, Kerr DN. Raised serum nickel concentrations in chronic renal failure. *Proc Eur Dial Transplant Assoc Eur Ren Assoc* 1985;**21**:241–6.
49. Misra UK, Kalita J, Yadav RK, Ranjan P. Thallium poisoning: emphasis on early diagnosis and response to hemodialysis. *Postgrad Med* 2003;**79**(928):103–5.
50. Kurisu S, Sumimoto Y, Ikenaga H, Ishibashi K, Fukuda Y, Kihara Y. Effects of chronic kidney disease on myocardial washout rate of thallium-201 in patients with normal myocardial perfusion on single photon emission computed tomography. *Ann Nucl Med* 2017;**31**(9):703–8.
51. Hoda RS, Sanyal S, Abraham JL, Everett JM, Hundemer GL, Yee E, Lauwers GY, Tolkoff-Rubin N, Misdraji J. Lanthanum deposition from oral lanthanum carbonate in the upper gastrointestinal tract. *Histopathology* 2017;**70**(7):1072–8.
52. Leussink BT, Nagelkerke JF, van de Water B, Slikkerveer A, van der Voet GB, Srinivasan A, et al. Pathways of proximal tubular cell death in bismuth nephrotoxicity. *Toxicol Appl Pharmacol* 2002;**180**(2):100–9.
53. Ahmad I, Khan B, Khan S, Khan MT, Schwab AP. Assessment of lead exposure among automobile technicians in Khyber Pakhtunkhwa, Pakistan. *Sci Total Environ* 2018;**633**:293–9. https://doi.org/10.1016/j.scitotenv.2018.03.160.
54. Gonick HC. Nephrotoxicity of cadmium & lead. *Indian J Med Res* 2008;**128**(4):335–52.
55. Schauder A, Avital A, Malik Z. Regulation and gene expression of heme synthesis under heavy metal exposure–review. *J Environ Pathol Toxicol Oncol* 2010;**29**(2):137–58.
56. Ekong EB, Jaar BG, Weaver VM. Lead-related nephrotoxicity: a review of the epidemiologic evidence. *Kidney Int* 2006;**70**: 2074–84.
57. Muntner P, He J, Vupputuri S, Coresh J, Batuman V. Blood lead and chronic kidney disease in the general United States population: results from NHANES III. *Kidney Int* 2003;**63**(3): 1044–50.
58. Kim NH, Hyun YY, Lee KB, Chang Y, Ryu S, Oh KH, Ahn C. Environmental heavy metal exposure and chronic kidney disease in the general population. *J Korean Med Sci* 2015;**30**(3):272–7.
59. Yu CC, Lin JL, Lin-Tan DT. Environmental exposure to lead and progression of chronic renal diseases: a four-year prospective longitudinal study. *J Am Soc Nephrol* 2004;**15**(4):1016–22.
60. Cheng Y, Schwartz J, Sparrow D, Aro A, Weiss ST, Hu H. Bone lead and blood Lead Levels in relation to baseline blood pressure and the prospective development of hypertension. The Normative Aging Study. *Am J Epidemiol* 2000;**153**(2):164–71.

61. Jedrychowski W, Perera F, Jankowski J, Rauh V, Flak E, Caldwell KL, et al. Prenatal low-level lead exposure and developmental delay of infants at age 6 months (Krakow inner city study). *Int J Hyg Environ Health* 2008;**211**(3–4):345–51.
62. Josephson J. Measuring lead effects: blood and bone together are better. *Environ Health Perspect* 2004;**112**(11):A636.
63. Burke MG, Miller MD. Practical guidelines for evaluating lead exposure in children with mental health conditions: molecular effects and clinical implications. *Postgrad Med* 2011;**123**(1): 160–8.
64. Sears ME. Chelation: harnessing and enhancing heavy metal detoxification–a review. *Sci World J* 2013:219840.
65. Farina M, Avila DS, da Rocha JB, Aschner M. Metals, oxidative stress and neurodegeneration: a focus on iron, manganese and mercury. *Neurochem Int* 2013;**62**(5):575–94.
66. Houston MC. Role of mercury toxicity in hypertension, cardiovascular disease, and stroke. *J Clin Hypertens* 2011;**13**(8):621–7.
67. Cohn I. Cause and prevention of some untoward reactions from mercurial diuretics. *N Y State J Med* 1950;**50**(12):1489–90.
68. Nigrovic V, Cho KC, Cafruny EJ. Diuretic response to mercuric cysteine: dependency on urinary pH. *J Pharmacol Exp Ther* 1970; **175**(3):741–8.
69. Park JD, Zheng W. Human exposure and health effects of inorganic and elemental mercury. *J Prev Med Public Health* 2012; **45**(6):344–52.
70. Syversen T, Kaur P. The toxicology of mercury and its compounds. *J Trace Elem Med Biol* 2012;**26**(4):215–26.
71. Wands JR, Weiss SW, Yardley JH, Maddrey WC. Chronic inorganic mercury poisoning due to laxative abuse. A clinical and ultrastructural study. *Am J Med* 1974;**57**(1):92–101.
72. Tang HL, Mak YF, Chu KH, Lee W, Fung SK, Chan TY, et al. Minimal change disease caused by exposure to mercury-containing skin lightening cream: a report of 4 cases. *Clin Nephrol* 2013; **79**(4):326–34.
73. Amaz S, Gross O, Krakamp B, Ortmann M, Dienes HP, Weber M. Membranous nephropathy from exposure to mercury in the fluorescent-tube-recycling industry. *Nephrol Dial Transplant* 2001; **16**(11):2253–5.
74. Miller S, Pallan S, Gangji AS, Lukic D, Clase CM. Mercury associated nephrotic syndrome: a case report and systematic review of the literature. *Am J Kidney Dis* 2013. https://doi.org/S0272-6386(13)00599-4.
75. Sommar JN, Svensson MK, Björ BM, Elmståhl SI, Hallmans G, Lundh T, Schön SM, Skerfving S, Bergdahl IA. End-stage renal disease and low level exposure to lead, cadmium and mercury; a population-based, prospective nested case-referent study in Sweden. *Environ Health* 2013;**12**:9. https://doi.org/10.1186/1476-069X-12-9.
76. Han S, Lemire J, Appanna VP, Auger C, Castonguay Z, Appanna VD. How aluminum, an intracellular ROS generator promotes hepatic and neurological diseases: the metabolic tale. *Cell Biol Toxicol* 2013;**29**(2):75–84.
77. Willhite CC, Ball GL, McLellan CJ. Total allowable concentrations of monomeric inorganic aluminium and hydrated aluminium silicates in drinking water. *Crit Rev Toxicol* 2012; **42**(5):358–442.
78. Matsushima F, Meshitsuka S, Funakawa K, Nose T. Effects of sodium chloride, acetic acid and citric acid on the dissolution of aluminum from aluminum cooking utensils. *Nihon Eiseigaku Zasshi* 1990;**45**(5):964–70.
79. Davis K, Pejović-Milić A, Chettle DR. In vivo measurement of bone aluminum in population living in southern Ontario, Canada. *Med Phys* 2008;**35**(11):5115–23.
80. Assunção JH, Malavolta EA, Gracitelli MEC, Filippi RZ, Ferreira Neto AA. Multifocal osteonecrosis secondary to occupational exposure to aluminum. *Acta Ortopédica Bras* 2017;**25**(3):103–6.
81. Davenport A, Newton KE, Toothill C, Will EJ, Davison AM. Effect of aluminum mobilization on hemoglobin during the first six months after transplantation. *Kidney Int* 1993;**43**(6):1313–8.
82. Lin CY, Hsiao WC, Huang CJ, Kao CF, Hsu GS. Heme oxygenase-1 induction by the ROS-JNK pathway plays a role in aluminum-induced anemia. *J Inorg Biochem* 2013;**128C**:221–8.
83. Shaw CA, Tomljenovic L. Aluminum in the central nervous system (CNS): toxicity in humans and animals, vaccine adjuvants,and autoimmunity. *Immunol Res* 2013. PMID: 23609067.
84. Zhu YZ, Liu DW, Liu ZY, Li YF. Impact of aluminum exposure on the immune system: a mini review. *Environ Toxicol Pharmacol* 2013; **35**(1):82–7.
85. Davenport A, Williams PS, Roberts NB, Bone JM. Sepsis: a cause of aluminum release from tissue stores associated with acute neurological dysfunction and mortality. *Clin Nephrol* 1988;**30**(1): 48–51.
86. Davenport A, Davison AM, Newton KE, Toothill C, Will EJ. Aluminium mobilization following renal allograft transplantation may have an immunomodulatory role by reducing the incidence of graft rejection. *Nephrol Dial Transplant* 1993;**8**(3):244–9.
87. Abhyankar LN, Jones MR, Guallar E, Navas-Acien A. Arsenic exposure and hypertension: a systematic review. *Environ Health Perspect* 2012;**120**(4):494–500.
88. Bolt HM. Arsenic: an ancient toxicant of continuous public health impact, from Iceman Ötzi until now. *Arch Toxicol* 2012;**86**(6): 825–30.
89. Chen Y, Graziano JH, Parvez F, Liu M, Slavkovich V, Kalra T, et al. Arsenic exposure from drinking water and mortality from cardiovascular disease in Bangladesh: prospective cohort study. *BMJ* 2011;**342**:d2431.
90. Robles-Osorio ML, Sabath-Silva E, Sabath E. Arsenic-mediated nephrotoxicity. *Ren Fail* 2015;**37**(4):542–7.
91. James K, Meliker JR. Is arsenic a contributor to CKD? *Am J Kidney Dis* 2013;**61**(3):364–5.
92. Zheng LY, Umans JG, Tellez-Plaza M, Yeh F, Francesconi KA, Goessler W, et al. Urine arsenic and prevalent albuminuria: evidence from a population-based study. *Am J Kidney Dis* 2013; **61**(3):385–94.
93. Hsu LI, Hsieh FI, Wang YH, Lai TS, Wu MM, Chen CJ, Chiou HY, Hsu KH. Arsenic exposure from drinking water and the incidence of CKD in low to moderate exposed areas of Taiwan: a 14-year prospective study. *Am J Kidney Dis* 2017;**70**(6):787–97.
94. Lee JY, Eom M, Yang JW, Han BG, Choi SO, Kim JS. Acute kidney injury by arsine poisoning: the ultra-structural pathology of the kidney. *Ren Fail* 2013;**35**(2):299–301.
95. Rubin GJ, Amlôt R, Page L. The London polonium incident: lessons in risk communications. *Health Phys* 2011;**101**(5):545–50.
96. Pahl MV, Culver BD, Vaziri ND. Boron and the kidney. *J Ren Nutr* 2005;**15**(4):362–70.
97. Wang T, Jia G, Zhang J, Ma Y, Feng W, Liu L, et al. Renal impairment caused by chronic occupational chromate exposure. *Int Arch Occup Environ Health* 2011;**84**(4):393–401.
98. Ibrahim KS, Ahmed SB, Amer NM. Study of kidney dysfunction in non-silicotic Egyptian workers. *Int J Hyg Environ Health* 2011; **214**(1):53–8.

99. Mukherjee I, Singh UK. Groundwater fluoride contamination, probable release, and containment mechanisms: a review on Indian context. *Environ Geochem Health* 2018. https://doi.org/10.1007/s10653-018-0096-x. PMID: 29572620.
100. Chandrajith R, Nanayakkara S, Itai K, Aturaliya TN, Dissanayake CB, Abeysekera T, et al. Chronic kidney diseases of uncertain etiology (CKDue) in Sri Lanka: geographic distribution and environmental implications. *Environ Geochem Health* 2011; **33**(3):267–78.
101. Chandrajith R, Dissanayake CB, Ariyarathna T, Herath HM, Padmasiri JP. Dose-dependent Na and Ca in fluoride-rich drinking water–another major cause of chronic renal failure in tropical arid regions. *Sci Total Environ* 2011;**409**(4):671–5.
102. Samuelson PN, Merin RG, Taves DR, Freeman RB, Calimlim JF, Kumazawa T. Toxicity following methoxyflurane anaesthesia. IV. The role of obesity and the effect of low dose anaesthesia on fluoride metabolism and renal function. *Can Anaesth Soc J* 1976; **23**(5):465–79.
103. Ludlow M, Luxton G, Mathew T. Effects of fluoridation of community water supplies for people with chronic kidney disease. *Nephrol Dial Transplant* 2007;**22**(10):2763–7.
104. Zuo H, Chen L, Kong M, Qiu L, Lü P, Wu P, Yang Y, Chen K. Toxic effects of fluoride on organisms. *Life Sci* 2018;**198**:18–24. https://doi.org/10.1016/j.lfs.2018.02.001. PMID: 29432760.
105. Chen B, Lamberts LV, Behets GJ, Zhao T, Zhou M, Liu G, et al. Selenium, lead, and cadmium levels in renal failure patients in China. *Biol Trace Elem Res* 2009;**131**(1):1–12.
106. Burk RF. Selenium in nutrition. *World Rev Nutr Diet* 1978;**30**: 88–106.
107. Salonen JT, Alfthan G, Huttunen JK, Pikkarainen J, Puska P. Association between cardiovascular death and myocardial infarction and serum selenium in a matched-pair longitudinal study. *Lancet* 1982;**2**:175–9.
108. Suadicani P, Hein HO, Gyntelberg F. Serum selenium concentration and risk of ischaemic heart disease in a prospective cohort study of 3000 males. *Atherosclerosis* 1992;**96**:33–42.
109. Moore JA, Noiva R, Wells IC. Selenium concentrations in plasma of patients with arteriographically defined coronary atherosclerosis. *Clin Chem* 1984;**30**:1171–3.
110. Ge K, Xue A, Bai J, Wang S. Keshan disease – an endemic cardiomyopathy in China. *Virchows Arch A Pathol Anat Histopathol* 1983; **401**:1–15.
111. Spiller HA. Rethinking mercury: the role of selenium in the pathophysiology of mercury toxicity. *Clin Toxicol (Phila)* 2018;**56**(5): 313–26.
112. He Y, Xiang Y, Zhou Y, Yang Y, Zhang J, Huang H, Shang C, Luo L, Gao J, Tang L. Selenium contamination, consequences and remediation techniques in water and soils: a review. *Environ Res* 2018; **164**:288–301. https://doi.org/10.1016/j.envres.2018.02.037. PMID: 29554620.
113. Kumar N, McEvoy KM, Ahlskog JE. Myelopathy due to copper deficiency produces a clinical picture like subacute combined degeneration. *Neurol* 2004;**63**:33–9.
114. Quadri JA, Sarwar S, Sinha A, Kalaivani M, Dinda AK, Bagga A, Roy TS, Das TK, Shariff A. Fluoride-associated ultrastructural changes and apoptosis in human renal tubule: a pilot study. *Hum Exp Toxicol* 2018;**1**. https://doi.org/10.1177/0960327118755257. PMID: 29441828.

QUESTIONS AND ANSWERS

Question 1

A 35-year-old man presented with increasing peripheral edema over a two-month period. He had been working in a factory making fluorescent light tubes for the last three years. On examination, he was hypertensive, blood pressure 160/95 mm Hg, with pitting edema in the lower legs. Urine dipstick testing revealed 4+ proteinuria, blood negative.

The most likely diagnosis is

A. Minimal change glomerulonephritis secondary to neon exposure
B. Membranous glomerulonephritis secondary to argon exposure
C. Focal segmental glomerulosclerosis secondary to fluorosis
D. Membranous glomerulonephritis secondary to mercury exposure
E. Lead-induced glomerulonephritis

Answer: D

Mercury exposure is an occupational hazard for workers in the light bulb industry. Mercury has been reported to cause minimal change and membranous glomerulonephritis, and, less frequently, focal segmental glomerulosclerosis and other forms of proliferative glomerulonephritis. The presence of hypertension suggests membranous glomerulonephritis rather than minimal change.

Question 2

A 28-year-old man was admitted to start his fourth course of cis-platinum-based chemotherapy for testicular carcinoma. Four days after starting chemotherapy he was found seizing in his bed by the nursing staff. The seizure was initially terminated with diazepam. Blood tests showed hemoglobin of 9.7 g/dL, BUN 25 mg/dL, and serum creatinine (S[Cr]) 3.5 mg/dL. Two hours later, he suffered a further grand mal tonic-clonic seizure.

The cause of the seizures was

A. Hypoglycaemia
B. Hypomagnesemia
C. Hypocalcemia
D. Hyponatremia
E. Hypokalemia

Answer: B

Although many metals predominantly cause proximal renal tubular damage, platinum-based compounds typically affect the distal tubule. Repeated courses characteristically cause distal tubular damage, excessive magnesuria, and hypomagnesemia. This patient has significant renal impairment, presumably secondary to the repeated renal damage caused by cis-platinum. The patient is most likely to be hypokalemic, despite the impaired renal function, but this is not the cause of the seizures. Typically hypokalemia does not repond to simple potassium repletion, and only starts to normalize once magnesium supplements have been administered.

Question 3

A 28-year-old woman with type 2 diabetes, nephrotic range proteinuria, and CKD stage 4 had a BMI of 45. She underwent gastric bypass surgery to lose weight. The operation was successful. She lost weight, from 135 kg to 95 kg over 4 months. She presented to the clinic with a two-week history of difficulty getting out of bed and chairs and had difficulty walking. On examination, she had an ataxic gait and some cerebellar signs.

Her neurological state was due to

A. Hypothyroidism
B. Vitamin B_{12} deficiency
C. Selenium deficiency
D. Zinc deficiency
E. Copper deficiency

Answer: E

Nephrotic range proteinurial reduces ceroplasmin levels. Therefore, this patient may be at risk of copper deficiency, due to increased urinary copper losses. Copper deficiency is a well-recognized complication of gastric bypass surgery, due to a combination of reduced appetite and reduced dietary copper intake. Small bowel bacterial intestinal overgrowth following removal of the acidic stomach barrier, which restricts bacterial entry into the small bowel, results in reduced copper absorption from the gastrointestinal tract. Although it is possible that some of the symptoms and signs could be secondary to vitamin B_{12} deficiency, body stores would be unlikely to become depleted and cause these symptoms within a few months of the operation.

Question 4

A 75-year-old man was brought to the outpatient clinic by his wife. He was unable to give a history. His wife explained that he had become demented over the previous 2 months. He had complained of difficultly reading and watching television, which had not improved with new glasses. He had also become somewhat hard of hearing. On examination, his blood pressure was 145/95 mm Hg. He had a tremor, worsening when his arms were outstretched, and had difficulty picking up small objects due to the tremor. He had a past medical history of hypertension, type 2 diabetes,

and CKD stage 3. Eighteen months earlier he had undergone successful left hip replacement. Blood tests showed a hemoglobin of 11.0 g/dL and S[Cr] 2.2 mg/dL.

What was the cause of his neurological decline?

A. Binswanger's disease
B. Alzheimer's dementia
C. Cobalt toxicity
D. Pick's disease
E. Cadmium toxicity

Answer C

Cobalt toxicity due to cobalt release from metal from metal artificial hips has been termed arthroprosthetic cobaltism. It results in neurological (hand tremor, incoordination, cognitive decline, depression, vertigo, hearing loss, and visual changes) and cardiac (arrhythmias and cardiomyopathy) abnormalities. As this patient had underlying CKD, he was likely to excrete cobalt released from the metal on the metal prosthetic hip joint. The tremors and difficulty with vision and hearing point away from Alzheimer's and Pick's dementias. Although cadmium can cause neurological damage, the movement disorder again would be somewhat atypical.

Question 5

A 66-year-old man was seen in the outpatient clinic complaining of recurrent generalized abdominal pain and constipation, nausea, and headaches. He continued to work in a glass factory specializing in stained glass windows. On examination, he was hypertensive, blood pressure was 170/105 mm Hg. He was anemic with hemoglobin 10.3 g/dL. S[Cr] was 2.6 mg/dL. Urine dipstick testing revealed 2+ protein, but no blood. A blood smear showed basophilic stippling.

The cause of his renal impairment was

A. Arsenic poisoning
B. Hypertension
C. Cadmium toxicity
D. Lead toxicity
E. Aluminum toxicity

Answer: D

The nonspecific gastrointestinal symptoms and abdominal pain are consistent with lead toxicity. Lead toxicity typically causes anemia and CKD, along with hypertension. Although CKD could simply be associated with hypertension, the presence of basophilic stippling on the blood smear, and the degree of anemia in light of the S[Cr] suggest lead, especially in view of industrial exposure to lead work in the making of stained glass. If he had gum discoloration, this would have clinched the clinical diagnosis.

Question 6

A 72-year-old Chinese woman was brought to the emergency department complaining of sudden onset of shortness of breath. She was dyspneic at rest, with a respiratory rate of 20 per minute. Her blood pressure was 170/110 mm Hg. She had atrial fibrillation at a rate of 140 beats per minute, confirmed on ECG. She also had pitting peripheral edema and pulmonary rales. She had generalized hair loss, brown spots on the palms of her hands, and leukonychia. Urine dipstick testing noted 2+ protein and 1+ blood. She was not known to take any regular prescription medicines but had regularly consulted a traditional Chinese medical practitioner.

The most likely cause of her atrial fibrillation was

A. Arsenic toxicity
B. Syphilis
C. Hypertensive heart disease
D. Thyrotoxicosis
E. Thallium poisoning

Answer: A

Thallium can cause cardiac toxicity with atrial fibrillation and hair loss. Thallium has occasionally been reported to contaminate some alternative medicines, but poisoning has usually been accidental when patients have taken rodenticide tablets in error or with contamination of foodstuffs. However, the combination of leukonychia and brown pigmentation on the palms is classically associated with low-level chronic arsenic toxicity. Arsenic exposure, probably from taking traditional medicine preparations, could account for her atrial fibrillation, hypertension, and CKD with proteinuria.

CHAPTER

45

Approach to the Patient with Chronic Glomerular Disease

Scott D. Cohen[a], *Gerald Appel*[b]

[a]Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States; [b]Division of Nephrology, Columbia University Medical Center, New York, NY, United States

Abstract

Glomerular diseases are a leading cause of chronic kidney disease (CKD). However, most treatment protocols for glomerulonephritis center on acute management. There are far less data on the treatment of CKD specifically caused by glomerular diseases. Most forms of glomerulopathy can progress to CKD, especially if not treated early when the disease process is most active. Risk factors for progression of glomerular disease to CKD include the presence of proteinuria especially in the nephrotic range or greater, decreased estimated glomerular filtration rate at baseline, and histologic evidence of crescentic glomerulonephritis, glomerulosclerosis, and tubulointerstitial fibrosis. The conservative treatment of all chronic renal diseases secondary to glomerulopathy includes blood pressure control, especially with medications of the renin–angiotension–aldosterone system inhibitor class, control of edema with diuretics and a low-sodium diet, avoidance of nephrotoxins, and moderation of dietary protein intake. Some therapies, such as control of dyslipidemia, will ameliorate the cardiovascular risk so common in CKD patients. Therapies to prevent tubulointerstitial fibrosis are currently being studied. This chapter will present an overview of management considerations for CKD secondary to glomerular diseases.

INTRODUCTION

Glomerular diseases are a frequent cause of morbidity and end-stage renal disease (ESRD) in the US.[1] In the 2017 report of the US Renal Data System "glomerulonephritis" (GN) accounted for between 15 and 20% of all prevalent cases of ESRD.[1] There have been significant advances made in the treatment of acute GN.[2,3] Perhaps because of better survival in ESRD secondary to glomerular disease as opposed to diabetic nephropathy and hypertensive nephrosclerosis, there remains less focus on the subset of patients with progressive GN leading to chronic kidney disease (CKD).[4] Even with successful treatment of the acute phase of GN or with partial remission of the nephrotic syndrome, glomerular diseases of diverse pathogenesis can transform into a phase of chronic progressive renal insufficiency with histologic changes consistent with secondary focal segmental glomerulosclerosis (FSGS) and increasing tubulointerstitial fibrosis.[5,6] Glomerular damage associated with hypertension and hyperfiltration are likely mediators of the disease process at this point (Figure 45.1).

There is compelling evidence that control of hypertension is essential in slowing the progression of all types of CKD, including those secondary to glomerular diseases. Moreover, for patients with glomerular diseases, elevated blood pressure should be treated with inhibitors of the renin–angiotensin–aldosterone system (RAAS), as clinically tolerated, to ameliorate the chronic effects of hyperfiltration. RAAS inhibitors have several effects on glomerular hemodynamics that make this class of medication especially beneficial in patients with chronic GN. Inhibition of RAAS leads to efferent arteriolar vasodilatation with a subsequent decrease in glomerular hyperfiltration, decreased aldosterone secretion, antifibrotic effects, reduced oxidative stress on the glomerulus, and preservation of the glomerular filtration barrier. There is little evidence for the appropriate target blood pressure in patients with glomerular disease and CKD, but lower goal blood pressures to less than 125/75 (or $<$ 130/80) mm Hg should be considered in those patients with proteinuria greater than 1 g/day.[7,8] The use of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) combinations has been associated with more cardiovascular events and episodes of AKI in two populations of

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00045-0

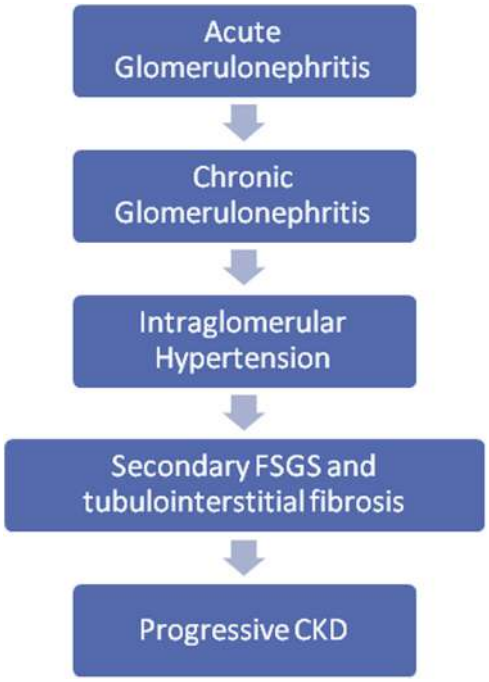


FIGURE 45.1 Development of chronic kidney disease (CKD) secondary to glomerular diseases: glomerular diseases can lead to CKD through increased glomerular hyperfiltration and secondary glomerular sclerosis leading to tubulointerstitial fibrosis. *FSGS*, focal segmental glomerulosclerosis.

patients at high risk for cardiovascular disease.[9,10] Combining ACEI and ARB has fallen out of clinical favor. Whether this should prohibit use of combination RAAS inhibitors in young individuals at high risk for progressive renal damage but lower risk for immediate cardiovascular disease is debated. There is increased interest in combining RAAS inhibitors with a mineralocorticoid receptor antagonist for enhanced antiproteinuric effects.

There are mixed results regarding the effects of dietary protein restriction to slow the progression of CKD secondary to glomerular diseases.[8,11,12] There are increasing data to support the use of sodium bicarbonate supplementation to treat the metabolic acidosis of CKD. In several small trials, patients with CKD and hypobicarbonatemia treated with sodium bicarbonate had a decrease in the rate of decline in estimated glomerular filtration rate (eGFR) compared to patients who did not receive sodium bicarbonate therapy.[13–15] Newer trials are also focusing on methods to prevent tubulointerstitial fibrosis and renal progression in CKD patients with glomerular diseases. There is interest in the role of transforming growth factor receptor-beta (TGF-β) inhibitors (pirfenidone and fresolimumab) to decrease the formation of glomerulosclerosis and tubulointerstitial fibrosis.[16,17] Bardoxolone, a new agent that may increase glomerular filtration rate (GFR) without affecting proteinuria through activation of the Nrf2 pathway and inhibition of the NF-kb pathway, is being studied in a variety of glomerular diseases including the genetic disease Alport's syndrome. This chapter will review the data on chronic glomerular diseases and risk factors for progression to CKD, and will focus on therapeutic strategies to halt the progression of chronic GN to ESRD.

NEPHROTIC SYNDROMES AND CHRONIC RENAL DISEASE

The nephrotic syndrome is classically defined by the triad of proteinuria greater than 3.0–3.5 g/day, edema, and hypoalbuminemia.[18] If the nephrotic syndrome is untreated, it can progress to CKD and ESRD. Other complications of the disease include hyperlipidemia, protein malnutrition, acute kidney injury (AKI), thromboembolic events, infections, vitamin D deficiency with associated osteomalacia, and decreases in thyroxine-binding globulin.[18–20] There are three common primary causes of adult nephrotic syndrome—minimal change disease (MCD), membranous nephropathy (MN), and FSGS.

Minimal Change Disease

MCD is felt to have an excellent long-term prognosis and little risk of progression to CKD. When worsening renal impairment is evident, a repeat renal biopsy should be considered to evaluate for possible misdiagnosis of FSGS or transformation to FSGS or other disease variants such as IgM and C1Q nephropathies.[21,22] It was previously felt that MCD and FSGS were part of the same disease process. However, advances in pathogenesis support the notion that MCD and FSGS are two separate entities. Approximately 25% of adult patients with MCD may present with or develop AKI.[22] AKI is a known major risk factor for the development of CKD.[23] Patients with AKI in the setting of MCD should initially be treated with steroids.[22] In some patients who develop severe episodes of AKI, there may be residual renal impairment that leads to CKD.[22,23] Once the AKI resolves, an ACEI or ARB should be used as the antihypertensive medication of choice for its antiproteinuric effect and to slow the progression of any residual renal impairment. Surveillance for recurrence of MCD should continue as the disease tends to have a relapsing and remitting course.[2,21,22] Patients with frequently relapsing or steroid-dependent MCD may benefit from steroid-sparing agents such as cyclosporine, cyclophosphamide (CYC), rituximab (RTX), or mycophenolate mofetil (MMF).[24,25]

Membranous Nephropathy

MN progresses to ESRD in approximately one-third of cases over 10 years, although the rates vary in different epidemiologic studies.[26–29] Risk factors for progressive CKD secondary to MN include nephrotic range proteinuria of greater than 8 g/day for more than 6 months, increased age, male gender, hypertension, and elevated serum creatinine concentration (S[Cr]) at baseline.[26–29] The presence of sclerotic glomeruli and tubulointerstitial fibrosis are also associated with progression to CKD. However, the pathology does not add additional independent risk beyond the clinical features mentioned above.[30] Likewise, a pathologic staging system for MN based on the location of electron dense deposits has not correlated with clinical outcomes.[30]

Initial management of patients with MN and CKD should focus on "conservative therapy" including diuretics to treat edema, low-sodium diet and moderation of protein intake, treatment of hyperlipidemia, and control of blood pressure with use of RAAS inhibitors where appropriate[26–29] (Figure 45.2). Use of ACEI or ARBS in patients with MN can slow the progression of CKD.[26–30] Use of statins was also shown in one study to reduce the risk of progression to ESRD in patients with MN. However, these data have not been confirmed by other studies.[30]

CKD patients with worsening renal insufficiency and evidence of persistently active immunologic injury on renal biopsy or by elevated levels of antiphospholipase A2 receptor antibody should receive immunomodulatory therapy as deemed clinically appropriate by the treating clinician.[31] Antiphospholipase A2 receptor antibody levels were shown to be present in approximately 70% of all patients with primary MN.[32] The ability to measure these antibody levels in patients with MN has revolutionized treatment. Persistent elevations in these antibody titers can assist in clinical decision-making to use additional immunosuppression to bring the disease into remission[31,33] Patients with low PLA2R antibody titers and lower levels of proteinuria may not be candidates for immunosuppression therapy, and treatment should focus on modifying risk factors for progressive CKD.

Immunosuppression treatment options for patients with MN include use of alkylating agents in combination with steroids, calcineurin inhibitors with or without steroids, mycophenolate MMF, RTX, and adrenocorticotropic hormone (ACTH).[26–29,34] CKD patients without evidence of immunologic activity either by a biopsy showing advanced glomerulosclerosis and severe tubulointerstitial fibrosis, and/or undetectable antiphospholipase A2 receptor antibody titers, should not receive immunomodulatory therapy.[31,33] The risks of

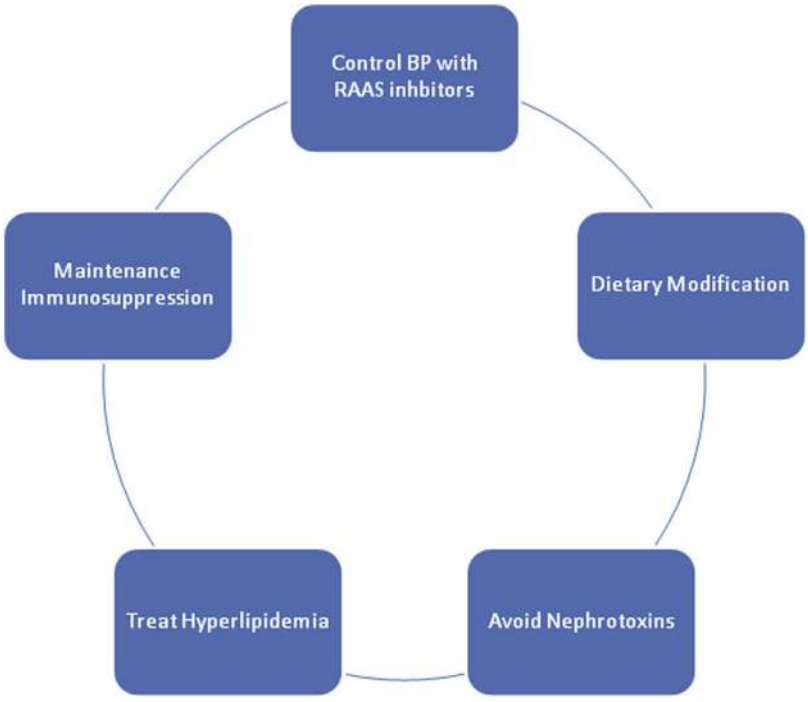


FIGURE 45.2 Treatment of chronic kidney disease (CKD) secondary to glomerular diseases: treatment includes control of blood pressure with renin–angiotensin–aldosterone inhibitor (RAAS) inhibitors unless otherwise contraindicated, dietary modification, avoidance of nephrotoxins, control of hyperlipidemia, and maintenance immunosuppression if there is active disease.

immunosuppression in this setting outweigh any remote benefits in patients with more advanced stages of CKD secondary to MN.

Patients with MN and advanced CKD with eGFR less than 20 mL/min/1.73 m^2 are candidates for renal transplantation. The risk of recurrent disease in this patient population ranges from 10 to 44%.[35,36] Until the past decade, there were little data on the optimal treatment for recurrent MN. Studies now support the use of RTX added on to standard maintenance immunosuppression protocols for the treatment of nephrotic range proteinuria in the setting of recurrent MN.[36]

Focal Segmental Glomerulosclerosis

FSGS represents a histologic glomerular injury pattern that is caused by diverse etiologies, including circulating permeability factors, genetic variants, viruses (including HIV and Parvovirus B19), medications (including interferon, bisphosphonates, sirolimus, and lithium) and secondary causes attributed to adaptive structural–functional responses.[37–39] FSGS is the most frequent glomerular disease to lead to progressive CKD and ESRD. Determining the etiology of FSGS, including whether the lesion represents a primary or secondary form, is essential because the rate and risk of progression to CKD and ESRD can be quite variable and dependent on the specific subtype of FSGS. Treatment differs for primary and most secondary forms of FSGS.[38,39] Research has continued into potential circulating permeability factors that can lead to primary FSGS but have produced mixed results. Circulating levels of the soluble urokinase receptor (suPAR) have been shown to be elevated in some patients with FSGS.[40,41] However, in other studies elevated suPAR levels have not distinguished between primary and secondary FSGS. Moreover, levels are elevated in many other disease states with CKD, making assay of circulating levels of little value in distinguishing FSGS with CKD from other proteinuric glomerular diseases.[42–44]

Untreated primary FSGS progresses to CKD and ESRD in the majority of cases.[45,46] In contrast to MN, rates of spontaneous remission are significantly lower.[45] Approximately 50% of patients who do not respond to therapy with a complete or partial remission will progress from CKD to ESRD over 10 years.[38,45,46] Patients with FSGS that are at greater risk for progressive CKD include those presenting with nephrotic range proteinuria and the full nephrotic syndrome, reduced eGFR at baseline; African Americans; and those with collapsed glomerular capillary tufts (the "collapsing variant") and tubulointerstitial fibrosis on biopsy and failure to achieve either a complete or partial remission.[38,39,45–47]

Until recently it was unclear why African Americans had a higher rate of progression to CKD and ESRD and increased rates of FSGS compared to Caucasians. A genetic breakthrough was made with the identification of unique apolipoprotein 1 (APOL1) genotypes on chromosome 22.[48–50] Certain allelic variants of apoL1 are able to lyse the pathogen *Trypanosoma brucei rhodesiense*, thereby conferring protection against African sleeping sickness.[48–50] Through natural selection, individuals of African descent have up to a 35% frequency of these allelic variants of APOL1.[48] Individuals with two mutant alleles of APOL1 have significantly higher rates of FSGS and progression to ESRD compared to those with one or no mutant alleles.[48–50] The exact mechanism whereby APOL1 mutants predispose to FSGS and renal disease is unclear and is undergoing further evaluation.[48–50] Mutated APOL1 gene products may predispose to podocytopathies through alterations in membrane ion flux, dysregulation of endolysosomal, mitochondrial and autophagic function, and increased cellular inflammatory pathways.[51] There is also recent evidence that suPAR interacts with APOL1 to activate integrin receptors, which can potentially lead to podocyte injury.[51]

Patients with FSGS and CKD should be treated with conservative therapy, including blood pressure control with maximization of RAAS inhibitors as clinically tolerated, statins to treat hyperlipidemia, low-sodium diet and moderation of animal protein intake, and diuretics as needed to control edema.[2,38] In animal models of FSGS, dietary protein restriction has been shown to reduce glomerular scarring through reductions in profibrotic cytokines including transforming growth factor-beta and platelet derived growth factor. Long-term protein restriction in humans with severe nephrotic syndrome remains controversial. The data are mixed regarding whether there is a beneficial impact of dietary protein restriction in slowing progression of glomerular diseases such as FSGS.[11,12]

It is not clear if adding additional immunosuppression therapy will slow progression of disease once advanced tubulointerstitial scarring and global glomerulosclerosis is present. Risks of immunosuppression should be balanced against any potential benefits. However, patients with severely reduced levels of eGFR are not likely to benefit from additional immunosuppression. Patients with secondary forms of FSGS should receive treatment directed at the underlying condition as opposed to immunosuppression with steroids. For example, observational studies show that patients with HIV-associated FSGS benefit from therapy with antiretroviral therapy to slow the progression of CKD.[52–55] Likewise, patients with obesity-induced glomerulomegaly and adaptive hyperfiltration secondary FSGS may benefit from weight reduction.[56]

In patients with primary FSGS and mild or moderate degrees of interstitial fibrosis and minimal glomerular sclerosis, immunosuppression options include a trial of corticosteroids. If the patient remains unresponsive after an adequate treatment trial, then second line therapies should be considered.[37,38,57] Calcineurin inhibitors can be considered as another option in patients with preserved GFR and steroid-resistant or steroid-dependent disease.[37,57] There is a direct effect of cyclosporine to stabilize the actin cytoskeleton in podocytes, thereby reducing proteinuria.[58] However, cyclosporine is contraindicated in patients with moderate or advanced CKD because constriction of the glomerular afferent arteriole can exacerbate the decline in GFR. MMF has been shown to be noninferior to cyclosporine at inducing remissions in corticosteroid-resistant FSGS.[59] There has also been research supporting a direct effect of RTX and ACTH on podocytes, potentially elucidating other mechanisms to decrease proteinuria.[60,61] There are clinical trials supporting the use of these agents in inducing remisssions of proteinuria in some but not all patients.[62,63] Additional studies are warranted to determine the precise role of calcineurin inhibitors, MMF, RTX, and ACTH as options for the treatment of patients with steroid-resistant disease.

NEPHRITIC SYNDROMES AND CHRONIC RENAL DISEASE

The nephritic syndrome is characterized by hypertension, proteinuria of usually less than 3.5 g/day, an active urine sediment including dysmorphic red blood cells (RBCs) and RBC casts, with or without AKI, and edema. There are a number of glomerular diseases associated with the nephritic syndrome that can progress to CKD and ultimately ESRD. Among others, these include postinfectious GN, IgA nephropathy, pauci-immune GN, antiglomerular basement membrane (anti-GBM) disease, and system lupus erythematous (SLE) nephritis. Another pattern of glomerulopathy that may present with either the nephritic syndrome, a nephrotic picture or asymptomatic urinary findings is membranoproliferative glomerulonephritis (MPGN). MPGN can be idiopathic or associated with a variety of secondary causes and pathogenetic mechanisms including immune complex renal disease with hepatitis C virus infection, SLE, paraproteinemias and lymphoproliferative disorders, thrombotic microangiopathies, and disorders of the alternative complement pathway system. Nephritic syndromes clearly make a contribution to the burden of CKD imposed by glomerular diseases.

Postinfectious Glomerulonephritis

Poststreptococcal glomerulonephritis (PSGN) was previously felt to be a relatively benign disease, especially in children with resolution of clinical findings and minimal clinical sequelae once treated with appropriate antimicrobial therapy.[64,65] However, a study in 1519 Australian Aboriginal residents living in a rural community found significantly higher levels of albuminuria and reduced eGFR <60 mL/min/1.73 m^2 in the 200 individuals who had at least one episode of PSGN.[66] This study highlights the importance of regular follow-up of patients once an episode of postinfectious GN resolves to assess for the clinical consequences of CKD. CKD in this patient population likely results from residual glomerular scarring leading to secondary FSGS with subsequent glomerular hyperfiltration and glomerulomegaly in the remaining functioning nephrons. This subset of patients should receive treatment strategies focused on slowing the progression of CKD and reducing extent of albuminuria, including treatment of hypertension with RAAS inhibitors where clinically appropriate.

Staphylococcus aureus-associated GN with or without endocarditis is surpassing PSGN as the most common cause of postinfectious GN in the US and other developed countries.[67] This is largely the result of widespread effective antistreptococcal antimicrobial therapy. There are little data on the risk of progressive CKD in the postinfectious staphylococcal population. Renal outcomes largely depend on the early eradication of infection, which will help ameliorate any ongoing immune complex-mediated glomerular injury. A particular subset of IgA dominant postinfectious GN, more common in patients with diabetes, may have a more treatment-resistant course with higher rates of progressive renal impairment.[68]

IgA Nephropathy

IgAN is the most common form of idiopathic GN worldwide.[2,69] Previously felt to have low risk for progression to CKD, epidemiologic studies show that IgAN can lead to ESRD in approximately 25% of cases at 10 years and up to 50% of cases at 25 years of follow-up.[70–72] Therefore, particular attention must focus on strategies to reduce CKD progression in this patient population.

The Renal Pathology Society developed the Oxford classification of IgA nephropathy based on key histologic criteria to provide an assessment of renal prognosis independent of clinical variables.[73] It was updated in 2016 to include the presence of crescents.[74] Renal histopathologic findings associated with a higher risk for progression include crescents, mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, and tubular atrophy/interstitial fibrosis.[73,74] Clinical risk factors for progression of IgAN are similar to other forms of renal disease and include decreased eGFR at baseline, higher degrees of proteinuria, and

the presence of hypertension.[2,70–72] Even an increase of proteinuria from 500 mg daily to over 1 g daily, which may be clinically insignificant in FSGS or MN, is highly prognostic of progressive disease in IgAN.[75] Reduction of heavier amounts of proteinuria to less than 1 g daily has been associated with improved prognosis.[76–78]

Decreased eGFR or CKD at initial presentation or during the disease observation period has been associated with significantly higher rates of progression to ESRD. Wakai et al.[71] evaluated 2270 Japanese patients with IgAN and found an almost 70% incidence of ESRD over seven years in patients who had S[Cr] greater than 1.68 mg/dL. Multiple studies have shown increased rates of proteinuria to be associated with worse renal outcomes. The incidence of CKD is highest in IgAN patients who present with nephrotic range proteinuria >3.5 g/day. The best prognosis was in those patients who had proteinuria of less than 1000 mg/day.[2,70–78] Hypertension is also associated with worse renal outcomes. Berthoux et al.[72] prospectively evaluated 332 patients with IgAN and found the incidence of ESRD and mortality to be significantly higher in those patients with hypertension (defined as blood pressure >140/90 mm Hg) at the time of initial diagnosis compared to normotensive patients. The incidence of dialysis was 15% at 10 years in those patients whose blood pressure was >140/90 mm Hg compared to 3% in patients whose blood pressure was well controlled. Because control of hypertension is essential to slowing the progression of CKD, much attention has focused on the dual benefit of RAAS inhibitors to reduce proteinuria and control blood pressure.

There are limited studies evaluating the effects of RAAS inhibitors in patients with IgAN. In addition to their antihypertensive effect, this class of medications is believed to decrease glomerular hyperfiltration and enhance the size-selectivity of the glomerular filtration barrier.[79] Several trials have shown a benefit to RAAS inhibitors in the setting of IgAN.[80–83] Use of ACEIs or ARBs has become the standard of care for all IgAN patients who present with more than 500 mg of proteinuria per day.

The use of combination RAAS inhibitor therapies including ACEI, ARB, and direct renin antagonists is significantly more controversial. Studies of dual RAAS inhibitor therapies in non-IgAN patients, including the ONTARGET[9] and ALTITUDE[10] trials, showed negative outcomes from combined RAAS inhibitors, including increased incidence of cardiovascular adverse outcomes, AKI, and hyperkalemia. However, these studies occurred largely in older patient populations at higher risk for major cardiovascular events, rather than younger individuals where reduction of proteinuria and slowing progressive renal disease may be paramount. At present, it appears safest to individualize combination use of ACE inhibitors and ARBs and only consider it in nondiabetic patients at low risk for cardiovascular events.

TABLE 45.1 Potential Therapeutic Options for Chronic Kidney Disease (CKD) Secondary to IgAN

Renin–angiotensin–aldosterone inhibitors
Nondihydropyridine calcium channel blockers
Statins to treat hyperlipidemia
Low sodium diet +/− diuretics
Fish oil
Tonsillectomy
Immunosuppression (unlikely to be effective with advanced CKD eGFR <30 mL/min/1.73 m^2)

eGFR, estimated glomerular filtration rate.

Other therapeutic options to reduce proteinuria and possibly slow CKD progression include use of nondihydropyridine calcium channel blockers such as diltiazem or verapamil, mineralocorticoid receptor antagonists such as spironolactone or eplerenone, low-sodium diet in combination with diuretics, and use of statins to treat significant hyperlipidemia (Table 45.1).[84] There is increased evidence supporting the pleiotropic effects of statins. Several reports support a role for statins to reduce proteinuria and slow the decline in eGFR.[85–88] On the basis of current evidence, statins should only be initiated when patients have poorly controlled hyperlipidemia and not for any potential unproven effect on slowing CKD progression.

There has been a longstanding interest in the use of fish oil to slow the progression of CKD secondary to IgAN. Donadio et al.[89] performed a randomized controlled trial of 12 g/day of fish oil supplementation or placebo in 106 patients. At 4 years of follow-up, there was a significantly lower incidence of mortality and progression to ESRD in patients who received fish oil. However, fish oil therapy had no effect on blood pressure or proteinuria. Subsequent studies have failed to show a beneficial effect of fish oils on IgAN.[90] Nevertheless, KDIGO guidelines recommend the use of fish oil in patients at high risk for progressive disease.[2] If used, fish oils should not replace other therapies such as RAAS blockade. Likewise, although there is some evidence to support a role for tonsillectomy in slowing the progression of IgAN, most studies are retrospective and imbalanced for use of ACEI and corticosteroids.[91–93] Thus, it is not clear if tonsillectomy provides additional benefits above standard of care to slow the progression of IgAN.

IgAN patients with advanced CKD are often resistant to immunosuppression treatments. Immunomodulatory therapies should not be offered to patients with later stages of CKD who have extensive glomerulosclerosis

or tubulointerstitial fibrosis on renal biopsy. When immunosuppression is offered, options include corticosteroids, cyclosphosphamide plus corticosteroids, MMF, ACTH, and RTX. Corticosteroids are the best studied. Although the conclusions of several studies are controversial, it appears that most studies have shown a significant decrease in proteinuria. The evidence is not conclusive. The data support a role for corticosteroids, particularly in patients with earlier stages of CKD (stages 2–3) with persistent proteinuria greater than 750 mg daily, despite maximum use of RAAS blockade.[94–99] There are mixed results using alkylating agents in combination with steroids, but this regimen should be considered in those IgAN patients with evidence of progressive disease manifested by crescentic GN on biopsy.[98,100] There are also inconclusive results with MMF in the setting of IgAN.[101–103] The risks of immunosuppression often outweigh any potential benefits in IgAN patients with advanced stage CKD. There is also an increased risk of adverse events including infections in those patients who receive immunosuppression.[98,99]

Lupus Nephritis

Approximately one-third to one-half of all patients with new onset SLE have evidence of GN.[104–106] The ISN/RPS classification categorizes SLE nephritis into six major subtypes including Class I–VI.[107,108] If there is a pure active inflammatory lupus nephritis (LN) lesion, this is denoted with (a), whereas purely chronic lesions are denoted with a (c). A mix of active and chronic lesions on biopsy will be labeled as (a/c). Classes III and IV are histologically characterized as focal and diffuse proliferative GN respectively. Clinically, Class III and IV SLE nephritis are characterized by the nephritic syndrome with or without nephrotic syndrome, whereas Class V SLE MN often presents only with proteinuria and/or the nephrotic syndrome. Classes I and II mesangioproliferative SLE nephritis usually have only mild clinical manifestations and are not associated with progressive nephropathy leading to advanced CKD.[108] Class VI LN patients are those with extensive glomerulosclerosis who are already progressing to ESRD.

Between 8–15% of patients with SLE nephritis display progressive CKD leading to ESRD.[109–111] The degree of activity and chronicity on renal biopsies (percent with glomerulosclerosis and degree of tubulointerstitial fibrosis) plays a key role in therapeutic decision-making.[108] The NIH activity and chronicity index scores reported by some renal pathologists can help the clinician in deciding if immunosuppression is warranted. It is common for SLE nephritis to transform from one class to another.[107,108] Therefore, prior to any potential intensification of immunosuppression, a repeat renal biopsy should at least be considered. In patients with proliferative LN, the risks of induction immunosuppression protocols outweigh the benefits in patients with evidence of chronic SLE GN without active inflammation.[108]

Decreased eGFR at baseline and increased proteinuria are associated with faster rates of CKD progression in SLE patients. African Americans, Hispanics, males, younger age at onset of SLE, and lower socioeconomic status all have previously been shown to be associated with worse clinical outcomes.[112–114] SLE patients with proteinuria benefit from optimizing blood pressure control with antagonism of RAAS where clinically feasible. As with other causes of CKD, SLE nephritis patients are at increased risk of developing cardiovascular disease. Reich et al. found that dyslipidemia was a risk factor for progression of CKD in LN patients.[115] Prescription of statins, where clinically appropriate, should be strongly considered in this patient population.

Immunosuppression for patients with chronic SLE nephritis with CKD should focus on maintenance therapies designed to prevent flares of this relapsing–remitting autoimmune disease. Maintaining a remission will control inflammation and slow CKD development and progression. MMF has become a first-line therapy for maintenance of remission in patients treated with SLE nephritis.[106,111] The Aspreva Lupus Management Study (ALMS)[110] was a multicenter trial of 227 patients comparing the outcomes of patients who received 36 months of treatment with azathioprine (AZA) compared to MMF. Those patients who received MMF were more likely to remain in remission from SLE nephritis compared to those on AZA. However, the results of the MAINTAIN trial in 105 patients who received induction therapy with CYC failed to show a statistically significant difference in flare rate over 4 years between those who received MMF and those on AZA.[116] It should be noted that differences in study design may well explain these differences. The ALMS trial was a multiethnic, multicontinental study with endpoints of renal failure and doubling of S[Cr]. The MAINTAIN trial had predominantly Caucasian patients with a study endpoint of time to renal flare. The duration of therapy required to keep patients in remission is unclear, but many clinicians will continue low-dose immunosuppression therapy with MMF with or without corticosteroids for at least 3–5 years or longer. Relapse rates of SLE nephritis range from 35 to 60% depending on the clinical study.[117,118] Recent studies of multitargeted therapy with steroids, tacrolimus, and mycophenolate, and the use of RTX have shown benefit in this population.[119–121] Transplantation remains a viable option for SLE patients. Outcomes are equivalent to other ESRD patients without SLE as their primary diagnosis.[122]

Pauci-Immune Glomerulonephritis

Pauci-immune GN is a form of small vessel vasculitis classically associated with rapidly progressive glomerulonephritis (RPGN).[123] On renal biopsy the hallmarks of the disease are the presence of crescents and segmental necrosis on light microscopy, and absence of immune deposits on immunofluorescence microscopy. The usual clinical presentation is that of a relapsing and remitting disease. If untreated, this form of GN often rapidly progresses to ESRD. There are also extrarenal manifestations depending on the disease process that may involve the upper and lower respiratory tract, nerves, skin, and musculoskeletal system. There is a subset of patients with pauci-immune GN who have a more indolent presentation for many years, with subtle findings on urinalysis characterized by microscopic hematuria and proteinuria.

Pauci-immune GN includes microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and drug-induced antineutrophil cytoplasmic antibody (ANCA)—associated vasculitis.[123] There is scant literature focused on specific aspects of CKD management in this patient population. Induction therapies for acute flares of pauci-immune GN have been well studied and include use of CYC for at least 3 months, with a corticosteroid taper followed by maintenance immunosuppression for up to 2 years with AZA or MMF.[124] The RAVE[125] and RITUXIVAS[126] trials showed RTX can be an effective induction therapy for pauci-immune ANCA-associated GN, with equivalent outcomes to CYC induction. RTX may be particularly effective in patients with relapsing disease. Because prevention of relapses and maintenance of remission are critical to slow CKD progression to ESRD in this group of patients, a number of trials have focused on repeat doses of RTX at set 6 month intervals or alternate agents to prevent relapse.

Predictors of relapse in the setting of ANCA-associated vasculitis include an initial clinical presentation with upper or lower respiratory tract involvement and presence of PR3-ANCA titer.[127] A prospective randomized trial, IMPROVE,[128] showed AZA was superior to MMF at maintenance of remission in this particular disease. Other forms of GN seem to respond better to MMF. Longer-term data on the RAVE trial[129] show initial RTX alone is as effective as CYC followed by further AZA in the maintenance of remission over an 18 month follow-up period. However, both groups had an unacceptable relapse rate leading to the maintenance studies mentioned above. The MAINRITSAN trial[130] showed a significantly higher number of patients who received RTX maintained a complete remission of ANCA vasculitis compared to those randomized to standard AZA-based maintenance immunosuppression.

Risk factors for progression to ESRD include an increased initial S[Cr] or decreased eGFR at baseline, older age, presence of pulmonary hemorrhage, and dialysis-dependent AKI.[131,132] The presence of glomerulosclerosis and tubulointerstitial fibrosis and atrophy on these renal biopsies is associated with worsened clinical outcomes.[131,132] As with other forms of CKD, patients with stable but decreased eGFR usually benefit from blood pressure control with long-term inhibition of RAAS axis to reduce glomerular hyperfiltration, low-sodium diet, and moderation of protein intake.

Antiglomerular Basement Membrane Disease

Antiglomerular Basement Membrane (anti-GBM) disease is another form of RPGN, which if untreated quickly progresses to ESRD. Unlike ANCA-associated vasculitis, anti-GBM disease usually does not recur once treated, and there is no need for long-term maintenance immunosuppression protocols. A subset of patients presenting as anti-GBM disease will be positive for both ANCA and anti-GBM antibodies. These patients are likely to be older, more likely to recover from severe renal failure, have a high relapse rate (about 50%), and a mortality similar to either the single ANCA and anti-GBM positive patients.[133] Thus, in this group of patients, long-term maintenance immunosuppression is required because they can follow a relapsing—remitting course similar to those with pauci-immune ANCA-associated GN.

Membranoproliferative Glomerulonephritis

The revised classification system for MPGN has changed the diagnostic approach to this disease. Previously classified by the location of immune deposits by electron microscopy, the updated system based on immunofluorescence (IF) staining for IgG and complement 3 (C3) is more representative of the heterogeneous nature of MPGN.[134] MPGN is similar to FSGS or MN in that it represents histologic patterns of glomerular injury caused by diverse etiologies. When the IF staining is positive for both C3 and immunoglobulins, this may be secondary to immune complex damage with infections such as Hepatitis C virus (HCV) or endocarditis, monoclonal gammopathies, lymphoproliferative disorders, or autoimmune diseases such as SLE. If there is only staining for C3 or the staining for C3 is two orders of magnitude greater than other immunoreactants, this supports a disorder of the alternative complement system pathway or C3 glomerulopathy.[135,136] Here, electron microscopy helps differentiate dense deposit disease from C3 GN. A MPGN pattern by light microscopy with negative IF staining for IgG and C3 is suggestive of chronic thrombotic microangiopathy.

Preventive CKD management is directed toward the underlying cause of the MPGN. If HCV infection has caused MPGN, then treatment of the virus should be considered. Interferon-based therapy regimens for HCV are no longer recommended. There is growing evidence of the efficacy of direct acting antiviral therapy with sustained virologic response rates in excess of 95% at 12 weeks.[137] Regimens containing sofosbuvir should be avoided in patients with eGFR <30 mL/min/1.73 m^2.[137] In patients with stage 4 or 5 CKD or treated with dialysis, guidelines recommend 12 weeks of elbasvir−grazoprevir for HCV genotypes 1, 1b, or 4 and an 8−16 week course of glecaprevir−pibrentasvir for HCV genotypes 1−6.[137] RTX may also play a role in treating HCV-infected patients with cryoglobulinemia.[138]

Treatment of immune complex forms of the disease such as LN has been discussed. Treatment of endocarditis with appropriate antimicrobial therapy may help ameliorate the course of MPGN. Treatment of the underlying lymphoproliferative disorder, whether related to chronic lymphocytic leukemia or plasma cell dyscrasia, may also improve renal outcomes of patients with MPGN.[139] Monoclonal gammopathies of unknown significance are increasingly recognized to be associated with MPGN and have been reclassified as monoclonal gammopathies of renal significance (MGRS).[139] Earlier initiation of therapy directed at the MGRS, which may be clinically significant, can be beneficial in slowing any potential progression to CKD.[139] Studies using a humanized monoclonal antibody against the fifth component of complement, eculizumab, have shown mixed results in C3 glomerulopathies.[140,141] MMF with corticosteroids for the treatment of C3 glomerulopathy showed some benefit particularly in the subset of patients with higher membrane attack complex levels.[142,143]

Although the prognosis of MPGN depends on the underlying pathogenesis, many forms of MPGN have a poor prognosis, with up to 50% of untreated patients progressing to ESRD over 5−10 years. Factors associated with a worse prognosis include evidence of CKD with decreased eGFR at baseline, nephrotic range proteinuria, poorly controlled blood pressure, evidence of crescentic GN (>50% crescents), and severe tubulointerstitial fibrosis. Blood pressure control with RAAS inhibitors if tolerated and dietary modifications including low sodium intake and moderation of protein intake may slow the progression of CKD secondary to MPGN.

Thrombotic Microangiopathies

A variety of glomerular and vascular diseases have been associated with pathophysiologic mediators of coagulation. Although in the past they were all combined diagnostically, they are now defined separately by pathophysiologic mechanisms.[144] Thus, thrombotic thrombocytopenic purpura is defined by a severe deficiency of ADAMTS 13, the von Willebrand cleaving enzyme, whereas the presence of Shiga toxin defines STEC + hemolytic uremic syndrome and antiphospholipid antibodies define the anticardiolipin syndrome. Atypical hemolytic syndrome is due to defects in the alternative complement pathway.[144] Each disease should be treated for the specific coagulation defect to prevent progressive CKD. Use of eculizumab, a humanized monoclonal blocker of the fifth component of complement (C5), has led to striking remissions of renal failure and the requirement for plasmapheresis in the patient population with complement-mediated TMA.[145]

Inherited Glomerulopathies

Alport syndrome (AS) can display X-linked, autosomal dominant, and autosomal recessive inheritance patterns.[146] AS is characterized as a disorder due to mutations that affect type 4 collagen proteins. Clinical manifestations in males are often more severe than in females. Males with X-linked AS due to a deletion mutation of the alpha 5 chain of type IV collagen usually progress to ESRD by the second or third decade of life. Likewise, patients with autosomal recessive AS due to mutations affecting alpha 3 or 4 chains of type IV collagen tend to progress to ESRD by age 30. Autosomal-dominant AS with heterozygous mutations of COL4A3 or COL4A4 usually has a slower progression of CKD. Treatment of CKD centers on blood pressure control with RAAS inhibitors where clinically appropriate.[146] Cyclosporine may be helpful in some patients with stage I and II CKD with significant proteinuria. Caution using calcineurin inhibitors is indicated in all patients with more advanced CKD stages due to potential nephrotoxicity.[146]

Thin Basement Membrane Nephropathy (TBMN) is caused by mutations in COL4A3 and COL4A4 and usually follows an autosomal dominant pattern of inheritance.[147] Previously termed "benign familial hematuria" because it was thought to have no risk for progression to renal failure, it is now recognized that this condition can in some instances be associated with CKD and can lead to secondary forms of FSGS.[147] The treatment of TBMN is conservative and includes blood pressure control with use of RAAS inhibitors as necessary.

Fabry disease is an X-linked disorder characterized by alpha-galactosidase A deficiency (alpha-Gal A). There is intracellular accumulation of neutral glycosphingolipids leading to glomerular injury from damage to visceral epithelial cells and ischemia due to impaired glomerular capillary flow from enlarged endothelial

cells. Patients with Fabry disease can develop proteinuria and microscopic hematuria by the third decade of life. There is typically slow CKD progression with ESRD by the fourth or fifth decade of life. Use of recombinant alpha-Gal A has been shown to stabilize eGFR and potentially reduce CKD progression.[148]

CONCLUSION

There have been significant advances in the diagnostic and therapeutic approaches to patients with the nephrotic syndrome and those with acute GN. There are fewer data on the optimal strategy for patients with chronic glomerulopathies to slow the progression of CKD. Maximization of conservative therapy with blood pressure control including use of RAAS inhibitors, low-sodium diet with or without diuretics to control edema, statins to treat hyperlipidemia, moderation of animal protein intake, and avoidance of nephrotoxins should be employed in patients with CKD secondary to glomerular diseases (Table 45.2). Randomized controlled trials are needed to determine optimal immunosuppressive therapies for patients with CKD secondary to glomerular diseases. With more effective strategies to diagnose and treat acute GN, the incidence of CKD secondary to glomerular disease should begin to decrease. A major challenge will be preventing progressive tubulointerstitial fibrosis in patients with glomerular diseases.

TABLE 45.2 Summary of Glomerular Diseases, Risk of Progression to End-Stage Renal Disease (ESRD), and Potential Therapeutic Options

Glomerular Disease	Risk of Progression to ESRD	Therapeutic Options
Minimal change disease (MCD)	Minimal risk	- Corticosteroids or other second-line therapies including cyclosporine, MMF, CYC, or RTX for acute flare-up - Consider ACEI or ARB for patients with hypertension and stable renal function without AKI
Membranous nephropathy	Approximately 1/3 over 10 years	- Consider ACEI or ARB as antihypertensive agent of choice - Consider statin therapy for significant hyperlipidemia - Low-sodium diet - Diuretics as needed to control edema - Moderation of protein intake - Immunomodulatory therapy should be considered only if there is evidence of continued immunologic activity based on the review of patient's renal pathology
Focal segmental glomerulosclerosis	Approximately 50% of patients who do not respond to therapy will progress to ESRD over 10 years	- Blood pressure control with RAAS inhibition as clinically tolerated - Statins to treat hyperlipidemia - Low-sodium diet and moderation of animal protein intake - Diuretics as needed to control edema - Caution is advised with immunosuppression protocols in patients with chronic and severely reduced eGFR (see text for additional details)
Postinfectious glomerulonephritis	Higher risk of progression in adults and the subset with IgA dominant disease	- Treatment of underlying infection - RAAS inhibition for BP control in those patients who develop CKD and proteinuria
IgA nephropathy	25% risk of ESRD at 10 years	See Table 45.1
SLE nephritis	Between 8–15% of patients with SLE nephritis progress to ESRD	- Optimize BP control with RAAS inhibitors - Maintenance immunosuppression therapies to consider include MMF vs. AZA - Treat hyperlipidemia with statins - Low-sodium +/− low-protein diet

TABLE 45.2 Summary of Glomerular Diseases, Risk of Progression to End-Stage Renal Disease (ESRD), and Potential Therapeutic Options—cont'd

Glomerular Disease	Risk of Progression to ESRD	Therapeutic Options
Pauci-immune glomerulonephritis	Untreated forms can rapidly progress (RPGN) to ESRD	- Prevention of relapse and maintenance of remission is critical to slow progression to CKD - Maintenance immunosuppression for patients in remission includes azathioprine for patients who received cyclophosphamide-based induction regimens - RAAS inhibition to optimize BP control where clinically feasible
Antiglomerular basement membrane disease	Untreated forms rapidly progress to ESRD (RPGN)	- Prompt initiation of induction therapy for acute disease with cyclophosphamide, corticosteroids, and plasmapheresis
Membranoproliferative glomerulonephritis	Approximately 50% of untreated patients progress to ESRD over 5–10 years	- Treatment of the underlying etiology such as infection, autoimmune disease, or lymphoproliferative disorder is essential

ACEI, angiotensin-converting enzyme inhibitor; *AKI*, acute kidney injury; *ARB*, angiotensin receptor blocker; *AZA*, azathioprine; *CKD*, chronic kidney disease; *CYC*, cyclophosphamide; *eGFR*, estimated glomerular filtration rate; *MMF*, mycophenolate mofetil; *RAAS*, renin–angiotensin–aldosterone inhibitors; *RTX*, rituximab; *RPGN*, rapidly progressive glomerulonephritis; *SLE*, system lupus erythematous.

References

1. United States Renal Data System. *2017 USRDS annual data report: epidemiology of kidney disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2017.
2. KDIGO. KDIGO clinical practice guidelines for glomerulonephritis. *Kidney Int Suppl* 2012;**2**:209.
3. Vincente F, Cohen SD, Appel GB. Novel B cell therapeutic targets in transplantation and immune mediated glomerular disease. *Clin J Am Soc Nephrol* 2010;**5**:142–51.
4. O'Shaughnessy MM, Montez-Rath ME, Lafayette RA, Winkelmayer WC. Patient characteristics and outcomes by GN subtype in ESRD. *Clin J Am Soc Nephrol* 2015;**10**(7):1170–8.
5. D'Agati V. Pathologic classification of focal segmental glomerulosclerosis. *Semin Nephrol* 2003;**23**:117–34.
6. Rennke HG, Klein PS. Pathogenesis and significance of nonprimary focal and segmental glomerulosclerosis. *Am J Kidney Dis* 1989;**13**:443–56.
7. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *J Am Med Assoc* 2003;**289**:2560–72.
8. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood pressure control on the progression of chronic renal disease. *N Engl J Med* 1994;**330**:877–84.
9. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril or both, in people at high vascular risk (the ONTARGET study): a multicenter, randomized, double-blind, controlled trial. *Lancet* 2008;**372**:547.
10. Parving H-H, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012;**367**:2204–13.
11. Fukui M, Nakamura T, Ebihara I, et al. Low-protein diet attenuates increased gene expression in platelet-derived growth factor and transforming growth factor-beta in experimental glomerular sclerosis. *J Lab Clin Med* 1993;**121**:224.
12. Nakamura T, Fukui M, Ebihara I, et al. Low protein diet blunts the rise in glomerular gene expression in focal glomerulosclerosis. *Kidney Int* 1994;**45**:1593.
13. Phisitkul S, Khanna A, Simoni J, et al. Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR. *Kidney Int* 2010;**77**:617–23.
14. Mahajan A, Simoni J, Sheather SJ, et al. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. *Kidney Int* 2010;**78**:303–9.
15. de Brito-Ashurst I, Varagunam M, Raftery MJ, et al. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol* 2009;**20**:2075–84.
16. Cho ME, Smith DC, Branton MH, et al. Pirfenidone slows renal function decline in patients with focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol* 2007;**2**:906–13.
17. Trachtman H, Fervenza FC, Gipson DS, et al. A phase 1 single dose study of fresolimumab, an anti-TGF-â antibody in treatment-resistant primary focal segmental glomerulosclerosis. *Kidney Int* 2011;**79**:1236–43.
18. Orth SR, Ritz E. The nephrotic syndrome. *N Engl J Med* 1998;**338**:1201–12.
19. Siddall EC, Radhakrishnan J. The pathophysiology of edema formation in the nephrotic syndrome. *Kidney Int* 2012;**82**:635–42.
20. Loscalzo J. Venous thrombosis in the nephrotic syndrome. *N Engl J Med* 2013;**368**:956–8.
21. O'Shaughnessy MM, Montez-Rath ME, Lafayette RA, Winkelmayer WC. Patient characteristics and outcomes by GN subtype in ESRD. *Clin J Am Soc Nephrol* 2015;**10**(7):1170–8.
22. Waldman M, Crew RJ, Valeri A, et al. Adult minimal-change disease: clinical characteristics, treatment, and outcomes. *Clin J Am Soc Nephrol* 2007;**2**:445–53.
23. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. *Kidney Int* 2012;**82**:516–24.
24. Ruggenenti P, Ruggiero B, Cravedi P, et al. Rituximab in steroid-dependent or frequently relapsing idiopathic nephrotic syndrome. *J Am Soc Nephrol* 2014;**25**(4):850–63.

25. Regunathan R, Canetta PA, Bomback AS, et al. *Rituximab treatment of MCD and FSGS in adults*. ASN; 2017. abstract.
26. Cattran DC, Brenchley PE. Membranous nephropathy: integrating basic science into improved clinical management. *Kidney Int* 2017;**91**(3):566.
27. Couser WG. Primary membranous nephropathy. *Clin J Am Soc Nephrol* 2017;**12**:983–97.
28. Cattran D. Management of membranous nephropathy: when and what for treatment. *J Am Soc Nephrol* 2005;**16**:1188–94.
29. Waldman M, Austin HA. Treatment of idiopathic membranous nephropathy. *J Am Soc Nephrol* 2012;**23**:1617–30.
30. Sprangers B, Bomback AS, Cohen SD, Radhakrishnan J, Valeri A, Markowitz GS, D'Agati V, Appel GB. Idiopathic membranous nephropathy: clinical and histologic prognostic features and treatment patterns over time at a tertiary referral center. *Am J Nephrol* 2012;**36**:78–89.
31. De Vriese AS, Glassock RJ, Nath KA, Sethi S, Fervenza FC. A proposal for a serology-based approach to membranous nephropathy. *JASN* 2017;**28**:421–30.
32. Beck Jr LH, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, Klein JB, Salant DJ. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009;**361**:11–21.
33. Ronco P, Debiec H. Pathogenesis of membranous nephropathy: recent advances and future challenges. *Nat Rev Nephrol* 2012;**8**: 203–13.
34. Bomback AS, Tumlin JA, Baranski J, Bourdeau JE, Besarab A, Appel AS, Radhakrishnan J, Appel GB. Treatment of nephrotic syndrome with adrenocorticotropic hormone (ACTH) gel. *Drug Des Dev Ther* 2011;**5**:147–53.
35. Briganti EM, Russ GR, McNeil JJ, Atkins RC, Chadban SJ. Risk of renal allograft loss from recurrent glomerulonephritis. *N Engl J Med* 2002;**347**:103–9.
36. Sprangers B, Lefkowitz G, Cohen SD, Stokes MB, Valeri A, Appel GB, Kunis C. Beneficial effect of rituximab in the treatment of recurrent idiopathic membranous nephropathy after kidney transplantation. *Clin J Am Soc Nephrol* 2010;**5**:790–7.
37. D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. *N Engl J Med* 2011;**365**:2398–411.
38. Korbet SM. Treatment of primary FSGS in adults. *J Am Soc Nephrol* 2012;**23**:1769–76.
39. D'Agati VD. Pathobiology of focal segmental glomerulosclerosis: new developments. *Curr Opin Nephrol Hypertens* 2012;**21**: 243–50.
40. Jefferson JA, Shankland SA. The pathogenesis of focal segmental glomeruloslcerosis. *Adv Chron Kidney Dis* 2014;**21**:408–16.
41. Wei C, El Hindi S, Li J, et al. Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. *Nat Med* 2011;**17**: 952–60.
42. Schlondorff D. Are serum suPAR determinations by current ELISA methodology reliable diagnostic biomarkers for FSGS? *Kidney Int* 2014;**85**:499–501.
43. Yu CC, Fornoni A, Weins A. Abatacept in B7-1-positive proteinuric kidney disease. *N Engl J Med* 2013;**369**(25):2416–23.
44. Delville M, Baye E, Durrbach A, et al. B7-1 blockade does not improve post-transplant nephrotic syndrome caused by recurrent FSGS. *J Am Soc Nephrol* 2016;**27**(8):2520–7.
45. Stirling CM, Mathieson P, Bolton-Jones JM, et al. Treatment and outcome of adult patients with primary focal segmental glomerulosclersosi in five UK renal units. *Q J Med* 2005;**98**:443–9.
46. Chun MJ, Korbet SM, Schwartz MM, Lewis EJ. FSGS in nephrotic adults: presentation, prognosis, and response to therapy of the histologic variants. *J Am Soc Nephrol* 2004;**15**:2169–77.
47. D'Agati VD, Alster JM, Jennette JC, et al. Association of histologic variants in FSGS clinical trial with presenting features and outcomes. *Clin J Am Soc Nephrol* 2013;**8**:399–406.
48. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic APOL1 variants with kidney disease in African Americans. *Science* 2010;**329**:841–5.
49. Freedman BI, Kopp JB, Langefeld CD, et al. The Apolipoprotein L1 (APOL1) gene and nondiabetic nephropathy in African Americans. *J Am Soc Nephrol* 2010;**21**:1422–6.
50. Kopp JB, Nelson GW, Sampath K, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol* 2011;**22**:2129–37.
51. Wyatt CM, Morgello S, Katz-Malamed R, et al. The spectrum of kidney disease in patients with AIDS in the era of antiretroviral therapy. *Kidney Int* 2009;**75**:428–34.
52. Cohen SD, Kopp JB, Kimmel PL. Kidney diseases associated with human immunodeficiency virus infection. *N Engl J Med* 2017;**377**: 2363–74.
53. Szczech LA, Edwards EJ, Sanders LL, et al. Protease inhibitors are associated with a slowed progression of HIV-related renal diseases. *Clin Nephrol* 2002;**57**:336–41.
54. Lucas GM, Eustace JA, Sozio S, et al. Highly active antiretroviral therapy and the incidence of HIV-1 associated nephropathy: a 12-year cohort study. *AIDS* 2004;**18**:541–6.
55. Szczech LA, Gupta SK, Habash R, et al. The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. *Kidney Int* 2004;**66**:1145–52.
56. D'Agati VD, Chagnac A, de Vries AP, et al. Obesity-related glomerulopathy: clinical and pathologic characteristics and pathogenesis. *Nat Rev Nephrol* 2016;**12**:453–71.
57. Faul C, Donnelly M, Merscher-Gomez S, et al. The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat Med* 2008;**14**:931–8.
58. Laurin LP, Gasim AM, Poulton CJ, et al. Treatment with glucocorticoids or calcineurin inhibitors in primary FSGS. *Clin J Am Soc Nephrol* 2016;**11**(3):386–94.
59. Gipson DS, Trachtman H, Kaskel FJ, et al. Clinical trial of focal segmental glomerulosclerosis in children and young adults. *Kidney Int* 2011;**80**:868–78.
60. Fornoni A, Sageshima J, Wei C, et al. Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. *Sci Transl Med* 2011;**3**. 85ra46.
61. Lindskog A, Ebefors K, Johansson ME, et al. Melanocortin 1 receptor agonists reduce proteinuria. *J Am Soc Nephrol* 2010;**21**:1290–8.
62. Baldwin DS. Poststreptococcal glomerulonephritis. A progressive disease? *Am J Med* 1977;**62**:1–11.
63. Hogan J, Bomback AS, Mehta K, Canetta PA, Rao MK, Appel GB, et al. Treatment of idiopathic FSGS with adrenocorticotropic hormone gel. *Clin J Am Soc Nephrol* 2013;**8**(12):2072–81.
64. Ruggenenti P, Ruggiero B, Cravedi P, Vivarelli M, Massella L, Marasa M, et al. Rituximab in steroid-dependent or frequently relapsing idiopathic nephrotic syndrome. *J Am Soc Nephrol* 2014; **25**(4):850–63.
65. Rodriguez-Iturbe B. Postinfectious glomerulonephritis. *Am J Kidney Dis* 2000;**35**:XLVI–XLVIII.
66. Hoy WE, White AV, Dowling A, et al. Post-streptococcal glomerulonephritis is a strong risk factor for chronic kidney disease in later life. *Kidney Int* 2012;**81**:1026–32.
67. Rodriguez Iturbe B, Musser JM. The current status of poststreptococcal glomerulonephritis. *J Am Soc Nephrol* 2008;**19**:1855–64.
68. Nasr SH, D'Agati VD. IgA-dominant postinfectious glomerulonephritis: a new twist on an old disease. *Nephron Clin Pract* 2011;**119**: c18–25.

69. Magistroni R, D'Agati VD, Appel GB, Kiryluk K. New developments in the genetics, pathogenesis, and therapy of IgA N. *Kidney Int* 2015;**88**:974–89.
70. Le W, Liang S, Hu Y, et al. Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population. *Nephrol Dial Transplant* 2012;**27**:1479–85.
71. Wakai K, Kawamura T, Endoh M, et al. A scoring system to predict renal outcome in IgA nephropathy: from a nationwide prospective study. *Nephrol Dial Transplant* 2006;**21**:2800.
72. Berthoux F, Mohey H, Laurent B, et al. Predicting the risk for dialysis or death in IgA nephropathy. *J Am Soc Nephrol* 2011;**22**: 752.
73. Working Group for the International IgA Nephropathy Network and the Renal Pathology Society, Cattran DC, Coppo R, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. *Kidney Int* 2009;**76**: 534.
74. Reich HN, Troyanov S, Scholey JW, et al. Remission of proteinuria improves prognosis in IgA nephropathy. *J Am Soc Nephrol* 2007;**18**: 3177–83.
75. Trimarchi H, Barratt J, Cattran DC, et al. IgAN classification working group of the International IgA nephropathy network and the Renal Pathology Society; Conference Participants. Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. *Kidney Int* 2017;**91**: 1014–21.
76. Coppo R, Royanov S, Bellur S, et al. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. *Kidney Int* 2014;**86**:828–36.
77. Donadio JV, Bergstralh EJ, Grande JP, Rademcher DM. Proteinuria patterns and their association with subsequent end-stage renal disease in IgA nephropathy. *Nephrol Dial Transplant* 2002;**17**:1197.
78. Rodrigues JC, Haas M, Reich HN. IgA nephropathy. *Clin J Am Soc Nephrol* 2017;**12**:677–86.
79. Remuzzi A, Perticucci E, Ruggenenti P, et al. Angiotensin converting enzyme inhibition improves glomerular size-selectivity in IgA nephropathy. *Kidney Int* 1991;**39**:1267.
80. Li PK, Leung CB, Chow KM, et al. Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. *Am J Kidney Dis* 2006;**47**:751.
81. Coppo R, Peruzzi L, Amore A, et al. IgACE: a placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria. *J Am Soc Nephrol* 2007;**18**:1880.
82. Praga M, Gutierrez E, Gonzalez E, et al. Treatment of IgA nephropathy with ACE inhibitors: a randomized and controlled trial. *J Am Soc Nephrol* 2003;**14**:1578.
83. Appel GB, Waldman M. The IgA nephropathy treatment dilemma. *Kidney Int* 2006;**69**:1939.
84. Floege J, Eitner F. Current therapy for IgA nephropathy. *J Am Soc Nephrol* 2011;**22**:1785–94.
85. Douglas K, O'Malley PG, Jackson JL. Meta-analysis: the effect of statins on albuminuria. *Ann Intern Med* 2006;**145**:117.
86. Atthobari J, Brantsma AH, Gansevoort RT, et al. The effect of statins on urinary albumin excretion and glomerular filtration rate: results from both a randomized clinical trial and observational cohort study. *Nephrol Dial Transplant* 2006;**21**:3106.
87. Ruggenenti P, Perna A, Tonelli M, et al. Effects of add-on fluvastatin therapy in patients with chronic proteinuric nephropathy on dual renin-angiotensin system blockade: the ESPLANADE trial. *Clin J Am Soc Nephrol* 1928;**5**:2010.
88. Strippoli G, Navaneethan SD, Johnson DW, et al. Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomized controlled trials. *BMJ* 2008;**336**:645.
89. Donadio Jr JV, Bergstralh EJ, Offord KP, et al. A controlled trial of fish oil in IgA nephropathy. Mayo Nephrology Collaborative Group. *N Engl J Med* 1994;**331**:1194.
90. Hogg RJ, Lee J, Nardelli N, et al. Clinical trial to evaluate omega-3 fatty acids and alternate day prednisone in patients with IgA nephropathy: report from the Southwest Pediatric Nephrology Study Group. *Clin J Am Soc Nephrol* 2006;**1**:467.
91. Xie Y, Nishi S, Ueno M, et al. The efficacy of tonsillectomy on long-term renal survival in patients with IgA nephropathy. *Kidney Int* 2003;**63**:1861.
92. Maeda I, Hayahsi T, Sato KK, et al. Tonsillectomy has beneficial effects on remission and progression of IgA nephropathy independent of steroid therapy. *Nephrol Dial Transplant* 2012;**27**: 2806–13.
93. Liu LL, Wang LN, Jiang Y, et al. Tonsillectomy for IgA nephropathy: a meta-analysis. *Am J Kidney Dis* 2015;**65**:80–7.
94. Lv J, Xu D, Perkovic V, et al. Corticosteroid therapy in IgA nephropathy. *J Am Soc Nephrol* 2012;**23**:1108.
95. Pozzi C, Bolasco PG, Fogazzi GB, et al. Corticosteroids in IgA nephropathy: a randomized controlled trial. *Lancet* 1999;**353**:883.
96. Pozzi C, Andrulli S, Del Vecchio L, et al. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. *J Am Soc Nephrol* 2004;**15**:157.
97. Manno C, Torres DD, Rossini M, et al. Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy. *Nephrol Dial Transplant* 2009;**24**:3694.
98. Rauen T, Eitner F, Fitzner C, et al. Stop-IgAN Investigators: intensive supportive care plus immunosuppression in IgA nephropathy. *N Engl J Med* 2015;**373**:2225–36.
99. Lv J, Zhang H, Wong MG, et al. TESTING Study Group: effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: the TESTING randomized clinical trial. *J Am Med Assoc* 2017;**318**:432–42.
100. Ballardie FW, Roberts IS. Controlled prospective trial of prednisolone and cytotoxics in progressive IgA nephropathy. *J Am Soc Nephrol* 2002;**13**:142.
101. Frisch G, Lin J, Rosenstock J, et al. Mycophenolate mofetil (MMF) vs placebo in patients with moderately advanced IgA nephropathy: a double-blind randomized controlled trial. *Nephrol Dial Transplant* 2005;**20**:2139.
102. Maes BD, Oyen R, Claes K, et al. Mycophenolate mofetil in IgA nephropathy: results of a 3-year prospective placebo-controlled randomized study. *Kidney Int* 2004;**65**:1842–9.
103. Tang S, Leung JC, Chan LY, et al. Mycophenolate mofetil alleviates persistent proteinuria in IgA nephropathy. *Kidney Int* 2005;**68**: 802–12.
104. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. *Clin J Am Soc Nephrol* 2017;**12**:825–35.
105. Parikh SV, Rovin BH. Current and emerging therapies for lupus nephritis. *J Am Soc Nephrol* 2016;**27**:2929–39.
106. Lau WL, Appel GB. Lupus nephritis in 2018: an update. *ASN Kidney News* 2017;**9**:17–8.
107. Markowitz GS, D'Agati VD. The ISN/RPS classification of lupus nephritis: an assessment at 3 years. *Kidney Int* 2007;**71**:491–5.
108. Giannico G, Fogo AB. Lupus nephritis: is the kidney biopsy currently necessary in the management of lupus nephritis? *Clin J Am Soc Nephrol* 2013;**8**:138–45.
109. Houssiau FA, Vasconcelos C, D'Cruz D, et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose versus high-dose intravenous cyclophosphamide. *Ann Rheum Dis* 2010;**69**:61–4.
110. Appel GB, Contreras G, Dooley MA, et al. Aspreva Lupus Management Study Group, Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009;**20**:1103–12.

111. Dooley MA, Jayne D, Ginzler EM, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med* 2011;**365**:1886–95.
112. Korbet SM, Schwartz MM, Evans J, Lewis EJ. Severe lupus nephritis: racial differences in presentation and outcome. *J Am Soc Nephrol* 2007;**18**:244–54.
113. Barr RG, Selgier S, Appel GB, et al. Prognosis in proliferative lupus nephritis: the role of socioeconomic status and race/ethnicity. *Nephrol Dial Transplant* 2003;**18**:2039–46.
114. Contreras G, Pardo V, Cely C, et al. Outcomes in African Americans and Hispanics with lupus nephritis. *Kidney Int* 2006;**69**:1846–51.
115. Reich HN, Gladman DD, Urowitz MB, et al. Persistent proteinuria and dyslipidemia increase the risk of progressive chronic kidney disease in lupus erythematosus. *Kidney Int* 2011;**79**:914–20.
116. Morris HK, Canetta PA, Appel GB. Impact of the ALMS and MAINTAIN trials on the management of lupus nephritis. *Nephrol Dial Transplant* 2013;**28**:1371–6.
117. Illei G, Takada K, Parkiin D, et al. Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy: long-term followup of a cohort of 145 patients participating in randomized controlled studies. *Arthritis Rheum* 2002;**46**:995–1002.
118. Mosca M, Bencivelli W, Neri R, et al. Renal flares in 91 SLE patients with diffuse proliferative glomerulonephritis. *Kidney Int* 2002;**61**:1502–9.
119. Weidenbusch M, Rommele C, Schrottle A, et al. Beyond the LUNAR trial. Efficacy of rituximab in refractory lupus nephritis. *Nephrol Dial Transplant* 2013;**28**:106–11.
120. Liu Z, Zhang H, Liu Z, Xing C, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. *Ann Intern Med* 2015;**162**:18–26.
121. Zhang H, Liu Z, Zhou M, et al. Multitarget therapy for maintenance treatment of lupus nephritis. *J Am Soc Nephrol* 2017;**28**:3671–8.
122. Ward MM. Outcomes of renal transplantation among patients with ESRD caused by lupus nephritis. *Kidney Int* 2000;**57**:2136.
123. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013;**65**:1–11.
124. Jayne D, Rasmussen N, Andrassy K, et al. Randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003;**349**:36–44.
125. Stone JH, Merkel PA, Spiera R, RAVE-ITN Research Group, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010;**363**:221–32.
126. Jones RB, Tervaert JW, Hauser T, European Vasculitis Study Group, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010;**363**:211–20.
127. Hogan SL, Falk RJ, Chin H, et al. Predictors of relapse and treatment resistance in ANCA small vessel vasculitis. *Ann Intern Med* 2005;**143**:621–31.
128. Hiemstra TF, Walsh M, Mahr A, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *J Am Med Assoc* 2010;**304**:2381–8.
129. Specks U, Merkel PA, Seo P, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 2013;**369**:417–27.
130. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 2014;**371**:1771–80.
131. Little MA, Pusey CD. Glomerulonephritis due to antineutrophil cytoplasm antibody-associated vasculitis: an update on approaches to management. *Nephrology* 2005;**10**:368–76.
132. Bajema IM, Hagen EC, Hermans J, et al. Kidney biopsy as a predictor for renal outcome in ANCA-associated necrotizing glomerulonephritis. *Kidney Int* 1999;**56**:1751–8.
133. McAdoo SP, Tanna A, Hruskova Z, et al. Patients double-seropositive for ANCA and anti-GBM antibodies have varied renal survival , frequency of relapse, and outcomes compared to single seropositive patients. *Kidney Int* 2017;**92**:693–702.
134. Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis—a new look at an old entity. *N Engl J Med* 2012;**366**:1119–31.
135. Appel GB. C3 glomerulopathy : a new disease comes of age. *Mayo ClinProc* 2018;**93**:968–9.
136. Bomback AS, Santoriello D, Avarsare RS, et al. C3 glomerulonephritis and dense deposit disease share a similar disease course in a large United States cohort of patients with C3 glomerulopathy. *Kidney Int* 2018;**93**:977–85.
137. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Unique populations: patients with renal impairment.
138. De Vita S, Quartuccio L, Isola M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum* 2012;**64**:843–53.
139. Leung N, Bridoux F, Hutchison CA, Nasr SH, et al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. *Blood* 2012;**120**:4292–5.
140. Herlitz LC, Bomback AS, Markowitz GS, et al. Pathology after eculizumab in dense deposit disease and C3 GN. *J Am Soc Nephrol* 2012;**23**:1229–37.
141. Le Quintrec M, Lapeyraque AL, Lionet A, et al. Patterns of clinical response to Eculizumab in patients with C3 glomerulopathy. *Am J Kidney Dis* 2018;**72**:84–92.
142. Avasare RS, Canetta PA, Bomback AS, et al. Mycophenolate mofetil in combination with steroids for treatment of C3 glomerulopathy: a case series. *Clin J Am Soc Nephrol* 2018;**13**:406–13.
143. Rabasco C, Cavero T, Roman E, et al. Effectiveness of mycophenolate mofteil in C3 glomerulonephritis. *Kidney Int* 2015;**88**:1153–60.
144. Tsai HM. Untying the knot of thrombotic thrombocytopenic purpura and atypical hemolytic uremic syndrome. *Am J Med* 2013;**126**:200–9.
145. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med* 2013;**368**:2169–81.
146. Savige J, Gregory M, Gross O, et al. Expert guidelines for the management of Alport syndrome and thin basement membrane nephropathy. *J Am Soc Nephrol* 2013;**24**:364–75.
147. Savige J, Rana K, Tonna S, et al. Thin basement membrane nephropathy. *Kidney Int* 2003;**64**:1169–78.
148. Jain G, Warnock DG. Blood pressure, proteinuria and nephropathy in Fabry disease. *Nephron Clin Pract* 2011;**118**:c43–8.
149. Lenz O, Waheed AA, Baig A, et al. Lupus nephritis: maintenance therapy for lupus nephritis—do we now have a plan? *Clin J Am Soc Nephrol* 2013;**8**:162–71.

QUESTIONS AND ANSWERS

Question 1

A 37-year-old woman with a history of SLE nephritis Class IV received successful induction therapy with intravenous CYC and steroids. She is currently in remission. Her S[Cr] is 1.2 mg/dL. Her most recent urinalysis shows no proteinuria and no hematuria. Based on the most current evidence, which of the following medications is best for this patient to maintain a remission of her LN?

A. RTX
B. CYC
C. MMF
D. Belimumab
E. ACTH

Answer: C

MMF is the best choice of the answers provided. Quarterly pulse CYC (Choice B) was shown to be inferior to MMF and AZA for maintenance of remission from SLE nephritis. There is a lack of evidence to support maintenance immunosuppression with RTX (Choice A), ACTH (Choice D), or belimumab (Choice E) at this time.[111,116,149]

Question 2

A 55-year-old man with CKD stage 4 secondary to IgA nephropathy presents to your office for an opinion on management. His S[Cr] is stable at 2.8 mg/dL. His most recent urine protein:creatinine ratio (UPCR) is 1500 mg/g creatinine. His blood pressure is 145/89 mm Hg and his examination is otherwise normal.

Which of the following therapies would be most effective in slowing the progression of his chronic kidney disease?

A. Lisinopril
B. MMF
C. CYC
D. Azathioprine
E. Amlodipine

Answer: A

Lisinopril would be most effective at slowing the progression of advanced CKD secondary to IgA nephropathy. There is a lack of evidence for immunosuppression in IgA patients with severe CKD (Choices B, C, and D). A trial of MMF at this level of renal function showed no beneficial effect (Choice B). Amlodipine (Choice E) is not the correct choice since ACEI (Choice A) is the preferable antihypertensive agent to slow the progression of CKD.[79–82]

Question 3

A 38-year-old woman with thin basement membrane disease presents to your office for advice regarding her risk of developing progressive CKD. Her S[Cr] is 0.8 mg/dL. Her UPCR is 350 mg/g creatinine, and blood pressure is 118/70 mm Hg. Which of the following statements is true regarding thin basement membrane disease?

A. There is no risk for progression to ESRD
B. There is a high risk for progression to ESRD in the next 5 years
C. There is a potential risk for progression to ESRD over the next 25 years
D. This is most commonly the result of a genetic defect in the alpha 5 chain of type IV collagen

Answer: C

There is a small risk for progressive CKD in the setting of thin basement membrane disease, with reports of secondary FSGS developing later in the disease course. The progression to CKD is far less likely than other forms of glomerulopathy. Therefore, Choices A and B are incorrect. The disease results from mutations in alpha chains type 3 and 4 of type IV collagen, therefore Choice D is incorrect.[146,147]

Question 4

A 41-year-old man is diagnosed with primary FSGS. His S[Cr] has remained stable at 1.9 mg/dL over the past 3 months. His UPCR decreased from 6000 mg/g creatinine to 800 mg/g creatinine after 6 months of steroid therapy. His medications include lisinopril 20 mg daily and simvastatin 20 mg daily. His blood pressure is 124/75 mm Hg and his examination is otherwise normal with no peripheral edema. Which of the following statements is true regarding this patient's risk of progression to ESRD?

A. This patient's partial remission places him at decreased risk for progression to ESRD
B. The presence of subnephrotic but persistent proteinuria places him at a high risk for progression to ESRD over the next five years
C. Absence of partial or complete remission from FSGS has no impact on this patient's risk for progressive CKD
D. RTX should be administered following completion of the corticosteroids

Answer: A

A partial or complete remission in the setting of primary FSGS confers a significantly more favorable renal prognosis and lower likelihood of progressive CKD compared to those patients who fail to respond to

immunosuppressive therapies. Therefore, Choice B and C are incorrect. Addition of RTX (Choice D) is not indicated in this patient who has had a significant response to corticosteroid therapy.[38,39,45,46]

Question 5

A 55-year-old woman with a history of CKD stage 4 secondary to PR3 ANCA positive pauci-immune GN presents to your office for an opinion on optimal management. Her S[Cr] has been stable at 2.7 mg/dL for the past 6 months, UPCR is 2500 mg/g creatinine, and PR3−ANCA titer is negative. The most recent urinalysis showed 3+ protein with no hematuria. The patient otherwise feels well, with no extrarenal manifestations of vasculitis. The patient had a peak S[Cr] of 4.8 mg/dL on presentation 2 years ago with renal-limited disease and no evidence of pulmonary involvement. Her medications for the past 18 months include azathioprine 100 mg daily, lisinopril 40 mg daily, and simvastatin 10 mg daily. Which of the following regimens is indicated to help to prevent progression of CKD?

A. Treatment with CYC 2.5 mg/kg/day for an additional six months followed by methotrexate for an additional 18 months
B. Continuation of the current medication regimen
C. Treatment with RTX 375 mg/m^2 weekly for 4 weeks
D. Discontinuation of lisinopril

Answer: B

This patient has CKD secondary to pauci-immune GN and is currently in remission. She is on appropriate treatment at this time, including maintenance immunosuppression with AZA and RAAS inhibition. RTX (Answer C) and CYC (Answer A) are incorrect choices because they are used in induction treatment of patients with active flares of disease. It is not appropriate to discontinue the lisinopril in this patient with stable CKD (Answer D).[124−126,128,129]

Question 6

A 52-year-old Hispanic woman, permanent resident of Honduras, presents to the office with a history of CKD stage 3 secondary to poststreptococcal GN, after renal biopsy 10 years ago. Her most recent S[Cr] is stable at 1.5 mg/dL. She has a UPCR of 1100 mg/g creatinine. Her urinalysis shows 3+ protein, no hematuria, and no cellular casts visualized. Blood pressure is 122/65 mm Hg and examination is normal without peripheral edema. Which of the following histologic lesions is most likely to be found on a repeat renal biopsy?

A. Diffuse endocapillary GN with subepithelial humps on EM
B. MN
C. Secondary FSGS
D. Collapsing focal and segmental glomerulosclerosis
E. MCD

Answer: C

The most likely histologic lesion in this patient with CKD caused by postinfectious GN is secondary FSGS. CKD from chronic GN with no residual active inflammation can appear as a form of focal glomerular scarring or as a form of secondary FSGS. Diffuse endocapillary GN with subepithelial humps on EM (Choice A) would classically be seen during the acute presentation of postinfectious GN. MN (Choice B), follapsing FSGS (Choice D), and MCD (choice E) are unlikely histologic renal lesions based on the clinical history provided.[66]

CHAPTER

46

Approach to the Patient with Hypertensive Nephrosclerosis

Aldo J. Peixoto[a], *George L. Bakris*[b]

[a]Section of Nephrology, Yale School of Medicine, and Hypertension Program at the Yale New Haven Hospital Heart and Vascular Center, New Haven, CT, United States; [b]Comprehensive Hypertension Center, Department of Medicine, The University of Chicago Medicine, Chicago, IL, United States

Abstract

Hypertensive nephrosclerosis (HN) is defined as chronic kidney disease caused by nonmalignant hypertension (HTN). HN is the presumed underlying disease in 10–30% of patients with end-stage renal disease worldwide. HN typically presents without proteinuria or any abnormalities in the urine sediment. The mechanisms of injury in HN are heterogeneous. In areas with preserved arteriolar myogenic responses (i.e. autoregulation), there is ischemic glomerular tuft collapse and interstitial fibrosis. In other areas with impaired autoregulation, the lesions reflect glomerular HTN leading to podocyte loss and glomerulosclerosis. Apolipoprotein-L1 gene mutations are associated with increased susceptibility to HN. The management of HN should focus on blood pressure control (target <140/90 mm Hg) using a blocker of the renin–angiotensin system as base therapy.

INTRODUCTION

The term nephrosclerosis refers to a morphologic diagnosis, while hypertensive nephrosclerosis (HN) is broadly defined as chronic kidney disease (CKD) caused by nonmalignant primary hypertension (HTN). Because relatively few patients in whom this diagnosis is entertained undergo a renal biopsy, HN is often a diagnosis applied to patients who present with CKD carrying a long-standing diagnosis of HTN, relatively low levels of albuminuria (i.e. <300 mg/day), and no other apparent cause for CKD.[1,2] Acknowledgment of this limitation and the frequent uncertainty of the diagnosis have led to use of the term "hypertension-attributed kidney disease." In this chapter, we will use the term "hypertensive nephrosclerosis" to refer to this broader category of HTN-attributed kidney disease despite the recognition that the histological features are confirmed only in a minority of cases. Our discussion will not cover acute/subacute renal injury in the setting of malignant HTN.

Scope of the Problem and Public Health Implications

According to estimates of the World Health Organization, HTN affects ~40% of the world population over the age of 25 years. Recently published guidelines from the American College of Cardiology and the American Heart Association proposed lower BP levels to define HTN (130/80 mm Hg vs. 140/90 mm Hg) and have, thereby, increased the relative prevalence of HTN among US adults by 43% (from 32% to 46%).[3] It is the most important modifiable cardiovascular risk factor, responsible for more than 50% of strokes and coronary artery disease events worldwide.[4,5] In fact, its overall impact on death and disability is impressive. HTN accounts for ~13.5% of all deaths and ~6% of all disability-adjusted life years lost.[4] While end organ damage attributable to HTN is most remarkable in the brain (strokes, transient ischemic attacks), heart (coronary artery disease, left ventricular hypertrophy [LVH], congestive heart failure), and peripheral arterial system, hypertensive vascular injury also occurs in the kidney and may result in the development of CKD.

An ongoing debate over many years focuses on whether nonmalignant HTN causes CKD or not, with some spirited opinions available in the literature. This is primarily driven by the lack of data from randomized clinical trials that the treatment of uncomplicated HTN leads to a reduction in CKD endpoints.[6] Other

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00046-2

considerations include the possible coexistence of a primary kidney disease as the driver of both the HTN and the loss of renal function during follow-up, the development of microvascular renal lesions acting as the primary driving factor, resulting in both HTN and loss of renal function,[7] and the frequent misclassification of patients as having HN while the actual diagnosis is an alternative one, such as ischemic nephropathy, atheroembolic kidney disease, or chronic interstitial nephritides.[2,8,9]

Although there is no question that renal injury is most remarkable in patients with malignant HTN, we believe that the current evidence supports nonmalignant HTN as the primary etiologic factor in many patients with stage 3 and 4 CKD. The first line of evidence came from a single center cohort of 500 untreated hypertensive patients followed until their death: 42% developed proteinuria and 18% had complications related to "nitrogen retention."[9] That study was followed by a series of small cohort studies that differed in their findings, with some demonstrating an association between higher blood pressure (BP) levels and increased risk for loss of renal function over time,[10,11] whereas others were unable to link BP and CKD.[12] The analysis of placebo-controlled trials of the treatment of nonmalignant HTN that reported renal outcomes reveals, most importantly, an absence of events.[6] Very few subjects in these trials with up to 7 years of follow-up developed "renal events" (investigator-defined increases in S[Cr] or end-stage renal disease (ESRD)). More than 90% of these events consisted of modest alterations in serum chemistries, and no apparent difference between active treatment or placebo.[6] It is important to recognize that because the incidence of ESRD is so low, all studies have been underpowered to address this issue. In fact, due to the other demonstrable benefits of antihypertensive therapy, a definitive study to test whether treatment of HTN prevents CKD or ESRD would be unethical to perform today.

Therefore, we must rely on observational studies to address the "chicken or egg" between HTN and CKD. Indeed, many recent large cohort studies have more definitively linked HTN and its severity to renal risk. Table 46.1 summarizes the salient features of each of these studies.[10,11,13–29] In aggregate, they indicate that, while the rates of severe renal dysfunction related to uncomplicated HTN are low (e.g. ESRD rates of ~0.2% over 10–25 years), they are strongly influenced by BP levels in a dose-dependent fashion, particularly in African-American individuals, where the overall risk is increased, likely due to genetic susceptibilities that are now being better understood (see below, under *Pathophysiology*). A meta-analysis of 16 observational cohorts including more than 315,000 patients with baseline BP in the prehypertensive and hypertensive range (>120/80 mm Hg) and normal renal function at baseline demonstrated a dose-dependent increase in risk of incident CKD (defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2) with increasing BP levels. For every 10 mm Hg increase in BP, there was an increase in CKD of 8% (relative risk 1.08 [1.04–1.11]) for systolic BP and 12% (relative risk 10.12 [1.04–1.20]) for diastolic BP).[30] Therefore, based on observational studies that performed systematic screening for kidney disease (renal function and urinalysis) at baseline in large cohorts, we believe there is good evidence supporting nonmalignant HTN as a cause of progressive CKD and ESRD.[30]

The global burden of presumed HTN-related CKD is large. Despite substantial geographic differences, registries from more than 22 countries representing all continents indicate that HN is listed as the primary diagnosis in about 10–30% of cases of advanced CKD requiring dialysis. In the US, the prevalence of the diagnosis of presumed HN among patients on dialysis is overrepresented among African-American patients. While African Americans represent about one-third of all US patients receiving dialysis for ESRD, they account for 46% of those whose primary diagnosis is HN.[31] No other ethnic group is overrepresented among dialysis patients. Unfortunately, extension of these observations to other areas of the world is not straightforward.

It is often difficult to ascertain the prevalence of HN as a function of ethnicity, as there are very few well-organized registries in Africa, where the leading etiology of CKD is glomerulonephritis.[32] There is marked variability in the prevalence of HN even in Western Europe[33] where most countries have small populations of African descent.

PATHOPHYSIOLOGY

Mechanisms of Renal Injury in Hypertension

The mechanisms resulting in renal injury in nonmalignant HTN are many, and yet not completely understood. Detailed reviews have been published elsewhere.[34–38] Figure 46.1 provides a schematic depiction of the processes discussed below.

The initial key element involved in parenchymal injury relates to changes in the regulation of afferent arteriolar tone in response to changes in pressure (myogenic reflex) and sodium excretion (tubuloglomerular feedback).[35,36,39] These abnormalities can have opposite effects resulting in potentially different types of vascular and glomerular lesions. For example, an increase in sensitivity of these mechanisms can result in excessive arteriolar vasoconstriction and ischemic glomerular injury. Arterioles with normal myogenic

TABLE 46.1 Summary of Studies Evaluating the Link Between Hypertension and Progressive Kidney Disease

Author, Year	Country	N	F/U (years)	Population	Comments
Lindeman, 1984[13]	US	446	>8	General population	MAP correlated with fall in CCr ($r = 0.32$, $p < 0.001$) on serial measurements over 10 years. Rate of CCr decline was 0.52 mL/min/year faster for every 10 mm Hg higher baseline MAP. Relationship not significant in group with MAP <107 mm Hg.
Rostand, 1989[11]	US	94	4.9	HTN	All subjects with HTN under treatment and preserved renal function at baseline. 15% had an increase in S[Cr] ≥0.4 mg/dL during follow-up, most (10/14) occurring in patients with controlled DBP (<90 mm Hg, average 84 mm Hg). AA subjects (32%) had twice the rate of development of increased S[Cr] (23% vs. 11% for whites).
Shulman, 1989[14]	US	8683	5	HTN	Hypertension Detection and Follow-Up Program. 2.3% developed S[Cr] ≥2 mg/dL and a rise by >25% above baseline. Average 5-year rise in S[Cr] was higher in black men (0.67 mg/dL) than white men (0.14 mg/dL) and all women (0.0 mg/dL). Baseline DBP and S[Cr] were the strongest predictors of rise in S[Cr] concentration during follow-up.
Rosansky, 1990[10]	US	115	9.8	Male veterans, both HTN and non-HTN	Historical cohort study of patients with normal baseline renal function, 49% with HTN. Adjusted increase in S[Cr] was 0.02 mg/dL/year higher among patients with HTN ($p = 0.03$). Development of S[Cr] >1.4 mg/dL was 13% among hypertensives, 7% among normotensives ($p = NS$).
Perneger, 1993[15]	US	1399	12–15	General population	16% of men and 11% of women developed abnormal S[Cr] concentration during follow-up (>1.3 mg/dL in men, >1.1 mg/dL in women). OR = 1.6 (per 20 mm Hg SBP) and 2.1 (per 20 mm Hg DBP) in men (both significant). OR = 1.5 and 1.6 in women (significant only for SBP). Associations significant only for baseline, not follow-up BP.
Perry, 1995[16]	US	11,912	9.4–14.2	Male veterans with HTN	2.1% of patients developed ESRD. Risk of ESRD significant for SBP 165–180 mm Hg (adjusted RR = 1.9) and >180/118 mm Hg (adjusted RR = 4.6). Any decrease in SBP during follow-up was associated with decreased risk of ESRD, most prominent for SBP fall >20 mm Hg (adjusted RR = 0.39).
Madhavan, 1995[17]	US	2125	5.3	HTN, males only	All patients treated. 2% progressed to S[Cr] >2 mg/dL. Baseline, not treated DBP was independently associated with the final S[Cr]. Black race was also an independent predictor of final S[Cr].
Iseki, 1996[18]	Japan	104,331	10	General population	0.18% developed ESRD. DBP was an independent predictor of ESRD development (adjusted OR = 1.39 per 10 mm Hg).
Klag, 1996[19] and Klag, 1997[20]	US	332,554	16	General population, males only	Multiple Risk Factor Intervention Trial screenees. 0.22% developed ESRD. RR for ESRD was 2.0 per SD of SBP [16 mm Hg], 1.6 per SD of DBP [11 mm Hg]. RR increased progressively according to HTN stage compared with normotensive levels (adjusted RR = 3.1 for 140–159/90–99 mm Hg, RR = 6.0 for 160–179/100–109 mm Hg, RR = 11.2 for 180–219/110–119 mm Hg, RR = 22.1 for >220/120 mm Hg). AAs had almost twice the risk as whites (adjusted RR = 1.87).

Continued

TABLE 46.1 Summary of Studies Evaluating the Link Between Hypertension and Progressive Kidney Disease—cont'd

Author, Year	Country	N	F/U (years)	Population	Comments
Siewert-Delle, 1998[21]	Sweden	686	20	HTN, males only	All patients treated. 8.9% of subjects developed S[Cr] >1.45 mg/dL on follow-up, 1.7% possibly due to HTN. Highest observed S[Cr] was 2.1 mg/dL; no cases of ESRD. No clinical differences between patients with and without a rise in S[Cr].
Hsu, 2005[22]	US	316,675	25	General population	Kaiser Permanente of Northern California. All subjects with preserved eGFR and normal urinalysis at baseline. 0.4% developed ESRD. Compared with normotensives (BP <120/80 mm Hg), increasing baseline BP resulted in dose-dependent increases in RR for ESRD (1.62 in the prehypertensive group, 4.25 in those with BP of 180–219/110–119 mm Hg). The association was not only stronger in AAs but also significant in whites.
Hanratty, 2010[23]	US	528	3.8	General population	Small fraction (5%) of Denver Health cohort with baseline BP. No independent effect of BP on incident CKD (new eGFR <60 mL/min/1.73 m^2 or albuminuria >30 mg/g). Linear analysis showed a trend toward faster loss of eGFR in patients with higher baseline BP (0.58 mL/min/year per 10 mm Hg SBP, $p = 0.09$).
Hanratty, 2011[24]	US	43,305	3.7	HTN	Kaiser Permanente Colorado. 12% developed new CKD (eGFR<60 mL/min/1.73 m^2 or albuminuria>30 mg/g). Adjusted HR for incident CKD was significant for SBP (1.06 per 10 mm Hg, both at baseline and in time-varying, updated models).
Chang, 2013[25]	US	123,058	4.8	General population	Kidney Early Evaluation Program. Increased risk of ESRD in both albuminuric and nonalbuminuric patients (HR 1.18–1.19 per 10 mm Hg SBP).
Cao, 2014[26]	China	1703	4.5	General population	Pre-HTN and HTN associated with incident CKD (HR 1.25 for pre-HTN, HR 1.62 for undiagnosed HTN, HR 1.98 for known HTN).
McMahon, 2014[27]	US	1323	30	General population	Framingham Offspring Study. Case-control study (441 cases of incident CKD, 882 controls). OR for HTN prior to the diagnosis of incident CKD was 1.76 at 30 years. Association also present at the 10- and 20-year marks.
Lohr, 2015[28]	US	15,221	4.8	Elderly veterans >70 years old (98% men)	VA cohort. Time-dependent SBP >140 mm Hg associated with progressive risk of incident CKD. However, time-dependent achieved SBP <130 mm Hg was associated with increased mortality.
Erikson, 2016[29]	Sweden	1299	5.6	General population	Repeat iohexol GFR evaluation, on average 5.6 years apart. HTN or baseline BP did not result in loss of renal function. In fact, higher BP resulted in less steep loss of GFR.

AA, African American; *CCr*, creatinine clearance; *CKD*, chronic kidney disease; *DBP*, diastolic blood pressure; *ESRD*, end-stage renal disease; *F/U*, follow-up; *eGFR*, estimated glomerular filtration rate; *HTN*, hypertension; *HR*, hazard ratio; *MAP*, mean arterial pressure; *OR*, odds ratio; *RR*, risk ratio; *SBP*, systolic blood pressure; *SD*, standard deviation; *VA*, Veterans Administration.

responsiveness can be slightly hypertrophic but do not have hyaline lesions.[40] Decreased sensitivity, on the other hand, allows direct transmission of the pressure load to the glomerulus resulting in intraglomerular HTN, glomerular hypertrophy, and progressive glomerulosclerosis.[34,40,41] Arterioles associated with these glomerular changes are dilated and show significant hyalinosis. This morphometric evidence is further supported by animal models of HTN indicating that glomerular injury occurs only after autoregulation is lost.[42] In models where the myogenic reflex remains intact, such as the spontaneously hypertensive rat, renal injury seldom occurs despite significant BP elevations. In other models where autoregulation is lost, such as the renal ablation model, the Dahl salt-sensitive rat, and the fawn-hooded hypertensive rat, renal injury

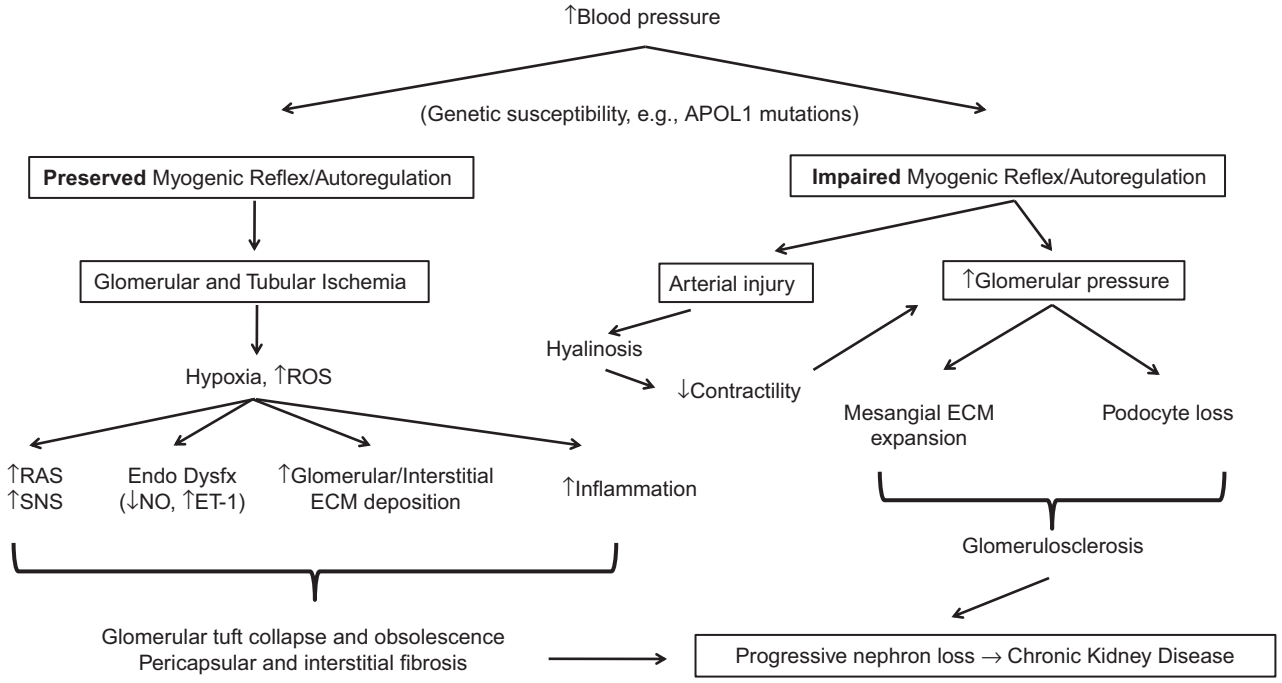


FIGURE 46.1 Mechanisms of blood pressure-induced kidney injury in hypertension. There are differences in the pattern of injury according to the presence or absence of an intact afferent arteriolar myogenic reflex (i.e. autoregulation). If autoregulation is normal, glomerular and tubular ischemia activates pathways that result in glomerular obsolescence and interstitial fibrosis. If autoregulation is abolished, arterial injury and glomerular hypertension result in glomerulosclerosis (or "solidification"). Both processes can occur in the same patient and both contribute to progressive nephron loss and kidney disease. *APOL1*, apolipoprotein-L1; *ECM*, extracellular matrix; *ET-1*, endothelin-1; *NO*, nitric oxide; *RAS*, renin–angiotensin system; *ROS*, reactive oxygen species; *SNS*, sympathetic nervous system.

occurs at much lower BP levels.[42] Similarly, interventions that lead to decreased afferent myogenic tone, such as high protein diet or administration of calcium channel blockers (CCBs), result in glomerular injury at relatively low BP levels. The mechanisms responsible for the abnormal myogenic reflex are not known. The fact that vessels retain their responsiveness to exogenous vasoconstrictors such as phenylephrine indicates that the problem is not related to the contracting apparatus, but more likely resides at the level of mechanotransduction of the pressure stimulus.[43] Finally, another mechanism of BP-induced renal injury is arterial stiffness, which amplifies the transmission of a pressure wave to the renal microvasculature.[39]

In the case of glomerular ischemia, decreased flow itself leads to glomerular tuft retraction. Chronic glomerular ischemia leads to production of reactive oxygen species and hypoxia-induced factors that generate increased expression of many proinflammatory and profibrotic factors.[44] Chronic glomerular ischemia also results in activation of the renin–angiotensin system, with resultant angiotensin II-mediated inflammation, oxidative stress, extracellular matrix production, and fibrosis,[36–38] which occur through the effects of several proinflammatory (MCP-1, osteopontin, endothelin-1) and profibrotic (TGF-β, endothelin-1) chemokines that are upregulated by angiotensin II.[36–38] Increased activity of the sympathetic nervous system and endothelial dysfunction (decreased nitric oxide availability, increased endothelin-1) add to this injury environment.[34,36–38]

Nonischemic injury, conversely, is mediated by both pressure-related and unrelated mechanisms. Increased intraglomerular pressure results in glomerular capillary endothelial cell injury and loop collapse with attendant podocyte injury and segmental sclerotic lesions.[38,45] The process of endothelial damage triggers further non-BP-mediated injury to the nephron unit through similar mediators as listed above for the ischemic process. Interestingly, there is marked nephron heterogeneity in the pattern of lesions. Both ischemic and nonischemic lesions often coexist in the same kidney,[7,40,46] are not the result of progression from one type to another,[7] and ischemic lesions appear to have a faster course toward glomerular destruction than the sclerosing, nonischemic lesions.[36]

Genetic Susceptibility

ESRD attributable to HTN is 2.5- to 20-fold more common among African Americans than whites based on

unadjusted data from the US Renal Data System. In models with multiple relevant adjustments, the excess risk is about twofold.[20] The discovery of apolipoprotein-L1 (APOL1) gene variants and their association with ESRD in African Americans has been an exciting development in the understanding of this relationship. Previous genome-wide analyses had mapped a strong signal to the area of chromosome 22 that includes the gene coding for APOL1. Exploring associations with focal and segmental glomerulosclerosis (FSGS) in African-American individuals, Genovese et al. identified two closely related and mutually exclusive mutations (G1 and G2) in the APOL1 gene that are associated with a 10.5-fold increased risk of FSGS and a 7.3-fold increase in risk of "hypertensive ESRD" in African-American individuals.[47] Further studies have identified increased risk of HIV nephropathy, lupus nephritis, albuminuria, diabetic kidney disease progression, and earlier age of onset of ESRD among black individuals.[48,49] A report of the African American Study of Kidney Disease (AASK) study examined the relationship between APOL1 mutations and clinical endpoints. Compared with African-American patients from another cohort without kidney disease, the presence of two APOL1 mutant alleles was associated with an overall 2.3-fold increase in the odds of having a clinical diagnosis of HN.[50] These odds increased to 6.3 to define a phenotype of HN with proteinuria>0.6 g/g on spot urine, and to 4.6 when the phenotype was defined by baseline S[Cr] >3 mg/dL.

APOL1 is a trypanolytic serum factor that protects against several *Trypanosoma* species that cause sleeping sickness. Serum from patients carrying the G1 or G2 mutations has lytic activity against *Trypanosoma brucei rhodesiense*. These mutations are common among Western Africans and may have occurred as a survival factor that, as a side effect, conferred increased risk of kidney disease.[51] Unfortunately, the mechanistic links between APOL1 and kidney injury remain incompletely understood.

APOL1 is normally expressed in glomeruli, tubular, and vascular endothelium in the kidney, and the expression pattern is abnormal in patients with FSGS as well as HIV nephropathy.[52] In transgenic mice, conditional overexpression of APOL1 in podocytes results in loss of podocyte integrity, foot process effacement, glomerulosclerosis, proteinuria, and progressive kidney failure.[53]. Based on early available evidence, APOL1 expression in podocytes mediates injury through mechanisms that include abnormal anion and cation fluxes that induce osmotic cell swelling and defective endolysosomal and autophagosome maturation. This results in autophagy block and accumulation of endocytic vacuoles that activate intracellular pathways including stress-activated protein kinase signaling, mitochondrial and endoplasmic reticulum damage, and inflammasome activation, resulting in caspase 1-mediated inflammatory cell death (pyroptosis).[49]

Because only about 20% of carriers of high-risk alleles develop clinical kidney disease, it is likely that a "second hit" is necessary for disease development.[7] Interferon induces APOL1 expression, so it has been postulated that interferon induction in the setting of viral infections, such as HIV or parvovirus B19, may be the link to mediate APOL1 toxicity.

Another possible second hit is chronic immune activation leading to increased production of soluble urokinase-type plasminogen activator receptor (suPAR).[54] suPAR interacts with the gene products of the abnormal G1 and G2 genes leading to enhanced activation of podocyte integrins that ultimately lead to the formation of autophagosomes, dysregulation of the actin cytoskeleton, and podocyte detachment. In patients with HN in the AASK study, the coexistence of high suPAR levels and high-risk APOL1 alleles resulted in faster rates of CKD progression.[54]

Because of the likely role of oxidative stress in the development of HN, a report in the AASK cohort identified increased risk of CKD progression in null carriers of the GSTM1 gene.[55] The GSTM1 gene codes for a glutathione-S-transferase that metabolizes reactive oxygen species and reactive aldehydes. Null allele homozygosity leads to complete lack of enzyme activity and is associated with increased cardiovascular risk and risk of development of several malignancies. Another report of the AASK study evaluated the relevance of interactions in APOL1 and GSTM1 genotypes in black patients with HN.[56] The study showed that the combination of high-risk APOL1 alleles with GSTM1 null carrier status was associated with higher levels of protein excretion and lower glomerular filtration rate (GFR) at baseline and the highest rates of progression of CKD during follow-up, thus possibly adding increased oxidative stress, in this case genetic in nature, as a possible second hit to APOL1.

Morphological Features of Hypertensive Nephrosclerosis

While several clinical characteristics define the disease for practical purposes, a renal biopsy is needed to confirm the diagnosis of suspected HN.[57] Findings on biopsy include typical vascular hypertrophic changes, interstitial fibrosis, and glomerulosclerosis (Figure 46.2). Glomerular density is decreased in biopsy-proven HN (2.0 vs. 3.2 glomeruli per mm^2 in comparison with samples from kidney donors), a finding that is more prominent among HN patients with proteinuria >1g/day than

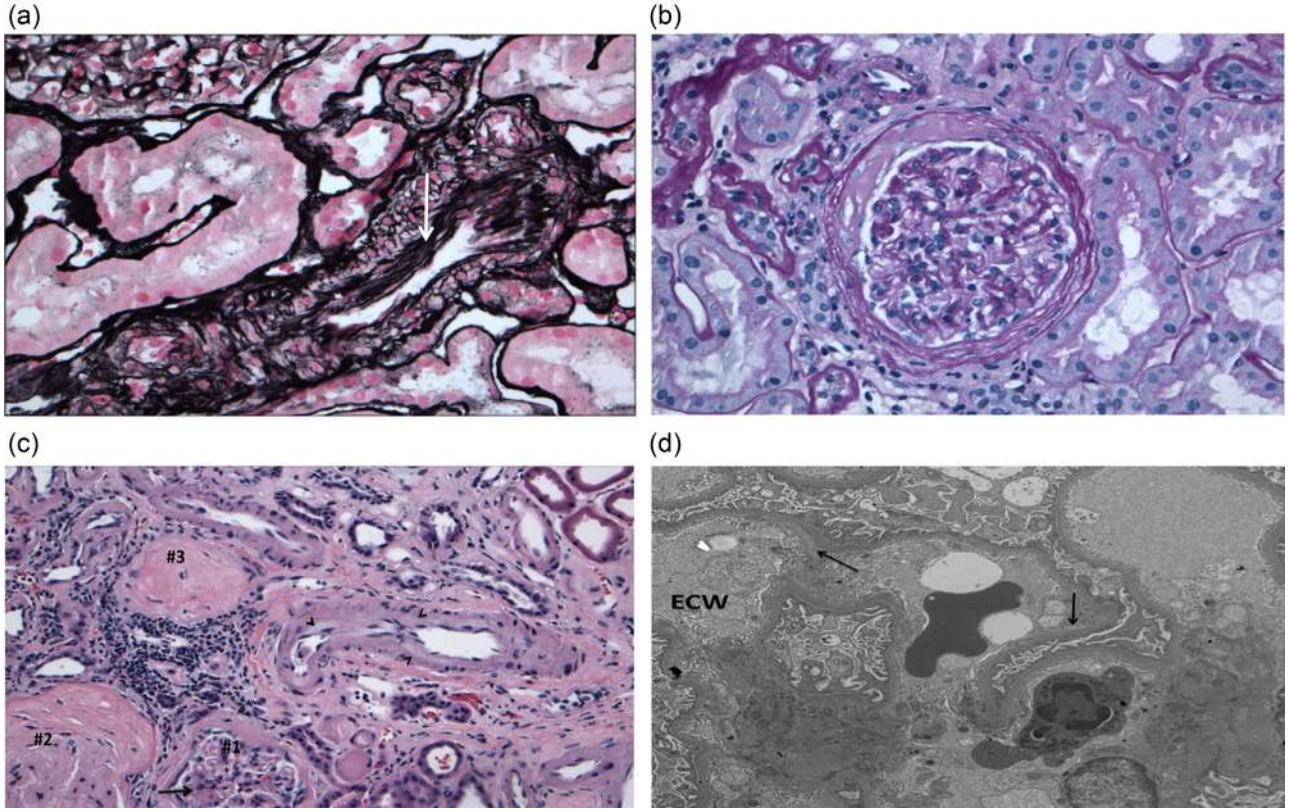


FIGURE 46.2 Histological findings in hypertensive nephrosclerosis. (a) Cross section of an arteriole showing vessel tortuosity and intimal fibrosis (*arrow*). Jones silver stain, 400×. (b) Glomerulus with pericapsular fibrosis and accumulation of collagenous material in Bowman's space. The capillary walls are diffusely thickened and the glomerular basement membrane is wrinkled with luminal collapse. PAS, 400×. (c) Arteriolar wall thickening with intimomedial mucoid degeneration (*small arrowheads*) and diffuse interstitial fibrosis and tubular atrophy. There are three glomeruli in different stages of injury: all have pericapsular fibrosis and some degree of collagen deposition in Bowman's space; #1 has early capillary loop thickening and mesangial sclerosis (*arrow*); #2 has more advanced global sclerosis and marked loss of capillary lumina; and #3 is completely obsolescent. H&E, 200×. (d) Typical electron microscopy findings with endothelial cell swelling (ECW), diffuse wrinkling of the glomerular basement membrane, expanded subendothelial space (lamina rara interna) (*arrows*), and focal collapse of foot processes. *Slides courtesy of Gilbert Moeckel, MD, PhD (Department of Pathology, Yale School of Medicine).*

those without it (1.8 vs. 2.2 glomeruli per mm^2, respectively).[58] The lobar and arcuate arteries are seldom visualized in renal biopsies, but when examined show typical signs of atherosclerosis, such as fibrous intimal thickening which, in conjunction with the frequently observed medial thickening, may produce luminal narrowing. The small interlobular arteries and afferent arterioles are tortuous and show hyalinization, fibroelastic intimal thickening, and reduplication of the internal elastic lamina.[36,57,59] In some chronic cases, there is mucoid degeneration of the arterial wall. This is typical of malignant HTN, but can be seen in the chronic phase even in patients who have never behaved clinically as having malignant HTN. The severity of arteriolar changes matches the severity of abnormalities in larger vessels, and there is an inverse relationship between the severity of these microvascular changes and renal function, but no consistent association with BP levels.[40,57,60] The interstitium shows diffuse widening due to ischemic tubular atrophy. The severity of interstitial atrophy is directly correlated with the severity of both arteriolar and glomerular changes (see below).

Approximately three-quarters of cases show evidence of glomerular ischemia as evidenced by tuft collapse.[59,61] The glomerular capillary loops appear to have increased wall thickness and decreased lumen diameter, a process that is due to wrinkling of the glomerular basement membrane.[61] Periglomerular fibrosis and thickening of Bowman's capsule are often observed.[36] When the process is long-standing, there is progressive glomerular shrinking and retraction toward the vascular pole as an eosinophilic "pink ball."[61] In addition, there is collagen accumulation in Bowman's space, thus filling the space left by the shrunken tuft, leading to glomerular obsolescence. In approximately one-quarter of the cases, the pattern of injury observed on light microscopy is different, consisting of segmental or global sclerosis, mesangial widening, and absence of collagen deposition in Bowman's space.[59,61] This pattern

is distinct from glomerular obsolescence and is called glomerular solidification. Patients with predominance of glomerular solidification have higher baseline BP and proteinuria and lower renal function than patients with predominant obsolescence.[62] In the US, this pattern is more common in African Americans with biopsy findings consistent with HN (53%),[46] but is also observed, in variable proportions (typically ~20–25%) among nonblacks in the US[46,59,63] and other countries.[59,63] Moreover, the percentage of solidified glomeruli in African Americans (25%) is three-fold higher than in Caucasians (8%), whereas the numbers of obsolescent glomeruli correlate with age but do not differ according to ethnicity.[46]

In most cases, immunofluorescence and electron microscopy (EM) add little to the pathological diagnosis of benign HN. On EM, there is conspicuous wrinkling and thickening of the glomerular basement membrane accompanied by widening of the subendothelial space as a result of subtle endothelial cell injury.[61] In patients with segmental glomerular sclerosis, the identification of focal foot process effacement is an important factor in the distinction between HTN-associated secondary glomerulosclerosis, as opposed to the diffuse effacement seen in primary FSGS.[46]

DIAGNOSIS

Establishing the Diagnosis of HN

CKD is defined as the presence of abnormalities of kidney structure or function, present for greater than 3 months, with implications for health. HN should be suspected in patients presenting for the evaluation of CKD who carry a diagnosis of HTN, especially in the absence of albuminuria, hematuria, or significant abnormalities on renal imaging. A long-standing history of HTN marked by prolonged periods of suboptimal control observed while renal function was still normal is an important characteristic of the disease. Because HTN is present in almost 90% of patients with advanced CKD, it is imperative to demonstrate the presence of uncontrolled HTN prior to the loss of kidney function. If this timeline cannot be ascertained, which is often the case in clinical practice,[2] the diagnosis of HN remains questionable. Further support for the diagnosis occurs if there is evidence of hypertensive injury to other target organs, particularly the heart.[64] Because of the common association of HTN with LVH, the presence of LVH on ECG or echocardiography is a useful correlate of hypertensive renal injury as it reflects duration of poor BP control. Retinal damage was also associated with renal injury in older studies, but this association was largely represented by patients with retinal features of malignant HTN.[65] Current evidence shows poor associations between retinal abnormalities and degree of renal injury in HN.[63,66–68] The presence of certain retinal findings, venous dilation in particular, is associated with the development of cardiovascular events in patients with CKD,[69] thus suggesting prognostic value of retinal examinations regardless of diabetic status; however, these were not findings of hypertensive retinopathy, so the relevance to hypertensive patients with HN is uncertain.

Analysis of renal imaging, typically ultrasound, although computed tomography (CT) and magnetic resonance (MR) imaging are also used, is essential in the diagnostic evaluation of patients with suspected HN, as it allows exclusion of other causes of nonproteinuric CKD, such as polycystic kidney disease and obstructive uropathy. Patients with HN often have kidneys of decreased size, lobulated contour, and atrophic cortices that are hyperechogenic on ultrasound. These are nonspecific abnormalities related to chronic small vessel damage. Because renovascular disease and ischemic nephropathy are commonly entertained diagnoses in patients with HTN and CKD, renovascular imaging with duplex ultrasound, CT angiography, or MR angiography may be necessary to discriminate between the two.

Proteinuria, albuminuria, and hematuria, often seen in malignant HTN, are not common in HN, which in its classic definition requires proteinuria to be low grade (i.e. levels no greater than 500–2000 mg/day based on 24-hour urine collection or spot urine protein:creatinine ratio <0.5–2 mg/g) and hematuria to be absent.[62–64] When these clinical parameters are applied to African-American patients, >90% have the histological features of HN on biopsy,[57] but we are not aware of any similar studies in other ethnic groups.

Among African Americans with presumed HN enrolled in the AASK trial, ~70% had proteinuria less than 300 mg/day.[70] Although most patients have minimal proteinuria, several series demonstrate variable rates of proteinuria in patients with biopsy-proven HN, many of whom have nephrotic-range proteinuria.[63,67,68,71–75] In a large series of 185 patients with biopsy-proven benign nephrosclerosis in the United Kingdom, ~70% had at least 300 mg of daily protein excretion, while 22% excreted >3 g/day.[73] Biopsy series, unfortunately, are skewed typically toward higher levels of proteinuria, as this finding often prompts a search for a primary glomerulopathy. However, we must recognize that a small subgroup of patients with pure HN on biopsy can present with very high levels of proteinuria.

Hematuria frequency in biopsy-proven cases of HN is 25–30%.[71,73] However, just as applicable to proteinuria, confounding by indication may be the reason explaining this high proportion, which may be as high as half of the

cases when high-grade proteinuria is also present.[74] Most patients with HN, however, have little or no proteinuria and no hematuria. When accompanied by long-standing HTN and evidence of other target-organ injury, a diagnosis of HN can be made with reasonable certainty, especially in African-American patients.[57] However, proteinuria, sometimes in the nephrotic range, and/or hematuria will be present in a minority of patients, in which case a renal biopsy should be considered to define the diagnosis.

In the absence of proteinuria, hematuria, or abnormalities on renal imaging, the differential diagnosis of HN is limited to chronic interstitial nephritides of any etiology (drugs, infections, autoimmune, etc.), atheroembolic renal disease, renovascular disease/ischemic nephropathy, and functional states of chronic renal hypoperfusion, such as the chronic forms of cardiorenal or hepatorenal syndromes. Identification of these conditions should be readily apparent based on other clinical, laboratory, and imaging features, although the assessment of their clinical relevance is often problematic, as in the case of renal artery stenosis as a cause of CKD, especially if unilateral.

Evaluation of Hypertension

Patients with HN typically have long-standing HTN and have undergone a detailed evaluation of secondary causes of HTN. As part of the approach to these patients, the nephrologist should revisit this issue with particular focus on conditions that are common and/or can be affected by specific treatment, such as primary aldosteronism, renovascular disease, sleep apnea, thyroid disorders, and pheochromocytoma. Appropriate diagnostic tests should be pursued according to level of suspicion.

Assessment of established extrarenal organ damage is essential in the management of patients with HN. This assessment helps confirm the presumptive diagnosis of HN and identifies comorbid conditions that may affect treatment choices related to HTN and cardiovascular risk management, choice of renal replacement modality, and—if applicable—vascular access creation. We perform a detailed cardiovascular, neurological, and peripheral vascular history and examination looking for findings suggestive of coronary artery disease, congestive heart failure, stroke, and peripheral arterial disease. Aside from "kidney-specific" tests such as serum chemistries, urinalysis, albuminuria, and/or spot protein:creatinine ratio, and some form of imaging, we uniformly evaluate the heart not only with an ECG but also with an echocardiogram to provide more precise measures of LVH, systolic and diastolic function, as they may have both prognostic and therapeutic implications.

BP Measurement and Monitoring

Office measurements should be performed with close attention to the American College of Cardiology/American Heart Association[3] guidelines and with routine performance of orthostatic measurements, particularly in older patients, given the high prevalence of orthostatic hypotension.[3] There is substantial evidence that BP monitoring outside of the office is a stronger predictor than office BP of cardiovascular events in essential HTN.[76] Home and 24-hour BPs provide a better overall assessment of average BP (i.e. closer proximity to one's "true BP") and BP variability, the characterization of BP in the ambulatory environment, and, in the case of 24-hour BP monitoring (ABPM), assessment of BP during sleep, all of which are stronger predictors of risk than clinic BP. The recent report of a registry-based, multicenter, Spanish cohort study of 63,910 adults who had 24-hour ABPMs and followed for a median of 4.7 years demonstrated a 58% increase in all-cause mortality among those with white coat and masked HTN. Masked HTN was more strongly associated with all-cause mortality (hazard ratio, 2.83; 95% CI, 2.12−3.79) than sustained HTN (hazard ratio, 1.80; 95% CI, 1.41−2.31) or white coat HTN (hazard ratio, 1.79; 95% CI, 1.38−2.32). Thus, ABPM is a stronger predictor of all-cause and cardiovascular mortality than clinic blood pressure measurements.[77]

The United Kingdom National Institute for Health and Care Excellence (NICE) BP guidelines recommend the use of 24-hour ABPM as the primary tool for *initial* diagnosis of primary HTN. This will result in cost savings as ~15% of patients do not require treatment due to a white coat effect (i.e. BP high in the office but normal at home) and ~10% require more stringent treatment due to a masked effect (i.e. BP normal in the office but high at home).[78] When ABPM is not available, home BP is a good alternative.[3,78] Similar recommendations now exist in the US. The US Preventive Services Task Force recommends the use of out-of-office BP to confirm the diagnosis of HTN prior to treatment initiation (https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/high-blood-pressure-in-adults-screening), and the ACC/AHA guidelines recommend the use of out-of-office BP both for diagnosis and treatment adjustments.[3]

The prevalence of masked and white coat effects is high in CKD. An analysis of 960 patients in 6 separate studies of out-of-office BP (home BP in 4 studies, ABPM in 2) showed that 40% of individuals with adequate office BP were high at home, and 31% of those with elevated office BP were controlled based on ambulatory values.[79] These observations have major implications regarding the assessment of HTN control and treatment monitoring and justify the recommendation

of integration of ABPM and/or home BP readings in the routine management of HTN. Additionally, an ABPM substudy performed in the AASK cohort demonstrated that 36% had masked HTN with office BPs in an acceptable range. A recent report presented data on 7518 patients from 5 cohorts from 4 different countries (two from the US and one each from Italy, Spain, and Japan).[80] In this analysis, the overall prevalence of white coat and masked HTN was 20% and 16%, respectively. However, there were significant differences in prevalence across cohorts. White coat HTN ranged from 3% to 30% (lower in the US, higher in other cohorts), whereas masked HTN ranged from 6% to 35%, with higher prevalence in the US and lower elsewhere.

In addition, as in primary HTN, studies supporting improved prognostication with ABPM or home BP in CKD are available.[81–83] All studies show better characterization of renal and cardiovascular risk using 24-hour, daytime and night-time BP levels. However, there is inconsistent evidence that the dipping status (i.e. whether BP falls by >10% during sleep or not) provides additional prognostic information that is independent of average BP levels. In the specific case of HN, the 5-year observation of 617 subjects enrolled in the AASK cohort study revealed that ABPM was a significant predictor of cardiovascular and renal events.[82] In fully adjusted models that included baseline clinic BP, each 10 mm Hg increase in 24-hour systolic BP was associated with 26% (12–41%, $p < 0.001$) increased risk of cardiovascular events (hospitalization for myocardial infarction, revascularization procedure, heart failure, or stroke), an effect that was more robust in patients with uncontrolled clinic BP. There was no independent predictive advantage of ABPM over clinic BP when the entire cohort was analyzed for the CKD endpoint (composite of doubling of S[Cr], ESRD, or death). However, among the 267 subjects with controlled clinic systolic BP (<130 mm Hg), each 10 mm Hg increase in 24-hour systolic BP was associated with a 33% (4–70%, $p = 0.02$) increase in risk of the CKD endpoint. This advantage over clinic BP was not noted among patients with uncontrolled clinic BP. In this study, dipping status was not an independent predictor of any of the outcomes. However, the high incidence of masked HTN may have played a role contributing to the negative outcome.

The severity of nocturnal HTN in HN was evaluated using baseline data from the 617 African-American patients with HN enrolled in the AASK cohort study.[84] In this cohort, 80% were nondippers using the definition of <10% BP decline during the night. Surprisingly, however, of the 377 with controlled office BP, 70% had a diagnosis of masked HTN, largely represented as nocturnal HTN (i.e. adequate office BP <135/85 mm Hg, adequate daytime ambulatory BP <140/90 mm Hg, but high night-time BP >120/70 mm Hg). This had clinical relevance as there was a graded relationship between the level of nocturnal HTN and the severity of organ damage, such as higher levels of proteinuria and LVH. Nocturnal BP was significantly higher in the AASK population than in patients from four other CKD studies (135 mm Hg in AASK vs. 122–124 mm Hg in the other cohorts), thus postulating a significant effect of black race and possibly the etiology of kidney disease on the prevalence on uncontrolled nocturnal HTN.[80] The possible value of nocturnal dosing of pharmacological therapy is discussed below.

TREATMENT

To appreciate fully how to treat HTN in HN, one needs to value the cornerstone of therapy for HTN in general, i.e. the importance of lifestyle intervention, especially sodium restriction to <2400 mg/day, reduced alcohol consumption, and aerobic exercise.[3] Studies evaluating the effect of sodium intake on BP control in people with stage 4 CKD show that for approximately every 400 mg above a sodium intake base of 3000 mg day requires an additional BP medication to maintain BP control.[85] Additionally, other than aerobic exercise, alternative therapies used by patients have no evidence to support their use.[86]

Blood Pressure Goals

Consensus guidelines regarding BP targets in patients with CKD are currently underway and have been the subject of substantial controversy. The recommended BP goal by the 2012 Kidney Disease: Improving Global Outcome (KDIGO) guidelines for patients with nephropathy, regardless of etiology, is <140/90 mm Hg.[87] Data to support this goal are derived from three prospective trials that randomized groups to different BP goals with the primary endpoint being CKD progression. The three trials were the Modification of Dietary Protein in Renal Disease (MDRD),[88] AASK,[70] and the Ramipril Efficacy in Nephropathy-2.[89] All three trials failed to show a slower decline in estimated GFR (eGFR) in the lower BP group.

The AASK study had similar BP targets to the MDRD study (mean arterial pressure [MAP] <92 mm Hg vs. 102–107 mm Hg) and failed to show a difference in eGFR decline after 5 years of follow-up.[70] The trial continued as a cohort study for five additional years maintaining BP at levels <130/80 mm Hg with the hypothesis that the duration of follow-up was too short.[90] However, even with this level of control, up to 65% of the cohort had progressive nephropathy.

The results of the Systolic Blood Pressure Intervention Trial (SPRINT)[91] spurred recommendations for a target <130/80 mm Hg by the ACC/AHA guidelines.[3] In SPRINT, nondiabetic patients with HTN and high cardiovascular risk were randomized to a systolic BP target of <140 or <120 mm Hg. Those randomized to the low target developed significantly fewer cardiovascular events and death.[91] SPRINT was enriched by a large number of CKD patients (N = 2646) and a separate analysis of CKD patients confirmed the same pattern of 19% fewer cardiovascular endpoints and 28% fewer deaths among those randomized to the lower target after 3.3 years of follow-up.[92] There were no differences in CKD progression or need for dialysis. Because of the improvements in nonrenal outcomes, these results led the ACC/AHA guidelines to recommend tighter BP targets (<130/80 mm Hg) among CKD patients.[3] KDIGO guidelines are being updated, with planned release in 2019.

There have been concerns about increased rates of acute kidney injury in patients subjected to more intensive BP lowering, both in patients with normal and abnormal baseline renal function.[91,92] In the SPRINT renal substudy, intensive therapy was associated with a 46% greater risk of hospitalization for acute kidney injury, though the overall rate was low (2.8% vs. 1.9%, HR 1.46, p = 0.01). Two recent publications looked at the long-term risk of ESRD and death in patients randomized to lower BP targets in AASK and MDRD. With respect to ESRD, early (within 3−4 months of randomization) fall in GFR >20% was associated with increased risk of ESRD, but there was no difference between intensive or usual BP target.[93] A fall in GFR between 5% and 20% was only associated with increased ESRD risk in the usual group. As it pertains to death risk, those with an early loss of GFR less than 20% had decreased mortality risk if randomized to the intensive BP arm, whereas no such protection was noted in the usual BP arm.[94] A fall in GFR >20% was associated with increased risk of death in the usual BP group only. These data indicate that, while significant loss of GFR is associated with increased risk of ESRD, this is not related to BP goals. Furthermore, in the intensive group, the death risk was lower among those randomized to intensive therapy even if there was an early GFR loss between 5% and 20%.

One explanation for the observation of high rates of progressive CKD despite lower BP targets in AASK is the inability to capture masked or nocturnal HTN with routine clinic BP measurements, as suggested by the AASK ABPM substudy where more than 33% of people had masked HTN.[84] Of relevance to this point, the manipulation of nocturnal HTN and abnormalities in the circadian BP rhythm by bedtime dosing of antihypertensive agents has been evaluated in HTN. In 21 randomized studies involving 1993 patients with HTN, evening dosing (6 p.m.−12 a.m.) of antihypertensive drugs resulted in a nominal but statistically significant advantage in 24-hour BP reduction (1.7/1.2 mm Hg) compared with morning dosing (6 a.m.−12 p.m.).[95] Bedtime dosing led to a significant 67% risk reduction in cardiovascular events compared with morning dosing among 2156 hypertensive patients treated for 5.6 years in a large single center randomized clinical trial.[96] The same investigators demonstrated a similar cardioprotective effect in the subgroup of patients enrolled in the study who had stage 2 or stage 3a CKD.[97] In another study of 32 nondipper CKD patients (22 with a diagnosis of HN), modification of the administration time of at least one agent from the morning to bedtime resulted in conversion from nondipper to dipper in 28 of 32 subjects, reduction in nocturnal BP by 7/4 mm Hg (p < 0.001) with an opposing increase in daytime BP by 3/1 mm Hg, p = not reported, and a concomitant association between degree of nocturnal BP fall and reduction in proteinuria.[98]

Most drugs are effective in achieving this effect, though the most consistent are blockers of the renin−angiotensin system, CCBs, and alpha blockers, whereas beta blockers are not effective in lowering night-time BP, except in patients with sleep apnea.[99] Despite the success of some investigators in lowering nocturnal pressure in nondipper CKD patients with this strategy,[98,100] a study of African Americans with HN (stage 4 CKD) was unsuccessful in lowering nocturnal BP with bedtime dosing.[101] Therefore, although promising, further data are necessary before we can recommend changes in therapy with the goal of reducing night-time BP, especially until we can define which patients should have ABPM prior to the change, if only nondippers should undergo the modifications, and if follow-up ABPM is indicated after each treatment change.

Taken together, prospective evidence supports a BP goal of <140/90 mm Hg to slow HN progression. Moreover, while nephropathy progression is slowed, it is not stopped as indicated by the clinical trial evidence of the long-term (10-year) AASK follow-up. However, based on data from SPRINT, cardiovascular events and death risk may be minimized by a tighter target (<120−130 mm Hg SBP), thus making these lower targets desirable, as long as well tolerated.

Overall Management Approach and Drug Choices

We refer the reader to Chapter 21 for a detailed discussion of drug choices in the treatment of HTN in CKD. Most of the data driving treatment choices in

HN come from people with advanced nondiabetic kidney disease having more than 300 mg of albuminuria per day. While only one trial randomized drug classes, i.e. AASK, the others randomized BP levels and also used ACE inhibitors (ACEIs) because angiotensin receptor blockers (ARBs) were not available when they were done. Mindful of the limitations of generalizability of these results to all HN patients, all results among these participants indicate that ACEIs are the preferred agents to be used for treatment. In AASK, ramipril was superior to either amlodipine or metoprolol for slowing the rate of progression of HN.[70] However, no other ACEIs have been tested in HN and a systematic review and meta-analysis by the Cochrane group found that there are not enough data to make claims that ACEIs prevent or delay any nephropathy in its early stages (CKD stage 1 or 2).[102] ARBs are often used interchangeably with ACEI, but the data on ARBs are restricted to diabetic nephropathy with no outcome data in nondiabetic HN CKD. However, given the mechanism of action and the benefit seen in diabetic nephropathy, there is no reason to think these agents would not be as effective in HN, as supported by studies in diabetic kidney disease.[103,104]

Thiazide-like diuretics (chlorthalidone and indapamide) have a strong evidence base for reducing cardiovascular risk even in patients with stages 1–3b CKD. However, their role in CKD outcome studies is unclear. *Post hoc* analyses of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated that chlorthalidone was as good as ACEIs for slowing CKD progression in stage 3 CKD.[105] This *post hoc* analysis of ALLHAT included both those with HN and diabetic nephropathy so the data are not definitive.

When used in patients with HN, both dihydropyridine (DHP) and nondihydropyridine CCBs are effective in lowering BP and CV events in high-risk populations. These agents are particularly efficacious for CV risk reduction when combined with an ACEI as shown by the results of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH).[106] In this trial, patients at high risk for CV events and CKD progression treated with a single pill combination of an ACEI (benazepril) with amlodipine had a 20% relative risk reduction in CV events and slower CKD progression when compared with those assigned to the benazepril/hydrochlorothiazide combination.

In addition, a prespecified *post hoc* analysis of ACCOMPLISH evaluated CKD outcomes showing that the DHP CCB plus ACEI decreased CKD progression to a greater extent than the ACEI and diuretic (hazard ratio 0.52, $p < 0.001$).[107] About 60% of the patients in this substudy were thought to have HN.

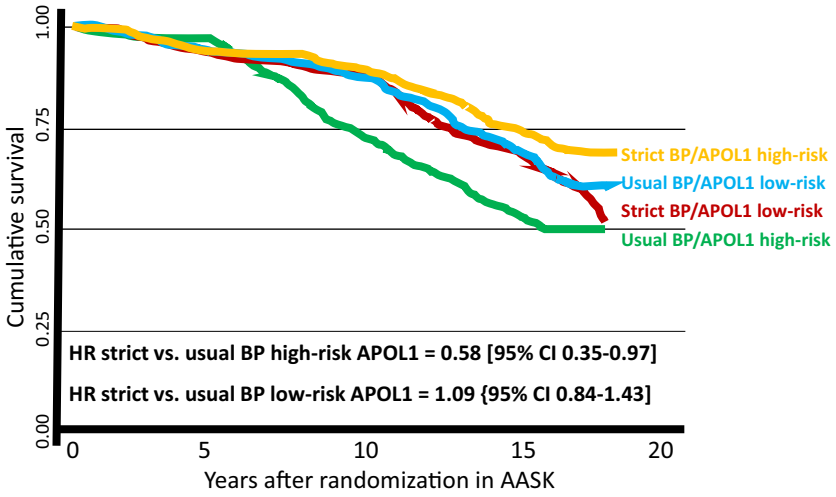
Beta blockers are no longer a first-line option to lower BP in the most treatment guidelines.[3] Some patients with HN have an increase in sympathetic activity and a high CV event rate and could benefit from β blockers. In the AASK study, subjects randomized to metoprolol had intermediate outcomes, better than amlodipine but worse than ramipril.[70] Therefore, in black patients with HN, metoprolol is a useful choice, in particular for patients who cannot tolerate an ACEI well, or who need additional therapy to achieve BP control.

None of the other drug classes has been systematically evaluated for treatment of HN in CKD. Their use in HN is acceptable as combination therapy to achieve BP control in patients with resistant HTN.

FUTURE HORIZONS: APOL1 GENOTYPE AND TREATMENT DECISIONS

In the AASK long-term follow-up study, compared with patients with none or 1 high-risk allele, those with 2 high-risk APOL1 alleles had 88% greater risk of doubling of S[Cr] or ESRD over 9 years of follow-up (HR 1.88, 95% CI 1.46–2.41).[48] Patients with proteinuria had faster progression than those without, but APOL1 genotype predicted risk similarly among patients with or without proteinuria at baseline. Finally, BP target assignment (MAP <92 [intensive] vs. 92–107 mm Hg [usual] and drug assignment [ramipril vs. metoprolol or amlodipine]) did not modify the impact of APOL1 genotype on renal outcomes.

Interestingly, a separate report of AASK that focused on nonrenal endpoints over 14.5 years of follow-up showed that patients with high-risk APOL1 genotypes (23% of the entire cohort) had the same risk of death than those with low-risk genotypes.[108] However, among high-risk APOL1 subjects, assignment to the intensive BP target group during the study resulted in 52% decrease in adjusted mortality risk (HR 0.48, 95% CI 0.28–0.84) (Figure 46.3). This effect became noticeable after ~5 years of follow-up and was not observed among patients with low-risk APOL1 genotypes. In addition, among high-risk APOL1 subjects, there was also a nonsignificant trend toward fewer cardiovascular events (HR 0.72, 95% CI 0.34–1.53). Therefore, it is plausible that, once APOL1 genotyping becomes more widely available, patients with two phenocopies of G1 or G2 APOL1 alleles should be treated more intensively than those with low-risk genotypes with the goal of preventing nonrenal events despite the apparent absence of renal benefit from such intervention. The prospective benefit of this approach has yet to be demonstrated.



Number at risk					
Usual BP/APOL1 low risk	264	261	235	192	59
Usual BP/APOL1 high-risk	78	78	65	50	12
Strict BP/APOL1 low-risk	261	256	235	186	57
Strict BP/APOL1 high-risk	79	79	71	62	20

FIGURE 46.3 Apolipoprotein-L1 (APOL1) genotype and death according to blood pressure (BP) target in the African-American Study of Kidney Disease (AASK). Hazard ratios (HR) are unadjusted. *From Ku et al.*[108] *with permission.*

SUMMARY

HN is defined as CKD attributed to HTN. Morphologically, HN is characterized by arteriolar sclerosis, glomerulosclerosis, and interstitial fibrosis. Clinically, HN presents as progressive loss of renal function in a patient with previously uncontrolled HTN, accompanied by minimal proteinuria, and normal urinary sediment and renal imaging. This condition is responsible for ~30% of cases of ESRD in the US and is more common in African Americans, a genetic susceptibility that is identified through mutations in the APOL1 gene, although the mechanistic implications of these mutations remain only partly understood. Treatment recommendations based largely on data from the AASK trial and observational studies include preferential use of a blocker of the renin–angiotensin system (ACEI or ARB) as the primary component of drug treatment to achieve a BP goal of <130/80 mm Hg.

References

1. Skorecki KL, Wasser WG. Hypertension-misattributed kidney disease in African Americans. *Kidney Int* 2013;**83**:6–9.
2. Zarif L, Covic A, Iyengar S, Sehgal AR, Sedor JR, Schelling JR. Inaccuracy of clinical phenotyping parameters for hypertensive nephrosclerosis. *Nephrol Dial Transplant* 2000;**15**:1801–7.
3. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018;**71**:1269–324.
4. Lawes CM, Vander Hoorn S, Rodgers A, International Society of H. Global burden of blood-pressure-related disease, 2001. *Lancet* 2008;**371**:1513–8.
5. Forouzanfar MH, Liu P, Roth GA, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. *J Am Med Assoc* 2017;**317**:165–82.
6. Hsu CY. Does treatment of non-malignant hypertension reduce the incidence of renal dysfunction? A meta-analysis of 10 randomised, controlled trials. *J Hum Hypertens* 2001;**15**:99–106.
7. Tracy RE. Renal vasculature in essential hypertension: a review of some contrarian evidence. *Contrib Nephrol* 2011;**169**:327–36.
8. Zucchelli P, Zuccala A. Can we accurately diagnose nephrosclerosis? *Nephrol Dial Transplant* 1995;**10**(Suppl. 6):2–5.
9. Perera GA. Hypertensive vascular disease; description and natural history. *J Chronic Dis* 1955;**1**:33–42.
10. Rosansky SJ, Hoover DR, King L, Gibson J. The association of blood pressure levels and change in renal function in hypertensive and nonhypertensive subjects. *Arch Intern Med* 1990;**150**:2073–6.
11. Rostand SG, Brown G, Kirk KA, Rutsky EA, Dustan HP. Renal insufficiency in treated essential hypertension. *N Engl J Med* 1989;**320**:684–8.
12. Magee JH, Unger AM, Richardson DW. Changes in renal function associated with drug or placebo therapy of human hypertension. *Am J Med* 1964;**36**:795–804.
13. Lindeman RD, Tobin JD, Shock NW. Association between blood pressure and the rate of decline in renal function with age. *Kidney Int* 1984;**26**:861–8.
14. Shulman NB, Ford CE, Hall WD, et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. *Hypertension* 1989;**13**:I80–93.

15. Perneger TV, Nieto FJ, Whelton PK, Klag MJ, Comstock GW, Szklo M. A prospective study of blood pressure and serum creatinine. Results from the 'Clue' Study and the ARIC Study. *J Am Med Assoc* 1993;**269**:488–93.
16. Perry Jr HM, Miller JP, Fornoff JR, et al. Early predictors of 15-year end-stage renal disease in hypertensive patients. *Hypertension* 1995;**25**:587–94.
17. Madhavan S, Stockwell D, Cohen H, Alderman MH. Renal function during antihypertensive treatment. *Lancet* 1995;**345**:749–51.
18. Iseki K, Iseki C, Ikemiya Y, Fukiyama K. Risk of developing end-stage renal disease in a cohort of mass screening. *Kidney Int* 1996;**49**:800–5.
19. Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. *N Engl J Med* 1996;**334**:13–8.
20. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Stamler J. End-stage renal disease in African-American and white men. 16-year MRFIT findings. *J Am Med Assoc* 1997;**277**:1293–8.
21. Siewert-Delle A, Ljungman S, Andersson OK, Wilhelmsen L. Does treated primary hypertension lead to end-stage renal disease? A 20-year follow-up of the Primary Prevention Study in Goteborg, Sweden. *Nephrol Dial Transplant* 1998;**13**:3084–90.
22. Hsu CY, McCulloch CE, Darbinian J, Go AS, Iribarren C. Elevated blood pressure and risk of end-stage renal disease in subjects without baseline kidney disease. *Arch Intern Med* 2005;**165**:923–8.
23. Hanratty R, Chonchol M, Miriam Dickinson L, et al. Incident chronic kidney disease and the rate of kidney function decline in individuals with hypertension. *Nephrol Dial Transplant* 2010;**25**:801–7.
24. Hanratty R, Chonchol M, Havranek EP, et al. Relationship between blood pressure and incident chronic kidney disease in hypertensive patients. *Clin J Am Soc Nephrol* 2011;**6**:2605–11.
25. Chang TI, Li S, Chen SC, et al. Risk factors for ESRD in individuals with preserved estimated GFR with and without albuminuria: results from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2013;**61**:S4–11.
26. Cao X, Xie X, Zhou J, Yuan H, Chen Z. Relationship between prehypertension and incidence of chronic kidney disease in a general population: a prospective analysis in central south China. *Int Urol Nephrol* 2014;**46**:2183–9.
27. McMahon GM, Preis SR, Hwang SJ, Fox CS. Mid-adulthood risk factor profiles for CKD. *J Am Soc Nephrol* 2014;**25**:2633–41.
28. Lohr JW, Golzy M, Carter RL, Arora P. Elevated systolic blood pressure is associated with increased incidence of chronic kidney disease but not mortality in elderly veterans. *J Am Soc Hypertens* 2015;**9**:29–37.
29. Eriksen BO, Stefansson VTN, Jenssen TG, et al. Elevated blood pressure is not associated with accelerated glomerular filtration rate decline in the general non-diabetic middle-aged population. *Kidney Int* 2016;**90**:404–10.
30. Garofalo C, Borrelli S, Pacilio M, et al. Hypertension and prehypertension and prediction of development of decreased estimated GFR in the general population: a meta-analysis of cohort studies. *Am J Kidney Dis* 2016;**67**:89–97.
31. USRDS - United States Renal Data System. *Annual data report 2012: incidence and prevalence tables*. Bethesda, MD: National Institutes of Health; 2012. http://www.usrds.org/adr.aspx.
32. Naicker S. End-stage renal disease in sub-Saharan Africa. *Ethn Dis* 2009;**19**. S1-13-5.
33. EDTA-ERA. *ERA-EDTA registry*. 2012. Amsterdam, http://www.era-edta-reg.org.
34. Griffin KA. Hypertensive kidney injury and the progression of chronic kidney disease. *Hypertension* 2017;**70**:687–94.
35. Bidani AK, Polichnowski AJ, Loutzenhiser R, Griffin KA. Renal microvascular dysfunction, hypertension and CKD progression. *Curr Opin Nephrol Hypertens* 2013;**22**:1–9.
36. Hill GS. Hypertensive nephrosclerosis. *Curr Opin Nephrol Hypertens* 2008;**17**:266–70.
37. Kopp JB. Rethinking hypertensive kidney disease: arterionephrosclerosis as a genetic, metabolic, and inflammatory disorder. *Curr Opin Nephrol Hypertens* 2013;**22**:266–72.
38. Mennuni S, Rubattu S, Pierelli G, Tocci G, Fofi C, Volpe M. Hypertension and kidneys: unraveling complex molecular mechanisms underlying hypertensive renal damage. *J Hum Hypertens* 2014;**28**:74–9.
39. Loutzenhiser R, Griffin K, Williamson G, Bidani A. Renal autoregulation: new perspectives regarding the protective and regulatory roles of the underlying mechanisms. *Am J Physiol Regul Integr Comp Physiol* 2006;**290**:R1153–67.
40. Hill GS, Heudes D, Jacquot C, Gauthier E, Bariety J. Morphometric evidence for impairment of renal autoregulation in advanced essential hypertension. *Kidney Int* 2006;**69**:823–31.
41. Hill GS, Heudes D, Bariety J. Morphometric study of arterioles and glomeruli in the aging kidney suggests focal loss of autoregulation. *Kidney Int* 2003;**63**:1027–36.
42. Bidani AK, Griffin KA, Williamson G, Wang X, Loutzenhiser R. Protective importance of the myogenic response in the renal circulation. *Hypertension* 2009;**54**:393–8.
43. Vavrinec P, Henning RH, Goris M, Landheer SW, Buikema H, van Dokkum RP. Renal myogenic constriction protects the kidney from age-related hypertensive renal damage in the Fawn-Hooded rat. *J Hypertens* 2013;**31**:1637–45.
44. Heyman SN, Khamaisi M, Rosen S, Rosenberger C. Renal parenchymal hypoxia, hypoxia response and the progression of chronic kidney disease. *Am J Nephrol* 2008;**28**:998–1006.
45. Wang G, Lai FM, Kwan BC, et al. Podocyte loss in human hypertensive nephrosclerosis. *Am J Hypertens* 2009;**22**:300–6.
46. Marcantoni C, Ma LJ, Federspiel C, Fogo AB. Hypertensive nephrosclerosis in African Americans versus Caucasians. *Kidney Int* 2002;**62**:172–80.
47. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010;**329**:841–5.
48. Parsa A, Kao WH, Xie D, et al. APOL1 risk variants, race, and progression of chronic kidney disease. *N Engl J Med* 2013;**369**:2183–96.
49. Beckerman P, Susztak K. APOL1: the balance imposed by infection, selection, and kidney disease. *Trends Mol Med* 2018;**24**:682–95.
50. Lipkowitz MS, Freedman BI, Langefeld CD, et al. Apolipoprotein L1 gene variants associate with hypertension-attributed nephropathy and the rate of kidney function decline in African Americans. *Kidney Int* 2013;**83**:114–20.
51. Friedman DJ, Pollak MR. Genetics of kidney failure and the evolving story of APOL1. *J Clin Investig* 2011;**121**:3367–74.
52. Madhavan SM, O'Toole JF, Konieczkowski M, Ganesan S, Bruggeman LA, Sedor JR. APOL1 localization in normal kidney and nondiabetic kidney disease. *J Am Soc Nephrol* 2011;**22**:2119–28.
53. Beckerman P, Bi-Karchin J, Park AS, et al. Transgenic expression of human APOL1 risk variants in podocytes induces kidney disease in mice. *Nat Med* 2017;**23**:429–38.
54. Hayek SS, Koh KH, Grams ME, et al. A tripartite complex of suPAR, APOL1 risk variants and alphavbeta3 integrin on podocytes mediates chronic kidney disease. *Nat Med* 2017;**23**:945–53.
55. Chang J, Ma JZ, Zeng Q, et al. Loss of GSTM1, a NRF2 target, is associated with accelerated progression of hypertensive kidney disease in the African American Study of Kidney Disease (AASK). *Am J Physiol Renal Physiol* 2013;**304**:F348–55.
56. Bodonyi-Kovacs G, Ma JZ, Chang J, et al. Combined effects of GSTM1 null allele and APOL1 renal risk alleles in CKD progression in the African American study of kidney disease and hypertension trial. *J Am Soc Nephrol* 2016;**27**:3140–52.

57. Fogo A, Breyer JA, Smith MC, et al. Accuracy of the diagnosis of hypertensive nephrosclerosis in African Americans: a report from the African American study of kidney disease (AASK) trial. AASK pilot study investigators. *Kidney Int* 1997;**51**:244–52.
58. Haruhara K, Tsuboi N, Kanzaki G, et al. Glomerular density in biopsy-proven hypertensive nephrosclerosis. *Am J Hypertens* 2015;**28**:1164–71.
59. Bohle A, Wehrmann M, Greschniok A, Junghans R. Renal morphology in essential hypertension: analysis of 1177 unselected cases. *Kidney Int Suppl* 1998;**67**:S205–6.
60. Tracy RE. Blood pressure related separately to parenchymal fibrosis and vasculopathy of the kidney. *Am J Kidney Dis* 1992; **20**:124–31.
61. Olson JL. Renal disease caused by hypertension. In: Jennette JC, Olson JL, Schwartz MM, Silva FG, editors. *Heptinstall's pathology of the kidney.* Philadelphia: Lippincott, Williams & Wilkins; 2007. p. 937–90.
62. Fogo AB. Hypertensive risk factors in kidney disease in African Americans. *Kidney Int Suppl* 2003:S17–21.
63. Caetano ER, Zatz R, Saldanha LB, Praxedes JN. Hypertensive nephrosclerosis as a relevant cause of chronic renal failure. *Hypertension* 2001;**38**:171–6.
64. Schlessinger SD, Tankersley MR, Curtis JJ. Clinical documentation of end-stage renal disease due to hypertension. *Am J Kidney Dis* 1994;**23**:655–60.
65. Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and prognosis. *Am J Med Sci* 1974;**268**:336–45.
66. Coll de Tuero G, Foguet Boreu Q, Vargas Vila S, Saez Zafra M, Barcelo Rado MA. The usefulness of ophthalmoscopy in risk evaluation of hypertensive patients. *Blood Press* 2002;**11**:263–9.
67. Mujais SK, Emmanouel DS, Kasinath BS, Spargo BH. Marked proteinuria in hypertensive nephrosclerosis. *Am J Nephrol* 1985;**5**: 190–5.
68. Narvarte J, Prive M, Saba SR, Ramirez G. Proteinuria in hypertension. *Am J Kidney Dis* 1987;**10**:408–16.
69. Grunwald JE, Pistilli M, Ying GS, et al. Retinopathy and the risk of cardiovascular disease in patients with chronic kidney disease (from the Chronic Renal Insufficiency Cohort study). *Am J Cardiol* 2015;**116**:1527–33.
70. Wright Jr JT, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *J Am Med Assoc* 2002;**288**:2421–31.
71. Liang S, Le W, Liang D, et al. Clinico-pathological characteristics and outcomes of patients with biopsy-proven hypertensive nephrosclerosis: a retrospective cohort study. *BMC Nephrol* 2016;**17**:42.
72. Dasgupta I, Porter C, Innes A, Burden R. "Benign" hypertensive nephrosclerosis. *QJM* 2007;**100**:113–9.
73. Innes A, Johnston PA, Morgan AG, Davison AM, Burden RP. Clinical features of benign hypertensive nephrosclerosis at time of renal biopsy. *Q J Med* 1993;**86**:271–5.
74. Morduchowicz G, Boner G, Ben-Bassat M, Rosenfeld JB. Proteinuria in benign nephrosclerosis. *Arch Intern Med* 1986;**146**:1513–6.
75. Takebayashi S, Kiyoshi Y, Hisano S, et al. Benign nephrosclerosis: incidence, morphology and prognosis. *Clin Nephrol* 2001;**55**: 349–56.
76. Piper MA, Evans CV, Burda BU, Margolis KL, O'Connor E, Whitlock EP. Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2015;**162**:192–204.
77. Banegas JR, Ruilope LM, de la Sierra A, et al. Relationship between clinic and ambulatory blood-pressure measurements and mortality. *N Engl J Med* 2018;**378**:1509–20.
78. National Institute for Health and Clinical Excellence. NICE Clinical Guideline 127. Hypertension: clinical management of primary hypertension in adults. In: *Unit NGDaR*. Newcastle; 2011. p. 36.
79. Bangash F, Agarwal R. Masked hypertension and white-coat hypertension in chronic kidney disease: a meta-analysis. *Clin J Am Soc Nephrol* 2009;**4**:656–64.
80. Drawz PE, Brown R, De Nicola L, et al. Variations in 24-hour BP profiles in cohorts of patients with kidney disease around the world: the I-DARE study. *Clin J Am Soc Nephrol* 2018;**13**:1348–57.
81. Agarwal R, Andersen MJ. Prognostic importance of clinic and home blood pressure recordings in patients with chronic kidney disease. *Kidney Int* 2006;**69**:406–11.
82. Gabbai FB, Rahman M, Hu B, et al. Relationship between ambulatory BP and clinical outcomes in patients with hypertensive CKD. *Clin J Am Soc Nephrol* 2012;**7**:1770–6.
83. Minutolo R, Agarwal R, Borrelli S, et al. Prognostic role of ambulatory blood pressure measurement in patients with nondialysis chronic kidney disease. *Arch Intern Med* 2011;**171**:1090–8.
84. Pogue V, Rahman M, Lipkowitz M, et al. Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. *Hypertension* 2009;**53**:20–7.
85. Boudville N, Ward S, Benaroia M, House AA. Increased sodium intake correlates with greater use of antihypertensive agents by subjects with chronic kidney disease. *Am J Hypertens* 2005;**18**:1300–5.
86. Brook RD, Appel LJ, Rubenfire M, et al. Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the american heart association. *Hypertension* 2013;**61**:1360–83.
87. Wheeler DC, Becker GJ. Summary of KDIGO guideline. What do we really know about management of blood pressure in patients with chronic kidney disease? *Kidney Int* 2013;**83**:377–83.
88. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 1994;**330**:877–84.
89. Ruggenenti P, Perna A, Loriga G, et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005; **365**:939–46.
90. Appel LJ, Wright Jr JT, Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010;**363**:918–29.
91. Wright Jr JT, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103–16.
92. Cheung AK, Rahman M, Reboussin DM, et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol* 2017;**28**:2812–23.
93. Ku E, Gassman J, Appel LJ, et al. BP control and long-term risk of ESRD and mortality. *J Am Soc Nephrol* 2017;**28**:671–7.
94. Ku E, Ix JH, Jamerson K, et al. Acute declines in renal function during intensive BP lowering and long-term risk of death. *J Am Soc Nephrol* 2018;**29**:2401–8.
95. Zhao P, Xu P, Wan C, Wang Z. Evening versus morning dosing regimen drug therapy for hypertension. *Cochrane Database Syst Rev* 2011:CD004184.
96. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. *Chronobiol Int* 2010;**27**:1629–51.
97. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Bedtime dosing of antihypertensive medications reduces cardiovascular risk in CKD. *J Am Soc Nephrol* 2011;**22**:2313–21.
98. Minutolo R, Gabbai FB, Borrelli S, et al. Changing the timing of antihypertensive therapy to reduce nocturnal blood pressure in CKD: an 8-week uncontrolled trial. *Am J Kidney Dis* 2007;**50**:908–17.

99. Vij R, Peixoto AJ. Management of nocturnal hypertension. *Expert Rev Cardiovasc Ther* 2009;**7**:607–18.
100. Crespo JJ, Pineiro L, Otero A, et al. Administration-time-dependent effects of hypertension treatment on ambulatory blood pressure in patients with chronic kidney disease. *Chronobiol Int* 2013; **30**:159–75.
101. Rahman M, Greene T, Phillips RA, et al. A trial of 2 strategies to reduce nocturnal blood pressure in blacks with chronic kidney disease. *Hypertension* 2013;**61**:82–8.
102. Strippoli GF, Craig M, Craig JC. Antihypertensive agents for preventing diabetic kidney disease. *Cochrane Database Syst Rev* 2005: CD004136.
103. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**:861–9.
104. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**: 851–60.
105. Rahman M, Ford CE, Cutler JA, et al. Long-term renal and cardiovascular outcomes in antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) participants by baseline estimated GFR. *Clin J Am Soc Nephrol* 2012;**7**:989–1002.
106. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008;**359**:2417–28.
107. Bakris GL, Sarafidis PA, Weir MR, et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. *Lancet* 2010;**375**:1173–81.
108. Ku E, Lipkowitz MS, Appel LJ, et al. Strict blood pressure control associates with decreased mortality risk by APOL1 genotype. *Kidney Int* 2017;**91**:443–50.

CHAPTER

47

Approach to the Patient with Chronic Kidney Disease and Renovascular Disease

Stephen C. Textor, Lilach O. Lerman

Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, United States

Abstract

Renovascular disease (RVD) results most commonly from atherosclerotic vascular occlusion. Although clinically significant loss of glomerular filtration rate develops with its more severe forms, RVD is often complicated by widespread cardiovascular manifestations and preexisting microvascular injury, making management of these patients challenging. The kidney adapts to moderate reductions of blood flow and oxygenation, but severe arterial occlusion eventually leads to tissue hypoxia and loss of kidney function. Recent studies demonstrate proinflammatory changes in the renal vasculature preceding kidney injury, which are followed by rarefication of renal microvessels. Tissue inflammation and fibrosis ensue and eventually produce irreversible structural injury that precludes recovery of glomerular filtration. Medical treatment of hypertension, comorbidities, anemia, and electrolyte disorders is fundamental to the management of these patients. Renal revascularization is beneficial for selected patients with progressive decline in kidney function, refractory hypertension, and/or recurrent circulatory congestion or pulmonary edema. Experimental studies indicate that evolving adjunctive measures, including cell-based therapy and mitochondrial protection, may attenuate injury or facilitate renal repair mechanisms for preservation of kidney function.

SCOPE OF THE PROBLEM

Occlusive vascular disease of the main renal arteries gained attention as an important cause of chronic renal failure—and one that could be potentially reversed—only as recently as the 1970s and 1980s.[1] Until then, beginning in the 1930s, renovascular disease (RVD) was recognized primarily as a "secondary" cause of hypertension. Most diagnostic tests until the 1980s were focused on identifying renovascular hypertension that effectively might be "cured" by revascularization. As medical therapy of renovascular hypertension has become more effective, many more kidneys are exposed to prolonged periods of reduced blood flow to the poststenotic kidney. The clinical focus has shifted to preserving and restoring glomerular filtration rate (GFR) by revascularization for carefully selected patients with chronic kidney disease (CKD) and RVD. Recognizing the transition from a hemodynamic process limiting GFR to an active injury with inflammatory, oxidative stress, and profibrotic processes represents an important and evolving paradigm shift in RVD.[2] Preventing irreversible kidney injury thereby can relieve the need for renal replacement therapy (RRT) in some patients and provide major clinical benefits.

Most clinical RVD derives from atherosclerosis and, therefore, is complicated by widespread associated cardiovascular disease and preexisting microvascular injury. The combination of reduced GFR, progressive hypertension, and atherosclerotic disease makes management of these patients exceptionally complex. Clinicians caring for such individuals often include cardiovascular specialists, internists, vascular surgeons, and others. Patients often present to nephrologists with advanced disease, near the time RRT, or maneuvers to manage fluid retention, such as dialysis or ultrafiltration, are being considered. Several prospective trials evaluating the additional role of endovascular stenting for RVD have failed to identify compelling benefits for large groups over the short term, when added to medical therapy. Although these trials have been controversial, the clinical application of renal revascularization has declined in many countries. One result has been the emergence of more patients identified later in the course of chronic renal disease related to vascular occlusion.

This chapter will summarize current and emerging concepts of the role of RVD in the development of

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00047-4

CKD. Although the kidney ordinarily has more blood flow than required for basic viability, critical loss of perfusion remains an important, reversible process nephrologists should understand and plan to identify and treat when indicated. A well-defined approach to a difficult clinical problem will result in better care for patients.

DEFINITION AND PREVALENCE

The term "ischemic nephropathy" was coined to identify patients with a loss of GFR associated with RVD, based on the assumption that reduced blood flow induced a deficit in oxygen supply resulting in kidney injury.[3] More than 80% of patients with occlusive RVD in the US have atherosclerosis. Other disorders including inflammatory vasculitides, such as Takayasu's arteritis, are more common in Southeast Asia where they may account for as many as 60% of cases.[4,5] Some patients develop progressive loss of kidney function with advancing RVD, sometimes leading to total occlusion. The degree of vascular occlusion required to produce these effects has been controversial. Physiologic studies of graded vascular occlusion indicate that development of a measurable pressure gradient, reductions in blood flow, and release of pressor materials such as renin require at least 60% lumen occlusion, and often require 75–80% occlusion (Figure 47.1).[6,7] Hence, biplane imaging studies utilizing estimates of 50% stenosis regularly include individuals with "incidental" or trivial disease without measurable hemodynamic effect. Some authors argue that subtle effects of lesser degrees of occlusion may be important, but this has been difficult to prove.

Community-based population screening studies using high-resolution Doppler ultrasound in the US indicate that up to 6.8% of individuals above age 65 have more than 60% occlusive RVD.[8] This is supported by the identification of visible renovascular lesions by CT angiography in nearly 5% of individuals presenting as potential kidney donors, with the prevalence highly related to age.[9] Most of these lesions are incidental and have minimal hemodynamic or clinical importance for many years. Not surprisingly, atherosclerotic RVD is associated with other vascular disease, such as coronary, aortic, and peripheral vascular disease. Numerous studies over the past two decades suggest that screening high-risk patients will identify coexistent RVD in 14–20% of those undergoing coronary angiography, rising to more than 35% of those with clinical manifestations of aortic and peripheral vascular disease.[10] A review of Medicare claims data indicated that individuals developing identifiable RVD were at substantially higher risk of cardiovascular disease complications, including stroke, new coronary disease, congestive heart failure (CHF), and death over the subsequent few years[11] (Figure 47.2). Such individuals are also at higher risk for progressive renal failure, although this is far less likely than other cardiovascular manifestations. As a result, several treatment trials, including the Angioplasty and STenting for Renal Artery Lesions (ASTRAL) and Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), seeking to examine the role of revascularization in preserving kidney function have been complicated by high rates of non-renal events.[12,13]

Does atherosclerotic RVD contribute to the rising incidence of end-stage renal disease (ESRD) in older individuals? It is widely recognized that stated "causes" of ESRD from the US Renal Data System

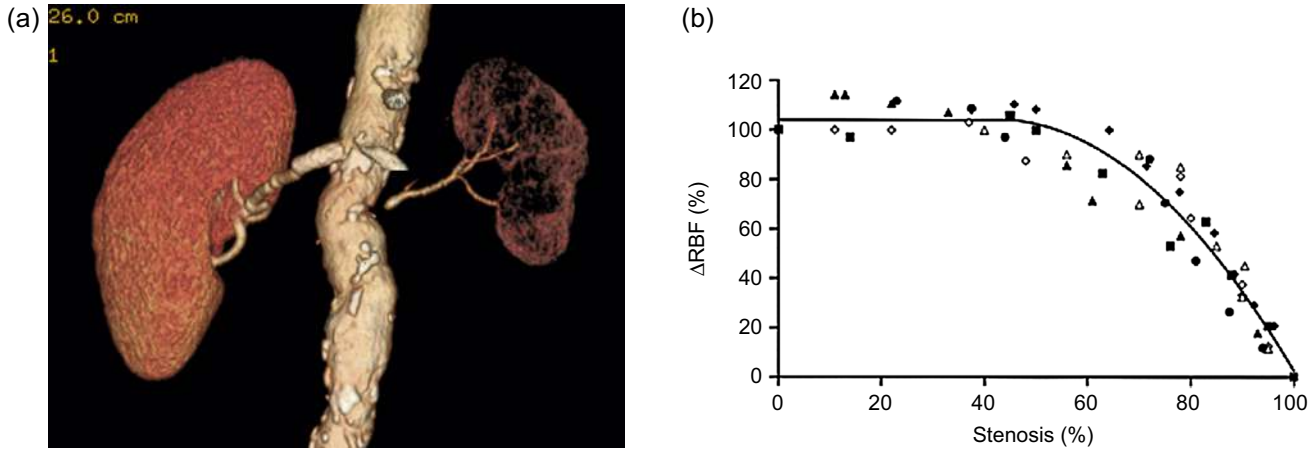


FIGURE 47.1 (a) Atherosclerotic RVD with evident loss of flow and volume. CT angiogram demonstrating vascular occlusion to the left kidney leading to loss of volume, cortical and medullary blood flow reductions, and impaired renal function due to ischemic nephropathy. (b) Measured changes in blood flow in relation to severity of stenosis. Studies of blood flow and metabolic function indicate that lumen occlusion up to 60–70% have little hemodynamic effect in the kidney. Stenoses beyond this degree produce major decrements in blood flow, eventually leading to insufficient perfusion to maintain function.

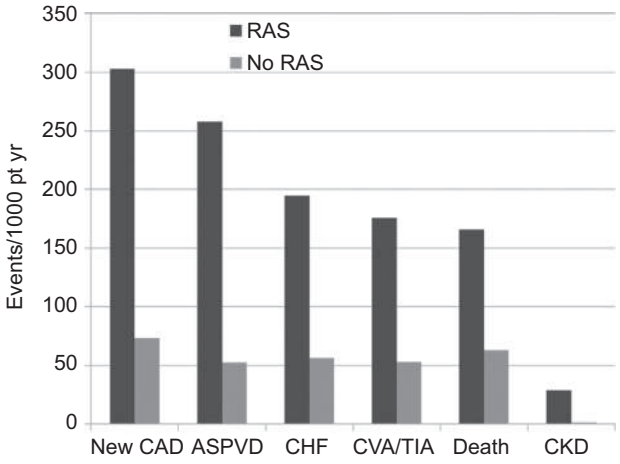


FIGURE 47.2 Relative risks for cardiovascular disease in patients with identified RAS in Medicare Claims data: Patients with newly identified atherosclerotic RAS in the Medicare claims group (*dark bars*) generate substantially more medical event claims over the subsequent 2 yr than those without RAS (*light bars*). These data highlight associated cardiovascular risks, including stroke, death, and congestive heart failure associated with RAS. Although progression to renal failure is more common with RAS than without this claim, it is far less likely than cardiovascular disease events. *ASPVD*, atherosclerotic peripheral vascular disease; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *CKD*, chronic kidney disease; *CVA*, cerebrovascular accident; *TIA*, transient ischemic attack. *After Kalra.*[11]

are highly subjective and rarely reflect precisely determined etiology. Rates of identifiable RVD in newly started dialysis patients without other diseases in small series range as high as 20–40%.[10,14,15] Medicare claims data for more than 160,000 individuals indicate that up to 9.7% of new ESRD patients have identified atherosclerotic RVD, but fewer than half were designated with this as the primary cause of renal disease. Hence, some authors estimate that about 5% of otherwise unexplained ESRD may be driven by occlusive RVD in the US.[16] Isolated case reports identify some individuals with substantial recovery of kidney function and/or stabilization of blood pressure and cardiovascular status after restoring blood flow to the kidney, although this is not common.[17] Retrospective series of azotemic patients undergoing renal revascularization indicate that between 25 and 30% of such individuals have meaningful recovery of kidney function, defined in one series as a fall in serum creatinine (S[Cr]) of more than 1.0 mg/dL.[18] Follow-up studies of patients whose GFR improves after revascularization indicate distinctly better survival and reduced morbidity as compared with those with deteriorating kidney function.[19,20] Enthusiasm for widespread renal revascularization has been tempered, however, by the fact that some patients have adverse events. No prospective treatment trial to date has demonstrated reduced overall rates of either renal or cardiovascular endpoints associated with renal revascularization. More than ever, careful selection is paramount for patients considered for either vascular or reparative intervention (see below).

PATHOPHYSIOLOGY OF CKD WITH RENOVASCULAR DISEASE

Atherosclerotic RVD can accelerate hypertension by multiple mechanisms that do not necessarily require reduction of GFR, including activation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic adrenergic system. RVD also complicates sodium homeostasis by impairing sodium excretion, leading both to resistance to antihypertensive drug therapy and to worsening circulatory congestion associated with heart failure. These features lead to multiple clinical manifestations separate from the loss of kidney function and are beyond the scope of this discussion.[21,22] We focus on specific mechanisms by which kidney function is threatened in this disorder.

Hemodynamic Features Specific to the Kidney

The kidney vasculature is complex and heterogeneous, consistent with localized functions of glomerular filtration in the cortex and active solute transport in deeper regions, particularly within the medulla. Whole kidney estimates indicate that less than 10% of blood flow is required strictly for the metabolic demands of the entire organ.[23] Cortical blood flow is several-fold higher than that to medullary regions, consistent with its function as a filtering site. The medulla is primarily the site of descending and ascending tubular structures associated with transepithelial electrolyte transport and developing concentration gradients that require ATP-dependent energy. As a result, oxygenation follows a gradient with high levels in the cortex decreasing to distinctly hypoxic levels in deeper medullary segments, leaving these regions continually near the brink of "hypoxia."[23] The normal kidney tolerates this oxygenation gradient remarkably well, and tissue oxygen levels within each region remain stable over a wide range of maneuvers that alter whole kidney blood flow[24] (Figure 47.3).

Studies using Blood Oxygen Level Dependent (BOLD) magnetic resonance in humans demonstrate that despite chronic reductions in renal blood flow averaging 25–30% beyond a stenotic lesion, tissue oxygenation within both cortex and medulla remain well preserved and similar to those of subjects with essential hypertension.[25] Preservation of oxygen supply appears partly due to reduced glomerular filtration and thereby reduced medullary oxygen consumption from active

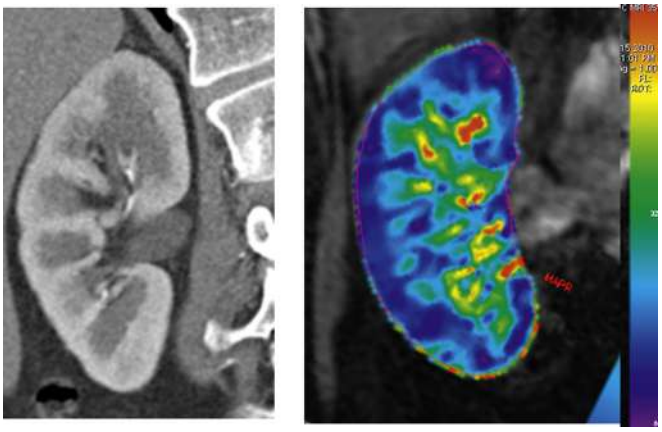


FIGURE 47.3 Coronal view of CT angiogram of a normal kidney (left panel) illustrating cortical and medullary contrast distribution associated with differential blood flows. The right panel contains an R2* parametric map from a Blood Oxygen Level Dependent MR image depicting levels of deoxyhemoglobin (scale on far right). Cortical levels of deoxyhemoglobin are low, reflecting high blood flows and abundant oxygenation. Deeper segments develop a gradient with progressively increasing deoxyhemoglobin in medullary segments with lower blood flow and high oxygen consumption (see text). These characteristics reflect the normal kidney's complex configuration of capillary beds in series, first to the cortex and glomerular filtration sites, then to post-glomerular capillaries extending into the medullary region.

transport. These observations provide reassurance that antihypertensive drug therapy to lower perfusion pressures and blood flows to many poststenotic kidneys may not directly induce or worsen hypoxic injury. Hence, medical therapy of renovascular hypertension as conducted in prospective trials for moderate RVD has been tolerated without identifiable kidney injury, sometimes for many years. Similar studies in patients with more advanced renovascular occlusion (identified by higher degrees of stenosis on duplex ultrasound and more severely reduced GFR) identify obvious limits to this point. Severe arterial occlusion eventually reduces blood flow, and tissue oxygenation, in both cortex and medulla[26,27] Hence, there are clearly limits of the kidney's ability to "adapt" to reduced blood flow and oxygenation beyond arterial occlusion.

EMERGING PARADIGMS OF KIDNEY INJURY BEYOND ARTERIAL OCCLUSIVE DISEASE

Large Vessel Pathology

Because of its dense vascular supply, the kidney is subject to alterations of vascular endothelial function, recognized as a prodromal phase associated with systemic atherosclerotic disease. Elevations of cholesterol, aging, and smoking induce limitations in the availability of nitric oxide (NO) and increase local production of endothelins.[28] These changes are associated with altered endothelial regulation of inflammatory cytokines, chemokines, and nuclear factor-kappa B throughout the systemic vasculature. Studies in the main renal artery segments from human subjects demonstrate that proinflammatory changes are evident before measurable renal dysfunction ensues.[29] These changes lead to alterations of T-cell function and distribution in circulatory lymphocytes. When vessels from such patients are examined at autopsy, the main renal arteries demonstrate intimal inflammatory changes as part of the atherosclerotic lesion proximal to the kidney. Histologic changes in the renal arterial wall resemble those occurring in other vascular beds during atherogenesis, and the ultimate plaque constituents are similar to coronary arterial lesions.[30]

Small Vessel Changes

The kidney is unique in having capillary beds in series, as the efferent glomerular vessels become the inflow to the vasa recta descending into medullary segments alongside renal tubules. These vessels are especially sensitive to changes in the microvascular milieu that can be affected by alterations in vasoactive substances, including NO, prostaglandins, endothelins, vascular endothelial growth factor (VEGF), and other factors that modify endothelial function. Modifications in endothelial function associated with dyslipidemia, smoking, diabetes, and aging alter vessel dimensions and remodeling that predispose to local fibrosis.[31] Short-term ischemia often leads to upregulation of growth factor expression and new vessel formation, yet this compensatory mechanism seems to be lost during exposure to chronic ischemia, particularly in the kidney. Furthermore, newly formed vessels are often fragile, hyperpermeable, and prone to dropout. Superimposing repeated episodes of reduced perfusion has the capacity to magnify functional rarefication of these vessels, effectively impairing local blood supply[31] (Figure 47.4a).

In the microenvironment of renal ischemia, microvessels are exposed to noxious insults like reactive oxygen species (ROS), which increase renal vascular tone and impair endothelial cell integrity, contributing to endothelial dysfunction.[32] The most prominent vascular changes associated with chronic RVD involve remodeling (e.g. wall thickening) and loss of intrarenal microvessels (<500 μm in diameter),[33] including interlobar, arcuate, interlobular arteries, and small arterioles (<200 μm), which are responsible for intrarenal distribution of blood. The spatial density of small outer cortical microvessels (<40 μm) in RVD correlates directly with GFR, implicating them in renal dysfunction.[34] Renal

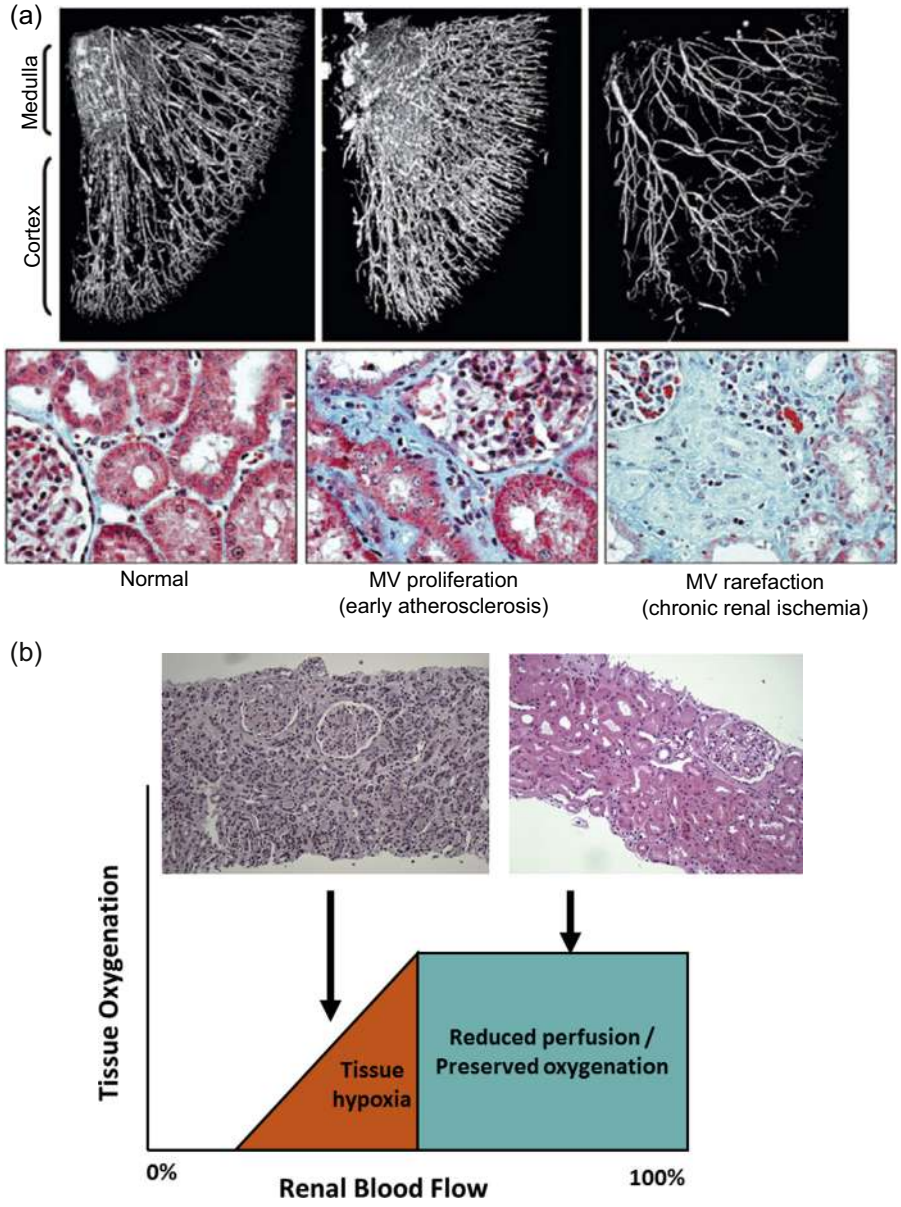


FIGURE 47.4 (a) Vascular rarefication developing beyond a stenotic lesion in experimental atherosclerotic RAS as shown by a postmortem micro-CT image. The complex vascular arrangements within the cortex and medulla are susceptible to both functional and structural "rarefication" during sustained reductions in perfusion, particularly when additional microvascular injury is present (see text). (b) Tissue oxygenation as a function of renal blood flow to the kidney. Unlike brain or heart muscle, tissue oxygenation is well preserved despite substantial decrements (up to 30–45%) in blood flow with relative preservation of tubular and glomerular structures. With more severe decrements in blood flow, tissue oxygenation falls and active inflammatory processes ensue, leading to loss of tubular structures in interstitial fibrosis (above). At some point, restoration of main vessel patency no longer abrogates this process and has little effect on restoring tissue integrity and/or function.

microvascular disease is also associated with decreased expression of angiogenic proteins, like VEGF, which promote cell functions essential to sustain and repair the renal microvasculature.[33]

Some authors emphasize the distinction between "functional" rarefication of these microvessels, in which perfusion is diminished but the vascular structures remain intact, and "structural" rarefication, in which the vessels are eliminated by progressive fibrosis.[35] This may be an important distinction, insofar as "functional rarefication" may have greater potential for vascular repair under the influence of local reparative mechanisms known to be active, particularly in the renal medulla.[36] Experimental studies demonstrate the capacity for infusions of VEGF or extracorporeal ultrasound shock wave therapy,[37] for example, to restore functional perfusion in renal microvessels in a swine model of RVD.[38]

Mitochondrial Dysfunction and Injury

RVD is associated with structural and functional abnormalities of renal mitochondria.[39] Prolonged hypoperfusion triggers oxidative stress and inflammation, impairing mitochondrial bioenergetics and compromising the integrity of the inner mitochondrial membrane. Rapid restoration of blood flow during angioplasty may also amplify inflammation and oxidative stress in the poststenotic kidney (ischemia-reperfusion injury), contributing to mitochondrial injury and inadequate recovery following percutaneous renal angioplasty (PTRA). Patients with RVD present with elevated urinary levels of mitochondrial DNA, surrogate markers of mitochondrial injury.[40] Urinary mitochondrial DNA correlates with markers of renal injury and dysfunction and varies as a function of estimated GFR (eGFR) after therapy, underscoring the role of this organelle in renal damage in human RVD.

Transition from Hemodynamic to Inflammatory Injury

A striking feature from pathologic examination of both experimental and human studies of atherosclerotic RVD is the presence of inflammation in advanced disease (Figure 47.4b). Nephrectomy samples from patients with total occlusion demonstrate clusters of T cells and enhanced transforming growth factor-beta (TGF-β) in many subjects, which are somewhat less prominent in patients treated with statins.[41] Experimental studies in Smad3 knockout animals missing the downstream effector pathway for TGF-β indicate a major degree of protection from tubular atrophy and interstitial fibrosis despite high-grade vascular occlusion.[42] Transjugular poststenotic kidney biopsies from humans demonstrate widespread tissue immunostaining for TGF-β and a stepwise increase in both T cells and macrophages (CD68+ cells), compared with implantation biopsies obtained from normal kidney donors.[43] Both experimental models of RVD and human studies indicate robust cytokine release, including net secretion of tumor necrosis factor (TNF)-alpha and IL-6, from the poststenotic kidney, consistent with the activation of inflammatory pathways.[44] Once these injury pathways have been activated, restoration of vessel patency has only limited effectiveness on restoring kidney function. Repeat measurements of renal vein cytokines three months after technically successful revascularization and resolution of evident tissue hypoxia measured by BOLD magnetic resonance techniques indicate ongoing release of inflammatory cytokines, suggesting that restoring vessel patency alone does not reverse this process.[45] Experimental studies confirm that high renal vein cytokine release in a swine model of RVD predicts blunted renal recovery after revascularization.[46]

Fibrogenesis

Ultimately, profibrotic pathways become activated and lead to interstitial fibrosis. As this process ensues, microvascular occlusion leads to structural breakdown of tubules and a high prevalence of atubular glomeruli. Even if fibrosis were reversed, the lack of structural nephron components effectively limits recovery of meaningful glomerular filtration. Taken together, CKD associated with RVD undergoes a gradual transition from a hemodynamic disorder induced by impaired blood flow (to which the kidney partially can adapt) to a disorder eventually characterized by activation of tissue inflammation and fibrosis that no longer depends mainly on hemodynamic compromise. Hence, while restoring vessel patency and blood flow may be critical to restore function at some time points, it is equally clear that revascularization alone is ineffective under conditions when CKD is no longer primarily a hemodynamic problem. This is an important point for nephrologists to recognize during clinical management of patients with RVD. Identifying this transition and developing tools to reverse parenchymal injury remain areas where improved diagnostic tools and adjunctive therapy are sorely needed.

CLINICAL SYNDROMES WITH RVD AND CKD

Table 47.1 summarizes clinical manifestations most commonly associated with atherosclerotic RVD. Most of these are nonspecific, and also associated with other causes of CKD. Hence, recognizing clinical features more specific to RVD depends on clinical suspicion and perhaps most importantly, the clinician's

TABLE 47.1 Clinical Manifestations of Atherosclerotic Renovascular Disease (RVD)

Incidental Renal Artery Stenosis: normal renal function and blood pressure
Renovascular Hypertension: *de novo* or accelerated phase of treated essential HTN
Chronic Kidney Disease: "ischemic nephropathy"
Unilateral asymmetric or atrophic kidney
Bilateral RVD and/or solitary functioning kidney
Deteriorating GFR during antihypertensive drug therapy
Acute "functional renal insufficiency" during ACEI/ARB therapy
Circulatory congestion with impaired sodium/volume control
Refractory congestive heart failure
Rapidly developing ("flash") pulmonary edema

commitment to intervene if high-grade RVD is identified. Much of this commitment depends on the perceived balance of risk vs. benefit for an individual patient. Hence, defining the actual severity of each of the following manifestations is the first step in evaluating RVD.

Hypertension

Hypertension is nearly universal in this disorder, although occasional cases of ischemic renal atrophy occur with normal blood pressures. Most often, patients have a background of essential hypertension and other cardiovascular risk factors, including smoking and dyslipidemias.[47] In the age group at risk for atherosclerotic disease, preexisting hypertension sometimes worsens with rapid development of target-organ injury (such as a stroke or encephalopathy). Such a rapid or recent change often leads to diagnostic studies that reveal the presence of RVD. How long it has been present or how directly it participated in the blood pressure change is often unclear. Previous studies of renovascular hypertension focused on cases of severe, refractory hypertension for which medical therapy was intolerable or ineffective.[48] With the widespread use of agents that block the RAAS and other potent antihypertensive drugs, refractory hypertension is less commonly encountered from RVD than before. Other factors including obesity, sleep apnea, medication adherence, and other forms of CKD likely are more commonly encountered. Several small prospective trials in the 1990s comparing drug therapy to renal revascularization (primarily with angioplasty) failed to demonstrate major differences for all but a small fraction of patients with renovascular hypertension.[49] Crossover rates from medical therapy to renal revascularization ranged from 26 to 44% in these trials conducted over 6 months to 2 yr,[50–52] but have been substantially lower in recent prospective trials (6% in ASTRAL). Based on the observation that many patients "adapt" to reduced blood flow without major loss of kidney function or demonstrable tissue hypoxia, many argue that RVD with hypertension should be treated primarily with drug therapy. If BP and renal function are stable, little is to be gained by further diagnostic studies and specific vascular intervention, as long as the degree of vascular occlusion and kidney function remain stable.

Rapidly Developing Circulatory Congestion

Rapidly developing or refractory circulatory congestion, sometimes designated "flash pulmonary edema," is an increasingly recognized syndrome associated most often with bilateral RVD.[53] This disorder has complex elements related to the impaired sodium and volume excretion associated with RVD and poor kidney perfusion. The syndrome also appears to be related to relatively rapid rises in blood pressure that produce sudden impairment of left-ventricular function.[53] Patients are often caught between extremes of hypertension with CHF followed by intensive diuresis leading to volume depletion and azotemia. Mortality rates for patients with CHF and RVD are higher than those with CHF alone.[19,54] Renal revascularization has been associated with dramatic improvement in symptoms of CHF and reduced hospitalizations.

Deterioration of Kidney Function

Deterioration of kidney function related to RVD is a major clinical issue. Moderate hemodynamic reduction of filtration appears to be within the range of adaptation of the normal human kidney. For such patients, restoring vessel patency can increase GFR and lead to "recovery" of renal function, even for some patients with reduced GFR for a long period of time.[17] It may be argued that essentially all patients with otherwise unexplained loss of GFR should undergo some evaluation to exclude reversible disease (such as obstructive uropathy and/or RVD). Such diagnostic studies frequently identify some degree of vascular occlusion. The challenge is to define (1) to what extent RVD is primarily responsible for the loss of GFR and (2) whether restoring renal vessel patency is likely to result in recovery or stabilization of function.

Loss of GFR with Renin–Angiotensin System Blockade

Loss of GFR associated with renin–angiotensin system blockade merits specific consideration. Physiologic studies in the dog established that under conditions of normal sodium intake and normal blood flow, filtration pressures throughout the length of the glomerulus are maintained without angiotensin.[55] As perfusion pressures and afferent blood flows are reduced, however, activation of the renin–angiotensin system becomes essential to support filtration by increasing efferent arteriolar resistance.[56] Blockade of this effect can lead to abrupt loss of transcapillary filtration pressures and reduced GFR, even at levels of blood flow that are sufficient to maintain the kidney parenchyma. Hence, this has been termed "functional" acute renal failure associated clinically first with ACE inhibitors, but thereafter with nearly all agents that block the renin–angiotensin system, including angiotensin-receptor blockers.[57] The first clinical reports of this phenomenon were from patients with bilateral renal artery

stenosis or stenosis to a solitary functioning kidney.[58] Later reports suggest that similar changes could occur in patients with microvascular disease, particularly under conditions of volume depletion and/or diuretic use. As a result, identifying an acute loss of GFR after starting ACEIs/ARBs merits strong consideration as a signal that RVD approaching a critical level is present. Some authors recommend routinely withholding RAAS blockade as patients develop advancing CKD for the same reason.[59]

Recent Development of Progressive CKD without Other Explanation

Many, if not most, causes of CKD in older patients follow a relatively indolent rate of progression, including those attributed to nephrosclerosis and diabetes. Average loss of GFR was −2 mL/min/1.73 m^2/yr in the AASK trial and approximately −4 mL/min/1.73 m^2/yr in the MDRD trial. Loss of GFR in patients with RVD can appear to be especially variable, particularly when changes appear to be associated with adjustment of blood pressure levels and therapy.[57,60,61] A series of prospectively studied patients subjected to renal revascularization indicates that the likely change in renal function, specifically whether the slope of change in GFR would be positive, was related directly to the rate of loss of GFR in the months preceding revascularization[62] (Figure 47.5).

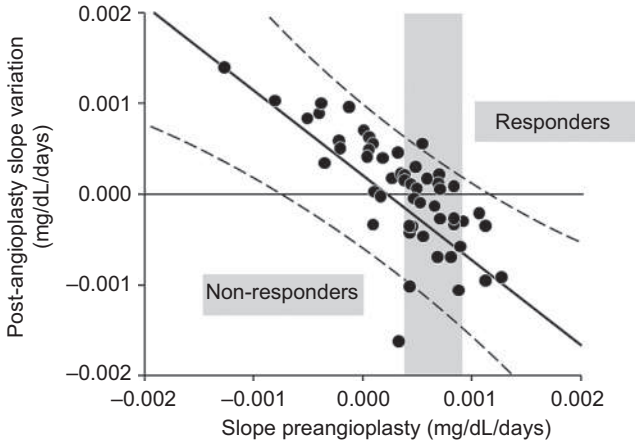


FIGURE 47.5 Plot of the rate of change in GFR (slope) before renal revascularization vs. the slope observed after revascularization. The likelihood of achieving a positive slope, i.e. recovery of kidney function, was strongly related to the rate of deterioration prior to undergoing renal revascularization. Other criteria, such as renal resistive index, biopsy characteristics, proteinuria, and evidence of tissue oxygenation, may provide insight as to the degree of reversibility but have not been studied in large populations prospectively. *Data from Muray et al.,[62] with permission.*

Loss of Kidney Function in Patients after Endovascular Stent Grafting

In recent years, endovascular grafts have gained widespread application to limit the risk of expanding abdominal aortic aneurysms. These aneurysms commonly are located adjacent to one or more renal arteries. Recent stent-graft designs sometimes migrate or are placed deliberately over the renal artery origins leading to an acquired iatrogenic form of renovascular occlusion.[63,64] Loss of renal function after endovascular aneurysm repair is a recognized risk associated with this therapy and carries measurable long-term risk for morbidity and mortality.[64,65] Recognition and restoration of blood flow can limit the loss of function and materially improve outcomes related to survival and avoidance of CKD.

DIAGNOSTIC CONSIDERATIONS IN CKD ASSOCIATED WITH RVD

The issues surrounding RVD are complex and include both characterizing the state of the vasculature and the state of the kidney. Implicitly, these questions must address both the severity of hemodynamic compromise and the viability of the poststenotic kidney, with particular emphasis on whether or not restoring blood flow will provide a net benefit or not.

The renal macro-vasculature is most commonly evaluated using noninvasive imaging modalities, including renal artery duplex ultrasound (RADUS), computerized tomographic (CT) angiography, and/or magnetic resonance (MR) angiography. Invasive contrast angiography remains the "gold standard" for most clinicians but is usually reserved for patients undergoing therapeutic intervention, usually with PTRA with stenting.

RADUS currently is the least expensive method of evaluating the renal vessels, primarily by evaluating Doppler velocities. Peak systolic velocities (PSVs) above 180−200 cm/sec and/or a renal to aortic ratio above 3.5 are thought to usually reflect a "significant" stenotic lesion. The correlation between PSV and severity of stenosis is variable, however, and the clinical significance rises with higher velocities. The CORAL trial set 300 cm/sec as a threshold for RADUS criteria to be considered for randomization.[66] This technique remains operator and center dependent and can demand both ultrasonographer expertise and time. In our center, these imaging values are most useful when "positive," as accessory vessels can sometimes be missed and areas of high velocity can be overlooked if the entire course of each renal artery is not imaged. Imaging segmental

vessels in both systole (end systolic velocity, or ESV) and diastole (end diastolic velocity or EDV) allows calculation of a "resistive index" defined as (1-(EDV/ESV)) × 100%. Higher levels of resistive index (nominally set above 80%) are associated with parenchymal fibrosis and a lower likelihood of recovering GFR after technically successful revascularization.[67] This has been questioned in other series,[68] but overall consensus has been that lower resistive index is associated with higher likelihood of preserved function.[69] Imaging the kidneys with ultrasound also provides measurements of kidney size, parenchymal thickness, cystic disease, and outflow tract obstruction.

CT angiography (Figure 47.1) provides ever higher resolution and precise characterization of main vessel anatomy, small vessel aberrations including fibromuscular dysplasia and renal arterial aneurysms, in addition to identifying vascular calcification, parenchymal thickness, perfusion, and structural integrity. Radiation exposure continues to fall as a function of multiple detector and rapid acquisition technology, as does contrast exposure.

MR angiography avoids radiation exposure and can provide excellent vascular imaging with gadolinium contrast. Its use in CKD patients with contrast has declined after reports of nephrogenic systemic fibrosis in patients with reduced GFR and repeated exposure. As a result, newer imaging techniques attempt to achieve vessel and perfusion measurements without contrast. BOLD MR has been proposed as a method to evaluate tissue oxygenation within both cortex and medulla, using the properties of deoxyhemoglobin as a paramagnetic modifier of local magnetic dipole polarization.[70–72] Analytical techniques for interpreting deoxyhemoglobin maps remain investigational, but these tools clearly are suited for identifying expanding hypoxic zones within kidneys severely affected by RVD.[73–75] They hold enormous promise for identifying hypoxic kidneys and for evaluating the effects of modifying blood flow and/or oxygen consumption in nearly "real time" without contrast or radiation exposure. Other experimental techniques using MR, such as diffusion-weighted imaging or MR elastography, offer the potential to examine development of kidney fibrosis *in vivo.*

The State of the Kidney

Remarkably little attention has been focused on the degree of parenchymal injury and potential for recovery in discussing CKD associated with RVD. Individuals with atherosclerotic RVD are typically older and have a long exposure history to the atherosclerotic milieu, often complicated by hypertension, obesity, and smoking. Histologic characterization of parenchymal injury in such patients is associated with reduced function and progressive CKD,[76] although these features are not closely related to the degree of stenosis.[61] Pathologic estimates of the degree of fibrosis and atherosclerotic disease from nephrectomy specimens vary widely.[41] Implantation biopsies from kidney donors demonstrate substantial preexisting interstitial fibrosis and changes attributed to "nephrosclerosis" as a function of age that are not closely related to blood pressure.[77,78] Intraoperative biopsy samples during renal revascularization identify evidence of atheroemboli in many patients (36%) that predicted poor long-term survival.[79] The presence of both interstitial inflammatory and fibrotic changes in these patients led some to suggest that vascular occlusive disease is only one of several contributors to the CKD in this setting.[80]

Recent studies emphasize the role of inflammatory changes, both in the renal vessels and in the kidney parenchyma. Kotliar et al. identified T-cell infiltrates within the vascular wall of early atherosclerotic RVD that corresponded to alterations in T-cell populations in peripheral blood.[29] These cell populations were vastly expanded in autopsy samples obtained in a different group of subjects, suggesting to the authors that early inflammatory changes within the renal vasculature precede both severe occlusion and clinical CKD. Gloviczki et al. reported findings obtained from transjugular biopsies of the poststenotic kidney in atherosclerotic RVD.[43] When compared to implantation biopsies from normal kidney donors or nephrectomy specimens from RVD with total occlusion, the moderate RVD patients had severely elevated tissue levels of TGF-β. Groups with more severe vascular occlusion demonstrated ever higher cellular infiltrates of T cells and macrophages (defined as CD68+ cells). Sampling of the renal veins demonstrated substantial increases in inflammatory cytokines, including monocyte chemoattractant protein-1, IL-6, and TNF-α, in addition to elevated circulating neutrophil gelatinase-associated lipocalin.[44] Although renal revascularization did improve cortical blood perfusion and reversed hypoxia in a group of patients with high-grade atherosclerotic RVD, it generally failed to reverse these inflammatory cytokine signatures or restore GFR.[45] Taken together, we interpret these data to indicate that vascular occlusive disease may initiate and/or provoke CKD and inflammatory injury, but once in progress, revascularization alone fails to reverse many of these processes.

TREATMENT OF CKD ASSOCIATED WITH RVD

Medical Therapy for CKD Associated with RVD

The mainstay of treating CKD in this instance is similar to that employed for most other causes, specifically achieving blood pressure control, limiting atherosclerotic risk and complications, treating anemia and electrolyte disorders, and monitoring progressive disease. Normally, these maneuvers will be essential both for initial and ongoing therapy, regardless of other interventions. Antihypertensive drug therapy with RAAS-blocking drugs in RVD has a particular predilection for unmasking "near critical" vascular occlusion by producing a functional fall in filtration. Remarkably, a clinically detectable rise in S[Cr] after RAAS blockade is uncommon even in patients with known bilateral RVD.[81] A prospective registry of 621 patients treated over a decade in the United Kingdom indicated that 357/378 (92%) of patients treated with RAAS blockade experienced no adverse events, including 54/69 (78%) of those with known RVD above 60% lumen occlusion. On a statistical basis, those treated with ACEI/ARB therapy had lower mortality during follow-up, an observation consistent with other reports.[82–84] 16 of 21 patients that were "intolerant" to RAAS blockade were rechallenged after revascularization and treated successfully with ACEIs. Hence, application of RAAS blockade should be part of medical therapy in this condition, albeit with awareness of the potential changes in both serum potassium (S[K]) and S[Cr] that sometime occur. These are usually evident within a few days after starting therapy, arguing for clinicians to recheck laboratory values sometime in the first week. Targeted therapy to withdraw tobacco use and administer statin-class therapy should be attempted—both for the likely reduction in atherosclerotic risk and for additional effects that appear to reduce inflammatory injury within the kidney parenchyma.

As with other vascular occlusive diseases, periodic reevaluation of the vascular stenosis generally is warranted. Prospective RADUS studies in the 1990s indicated that high-grade (>60%) occlusion from atherosclerotic disease progresses in severity in more than half the cases (defined as a rise in velocity by more than 100 cm/sec).[85] Remarkably, these changes are often barely detectable clinically, with a fall in kidney length by more than 1 cm developing in 5.5–20% depending on initial severity, and a measurable rise in S[Cr] in less than 10%.[86] As a practical matter, the clinical issue resides primarily in whether progressive disease now affects the entire functioning renal mass, i.e. both kidneys or stenosis to a solitary functioning kidney.

Some authors argue that progressive deterioration in GFR—from nearly any cause—merits withdrawal of RAAS blockade.[59] For CKD associated with RVD, this approach makes especially good sense and may allow recovery of renal function on a hemodynamic basis. Such a development may signal the potential benefit of revascularization as noted above.

Renal Revascularization for CKD Associated with RVD

Removing vascular obstruction would seem to be an obvious step in treating RVD. From the perspective of interventionalists and vascular surgeons, this has immediate face validity, although multiple series and several small, prospective trials until now fail to identify consistent or clinically significant recovery of function. An important element in this discussion is the heterogeneity of outcomes for all forms of revascularization, including angioplasty, endovascular stenting, and surgical bypass. Results from more than 300 azotemic patients (pretreatment S[Cr] >2.0 mg/dL) subjected to surgical revascularization indicate that nearly 28% had a "significant" fall in S[Cr] (i.e. more than 1.0 mg/dL).[18] Most (52%) experienced essentially no change, whereas 20% actually had important worsening of kidney function (rise of S[Cr] by more than 1.0 mg/dL). As a result, overall group average levels of S[Cr] did not change. Similar results have been seen in numerous series, regardless of the specific revascularization procedure or level of change in function defined as "worthwhile."[87,88] There is little doubt that the group with improved renal function in this series had a major clinical benefit, with improvement in function and blood pressure control evident for years. Those with no change, it may be argued, were unlikely to develop progressive disease. The group with deterioration of kidney function, however, commonly developed ESRD within the year and/or died. Similar outcomes have been reported in surgical series from Wake Forest, in which long-term survival improved only in those with increased eGFR after successful surgical revascularization.[89]

In recent years, endovascular stenting has become the initial and preferred procedure for renal revascularization in atherosclerotic RVD,[64] with surgical reconstruction being limited to failed stenting and/or complex aortic surgical reconstructions. The results of surgical series have been expanded within the context of recent prospective trials conducted over relatively short terms. In the STAR trial, reductions in creatinine clearance occurred in 16–22% but were not different between those treated with stents or medical therapy only.[90] Results from the ASTRAL trial indicate progression to a "renal endpoint" in 20–22% after 5 yr, but outcomes

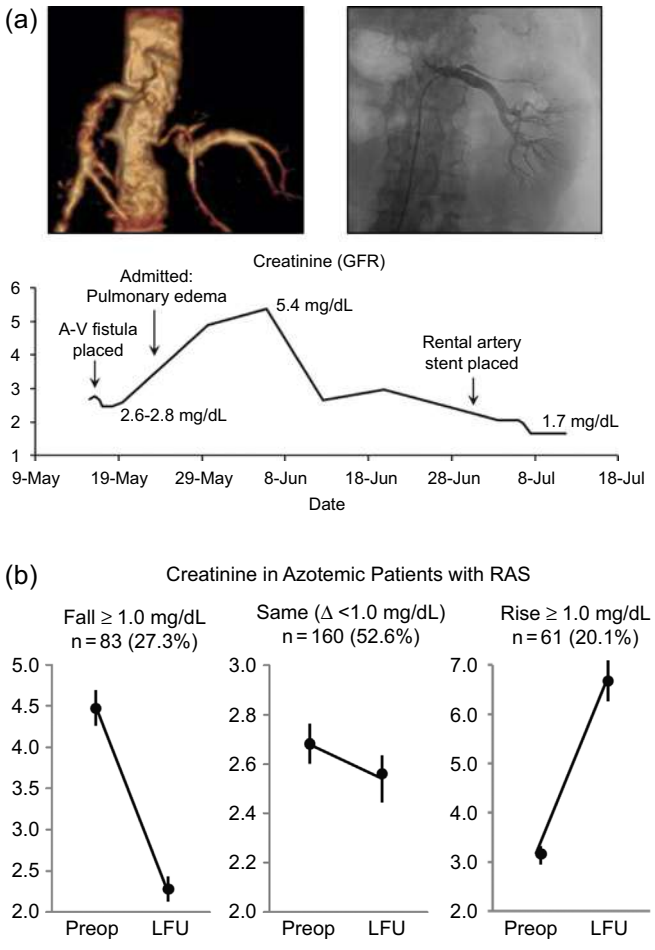


FIGURE 47.6 (a) S[Cr] levels during progression of RVD in a 62-yr-old woman with a solitary functioning kidney. Gradual development of azotemia led to creation of an arteriovenous fistula and preparation for dialysis. An episode of pulmonary edema, severe hypertension, and worsening kidney function prompted identification of a high grade lesion with RVD. Temporarily withholding RAAS blockade and renal artery stenting led to recovery of kidney function. Blood pressure control and kidney function have now been stable for more than 5 yr without requiring dialytic support. (b) Follow-up values of S[Cr] in more than 300 patients with S[Cr] levels above 2.0 mg/dL subjected to renal revascularization. Although 27% of these individuals had major clinical improvements in GFR, these were offset by 20% whose function deteriorated soon afterward. As a result, mean values for the entire group did not change. These results are consistent with numerous other reports and prospective trials indicating heterogeneous outcomes after all forms of revascularization to date. *From reference 10, with permission.*

did not differ, on average, between those with stenting and those without.[12] Overall cardiovascular outcomes did not differ in CORAL, for which progressive renal dysfunction (16–20%) was the single most common outcome in both stented and nonstented patients.[13] Such group averages obscure the differences between those with clinical improvement and those whose renal dysfunction progressed. In the latter two trials, reported overall cardiovascular endpoints were two- to threefold more common than renal events.[91] As a result, heterogeneity among patients and their comorbid diseases has been so great as to make clinical benefits from restoring the blood supply to the kidney in RVD unpredictable.

Do the negative results from these trials indicate that revascularization of the kidney is of no benefit? Figure 47.6 illustrates one case in which progressive CKD was identified in a woman with a solitary functioning kidney and a nonfunctioning kidney related to multiple cysts. With the development of rising S[Cr], preparation for RRT was made with creation of dialysis access. After an episode of worsening hypertension and azotemia, the responsible clinicians identified high-grade RVD to the functioning kidney. Renal function improved slightly after removing the ACEI in her drug regimen. Renal artery stent placement lowered blood pressures and restored kidney function to baseline levels consistent with her solitary kidney. This individual now has done well for more than 5 yr after revascularization. Observational series from "high-risk" subsets with rapidly deteriorating GFR and severe hypertension, as well as episodes of circulatory congestion, demonstrate major improvements in survival as compared with medical therapy alone.[19] In such instances, the net benefit of identifying and treating RVD has major outcome and mortality consequences that should not be overlooked. Table 47.2 summarizes a recent review of renal artery stenting and the recommendations that might be applied in considering the relative merits of medical therapy and surveillance only vs. medical therapy and revascularization. Development of additional tools to identify "viable" or "hibernating" kidneys that can benefit from revascularization and recover GFR is a high priority in this field (Table 47.3).

Adjunctive Therapy: Role of Mitochondrial Protection, Cell-Based Therapy, and Other Protective Measures

The aforementioned clinical data indicate that CKD associated with RVD often does not reverse after restoring vessel patency alone. The processes of injury within the kidney are dynamic and undergo a transition from a hemodynamic to inflammatory/profibrotic processes. It is also possible that suddenly flooding the kidney with highly oxygenated blood after a period of prolonged flow reduction may induce "ischemia/reperfusion" injury, analogous to that observed in muscle and

TABLE 47.2 Functional Classification for Atherosclerotic Renal Artery Stenosis

Grade	Manifestations
Grade I	Renal artery stenosis present, but no clinical manifestations (normal blood pressure and normal renal function)
Grade II	Renal artery stenosis present, but patients have medically controlled hypertension and normal renal function
Grade III	Renal artery stenosis present and patients have evidence of abnormal renal function, medically refractory hypertension, or evidence of volume overload

TABLE 47.3 Major Features That Influence Revascularization vs. Surveillance Therapy for Occlusive Renovascular Disease

FACTORS FAVORING MEDICAL THERAPY AND REVASCULARIZATION FOR RENAL ARTERY STENOSIS
Progressive decline in GFR during treatment of hypertension
Failure to achieve adequate blood pressure control with optimal medical therapy
Rapid or recurrent decline in the GFR in association with a reduction in systemic pressure
Decline in GFR during therapy with ACEIs or ARBs
Recurrent congestive heart failure in a patient in whom the adequacy of left ventricular failure does not explain the cause
Absence of other primary kidney disease and/or proteinuria
FACTORS FAVORING MEDICAL THERAPY AND SURVEILLANCE OF RENAL ARTERY DISEASE
Controlled blood pressure with stable renal function
Stable renal artery stenosis without progression on surveillance studies (e.g. serial duplex ultrasound)
Advanced age and/or limited life expectancy
Extensive comorbidities that make revascularization too risky
High risk or previous experience with atheroembolic disease
Other concomitant renal parenchymal diseases that cause progressive renal dysfunction (e.g. diabetic nephropathy)
Proteinuria

Modified from the writing group for Atherosclerotic Peripheral Vascular Disease Symposium.[100]

many other tissues.[92,93] In these cases, abundant oxygen may be delivered into tissue with damaged mitochondrial electron transport chains that generate toxic ROS.[94] Studies in an experimental swine model and human subjects indicate that preinfusion with an agent that stabilizes the mitochondrial transition pore produces improvements in microvascular recovery and GFR after renal artery angioplasty.[95,96]

An additional strategy for recovering renal function derives from the observation that microvascular rarefication and inflammatory injury pathways persist after restoring renal perfusion. Experimental work with endothelial progenitor cells indicates that such vessels can be repaired with intrarenal cell therapy targeted at angiogenesis,[97] even without revascularization. Further work using autologous, adipose-derived mesenchymal stem cells (MSCs) delivered into the kidney indicates that microvessels can be repaired, along with reduction in inflammatory signaling, oxidative stress, and macrophage activation[98] (Figure 47.7a and b). Initial studies in human subjects with atherosclerotic RVD demonstrate a rise in cortical blood flow and reduced tissue hypoxia three months after infusion of autologous MSC.[99] These studies indicate that adjunctive, cell-based maneuvers targeted to local injury mechanisms may provide important supplemental pathways that allow repair and restoration of microvascular structures.

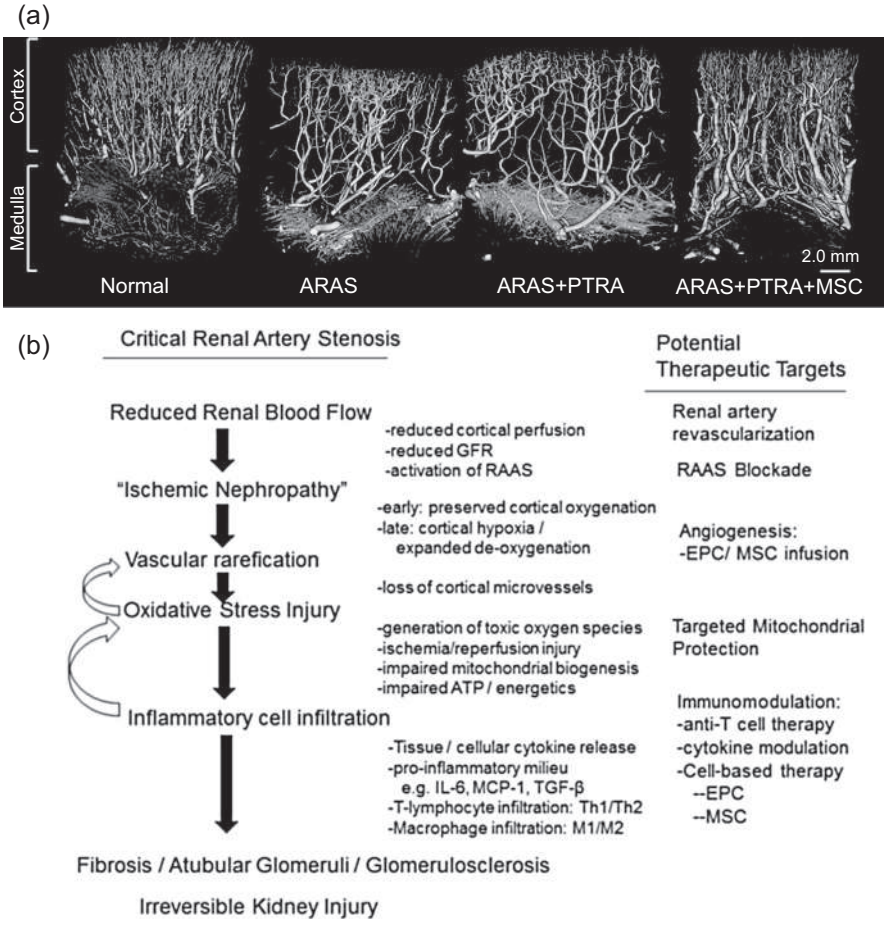


FIGURE 47.7 (a) Cell-based therapy as an adjunct to renal revascularization: Micro-CT images from experimental atherosclerotic RVD treated with PTRA with or without intrarenal administration of adipose-derived MSC. Loss of microvessels within the stenotic kidneys is only partially restored with PTRA alone, whereas addition of MSC to PTRA allowed restoration of microvessels associated with improvements in blood flow and GFR. *PTRA*, percutaneous renal angioplasty. (b) Injury pathways and potential targets in atherosclerotic RVD. This schematic highlights pathways of vascular rarefication, oxidative stress injury, and inflammatory mechanisms in the poststenotic kidney. The right panel identifies specific therapeutic targets that may alleviate these injury pathways, over and above restoring blood flow. *EPC*, endothelial progenitor cells; *MCP*, monocyte chemoattractant protein; *MSC*, mesenchymal stem cells. *(a) Reproduced from reference 98, with permission. (b) Reproduced from reference 2, with permission.*

CONCLUSION

Large vessel RVD is a common manifestation of atherosclerosis, particularly in aging populations. Under some conditions, RVD functions as the critical pathway that reduces blood flow and eventually worsens hypoxia within the kidney, associated with vascular rarefaction. Eventually, these processes activate tissue injury with cytokine release, mitochondrial dysfunction, activation of TGF-β, and accumulation of cellular inflammatory infiltrates with both T cells and macrophages. Tissue fibrosis ensues. The time course for these events appears widely variable and reflects additional factors such as age, atherosclerotic milieu, diabetes, and smoking, among others. Although restoring vessel patency and improving tissue perfusion would seem to be a rational approach, the net benefit of revascularization alone is limited and appears to depend on the state of the poststenotic kidney regarding ongoing inflammatory injury. Both the timing and achieved benefit of renal revascularization depend on experienced clinicians recognizing the hemodynamic severity of RVD and the variability in determinants of recovering function, including kidney size, duration of occlusion, vascular rarefaction, and inflammatory injury. Successful management of RVD in the future will depend on developing more precise evaluation of these factors, and likely will require adjunctive maneuvers to reverse ischemia/reperfusion and induce reparative pathways.

References

1. Besarab A, Brown RS, Rubin NT, Salzman E, Wirthlin L, Steinman T, et al. Reversible renal failure following bilateral renal artery occlusive disease. Clinical features, pathology, and the role optraf surgical revascularization. *J Am Med Assoc* 1976;**235**(26): 2838–41.
2. Textor SC, Lerman LO. Paradigm shifts in atherosclerotic renovascular disease: where are we now? *J Am Soc Nephrol* 2015;**26**: 2074–80.
3. Jacobson HR. Ischemic renal disease: an overlooked clinical entity. *Kidney Int* 1988;**34**:729–43.
4. Chaudhry MA, Latif F. Takayasu's arteritis and its role in causing renal artery stenosis. *Am J Med Sci* 2013;**346**(4):314–8.
5. Chugh KS, Sakhula V. Takayasu's arteritis as a cause of renovascular hypertension in Asian countries. *Am J Nephrol* 1992;**12**:1–8.
6. Lemoine S, Papillard M, Belloi A, Rognant N, Fouque D, Laville M, et al. Renal perfusion: noninvasive measurement with multidetector CT versus flourescent microspheres in a pig model. *Radiology* 2011;**260**:414–20.
7. De Bruyne B, Manoharan G, Pijls NHJ, Verhamme K, Madaric J, Bartunek J, et al. Assessment of renal artery stenosis severity by pressure gradient measurements. *J Am Coll Cardiol* 2006;**48**: 1851–5.
8. Hansen KJ, Edwards MS, Craven TE, Cherr GS, Jackson SA, Appel RG, et al. Prevalence of renovascular disease in the elderly: a population based study. *J Vasc Surg* 2002;**36**:443–51.
9. Lorenz EC, Vrtiska TJ, Lieske JC, Dillon JJ, Stegall MD, Li X, et al. Prevalence of renal artery and kidney abnormalities by computed tomography among healthy adults. *Clin J Am Soc Nephrol* 2010;**5**: 431–8.
10. de Mast Q, Beutler JJ. The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review. *J Hypertens* 2009;**27**:1333–40.
11. Kalra PA, Guo H, Kausz AT, Gilbertson DT, Liu J, Chen SC, et al. Atherosclerotic renovascular disease in United States patients aged 67 years or older: risk factors, revascularization and prognosis. *Kidney Int* 2005;**68**:293–301.
12. The ASTRAL Investigators. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med* 2009;**361**:1953–62.
13. Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med* 2014;**370**(1):13–22.
14. Fatica RA, Port FK, Young EW. Incidence trends and mortality in end-stage renal disease attributed to renovascular disease in the United States. *Am J Kidney Dis* 2001;**37**:1184–90.
15. Coen G, Manni M, Giannoni MF, Calabria S, Mantella D, Pigorini F, et al. Ischemic nephropathy in an elderly nephrologic and hypertensive population. *Am J Nephrol* 1998;**18**:221–7.
16. Guo H, Kalra PA, Gilbertson DT, Liu J, Chen SC, Collins AJ, et al. Atherosclerotic renovascular disease in older US patients starting dialysis, 1996-2001. *Circulation* 2007;**115**:50–8.
17. Textor SC, McKusick MM. Renal artery stenosis: if and when to intervene. *Curr Opin Nephrol Hypertens* 2016;**25**(2):144–51.
18. Textor SC, Wilcox CS. Renal artery stenosis: a common, treatable cause of renal failure? *Annu Rev Med* 2001;**52**:421–42.
19. Ritchie J, Green D, Chrysochou C, Chalmers N, Foley RN, Kalra PA. High-risk clinical presentations in atherosclerotic renovascular disease: prognosis and response to renal artery revascularization. *Am J Kidney Dis* 2014;**63**(2):186–97.
20. Hansen KJ, Cherr GS, Craven TE, Motew SJ, Travis JA, Wong JM, et al. Management of ischemic nephropathy: dialysis-free survival after surgical repair. *J Vasc Surg* 2000;**32**(3):472–81. discussion 81-2.
21. Textor SC. Renovascular hypertension and ischemic nephropathy. In: Skorecki K, Chertow GM, Marsden PA, Taal MW, Yu ASL, Wasser WG, editors. *Brenner and rector's: the kidney.* 10th ed. Philadelphia: Elsevier; 2016. p. 1567–609.
22. Textor SC, Lerman L. Renovascular hypertension and ischemic nephropathy. *Am J Hypertens* 2010;**23**(11):1159–69.
23. Heyman SN, Khamaisi M, Rosen S, Rosenberger C. Renal parenchymal hypoxia, hypoxia response and the progression of chronic kidney disease. *Am J Nephrol* 2008;**28**:998–1006.
24. Evans RG, Gardiner BS, Smith DW, O'Connor PM. Intrarenal oxygenation: unique challenges and the biophysical basis of homeostasis. *Am J Physiol Renal Physiol* 2008;**295**(5):F1259–70.
25. Gloviczki ML, Glockner JF, Lerman LO, McKusick MA, Misra S, Grande JP, et al. Preserved oxygenation despite reduced blood flow in poststenotic kidneys in human atherosclerotic renal artery stenosis. *Hypertension* 2010;**55**(4):961–6.
26. Gloviczki ML, Glockner JF, Crane JA, McKusick MA, Misra S, Grande JP, et al. Blood oxygen level-dependent magnetic resonance imaging identifies cortical hypoxia in severe renovascular disease. *Hypertension* 2011;**58**(6):1066–72.
27. Saad A, Crane J, Glockner JF, Herrmann SMS, Friedman H, Ebrahimi B, et al. Human renovascular disease: estimating fractional tissue hypoxia to analyze blood oxygen level-dependent MR. *Radiology* 2013;**268**(3):770–8.
28. Chade AR, Rodriguez-Porcel M, Grande JP, Krier JD, Lerman A, Romero JC, et al. Distinct renal injury in early atherosclerosis and renovascular disease. *Circulation* 2002;**106**:1165–71.
29. Kotliar C, Juncos L, Inserra F, de Cavanagh EMV, Chuluyan E, Aquino JB, et al. Local and systemic cellular immunity in early renal artery atherosclerosis. *Clin J Am Soc Nephrol* 2012;**7**:224–30.
30. Kataoka T, Mathew V, Rubinstein R, Rihal CS, Lennon R, Lerman LO, et al. Association of plaque composition and vessel remodeling in atherosclerotic renal artery stenosis: a comparison with coronary artery disease. *JACC Cardiovasc Imaging* 2009;**2**: 327–38.
31. Maric-Bilkan C, Flynn ER, Chade AR. Microvascular disease precedes the decline in renal function in the streptozotocin-induced diabetic rat. *Am J Physiol Renal Physiol* 2012;**302**:F308–15.
32. Lerman LO, Textor SC, Grande JP. Mechanisms of tissue injury in renal artery stenosis: ischemia and beyond. *Prog Cardiovasc Dis* 2009;**52**(3):196–203.
33. Chade AR. Renal vascular structure and rarefaction. *Compr Physiol* 2013;**3**(2):817–31.
34. Eirin A, Zhu XY, Urbieta-Caceres VH, Grande JP, Lerman A, Textor SC, et al. Persistent kidney dysfunction in swine renal artery stenosis correlates with outer cortical microvascular remodeling. *Am J Physiol Renal Physiol* 2011;**300**:F1394–401.
35. Antonios TF, Singer DR, Markandu ND, Mortimer PS, MacGregor G. Structural skin capillary rarefaction in essential hypertension. *Hypertension* 1999;**33**:998–1001.
36. Levy BI, Schiffrin EL, Mourad JJ, Agostini D, Vicaut E, Safar ME, et al. Impaired tissue perfusion: a pathology common to hypertension, obesity, and diabetes mellitus. *Circulation* 2008;**118**:968–76.
37. Zhang X, Krier JD, Amador Carrascal C, Greenleaf JF, Ebrahimi B, Hedayat AF, et al. Low-energy shockwave therapy improves ischemic kidney microcirculation. *J Am Soc Nephrol* 2016;**27**(12): 3715–24.
38. Chade AR, Kelsen S. Reversal of renal dysfunction by targeted administration of VEGF into the stenotic kidney: a novel potential therapeutic approach. *Am J Physiol Renal Physiol* 2012;**302**(10): F1342–50.
39. Eirin A, Lerman A, Lerman LO. Mitochondria: a pathogenic paradigm in hypertensive renal disease. *Hypertension* 2015;**65**(2): 264–70.
40. Eirin A, Saad A, Tang H, Herrmann SM, Woollard JR, Lerman A, et al. Urinary mitochondrial DNA copy number identifies chronic renal injury in hypertensive patients. *Hypertension* 2016;**68**(2): 401–10.

41. Keddis M, Garovic V, Bailey K, Wood C, Raissian Y, Grande J. Ischemic nephropathy secondary to atherosclerotic renal artery stenosis: clinical and histopathological correlates. *Nephrol Dial Transplant* 2010;**25**:3615–22.
42. Warner GM, Cheng J, Knudsen BE, Gray CE, Deibel A, Juskewitch JE, et al. Genetic deficiency of Smad3 protects the kidneys from atrophy and interstitial fibrosis in 2K1C hypertension. *Am J Physiol Renal Physiol* 2012;**302**(11):F1455–64.
43. Gloviczki ML, Keddis MT, Garovic VD, Friedman H, Herrmann S, McKusick MA, et al. TGF expression and macrophage accumulation in atherosclerotic renal artery stenosis. *Clin J Am Soc Nephrol* 2013;**8**(4):546–53.
44. Eirin A, Gloviczki ML, Tang H, Gossl M, Jordan KL, Woollard JR, et al. Inflammatory and injury signals released from the post-stenotic human kidney. *Eur Heart J* 2013;**34**(7):540–548a.
45. Saad A, Herrmann SMS, Crane J, Glockner JF, McKusick MA, Misra S, et al. Stent revascularization restores cortical blood flow and reverses tissue hypoxia in atherosclerotic renal artery stenosis but fails to reverse inflammatory pathways or glomerular filtration rate. *Circ Cardiovasc Interv* 2013;**6**(4):428–35.
46. Eirin A, Ebrahimi B, Zhang X, Zhu XY, Tang H, Crane JA, et al. Changes in glomerular filtration rate after renal revascularization correlate with microvascular hemodynamics and inflammation in swine renal artery stenosis. *Circ Cardiovasc Interv* 2012;**5**: 720–8.
47. Chrysochou C, Kalra PA. Epidemiology and natural history of atherosclerotic renovascular disease. *Prog Cardiovasc Dis* 2009; **522**:184–95.
48. Garovic V, Textor SC. Renovascular hypertension and ischemic nephropathy. *Circulation* 2005;**112**:1362–74.
49. Ives NJ, Wheatley K, Stowe RL, Krijnen P, Plouin PF, van Jaarsveld BC, et al. Continuing uncertainty about the value of percutaneous revascularization in atherosclerotic renovascular disease: a meta-analysis of randomized trials. *Nephrol Dial Transplant* 2003;**18**:298–304.
50. van Jaarsveld BC, Krijnen P, Pieterman H, Derkx FHM, Deinum J, Postma CT, et al. The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. *N Engl J Med* 2000; **342**:1007–14.
51. Webster J, Marshall F, Abdalla M, Dominiczak A, Edwards R, Isles CG, et al. Randomised comparsion of percutaneous angioplasty vs continued medical therapy for hypertensive patients with atheromatous renal artery stenosis. *J Hum Hypertens* 1998; **12**:329–35.
52. Plouin PF, Chatellier G, Darne B, Raynaud A. Blood Pressure outcome of angioplasty in atherosclerotic renal artery stenosis: a randomized trial. *Hypertension* 1998;**31**:822–9.
53. Messerli FH, Bangalore S, Makani H, Rimoldi SF, Alleman Y, White CJ, et al. Flash pulmonary oedema and bilateral renal artery stenosis: the Pickering Syndrome. *Eur Heart J* 2011;**32**(18):2231–7.
54. Kane GC, Xu N, Mistrik E, Roubicek T, Stanson AW, Garovic VD. Renal artery revascularization improves heart failure control in patients with atherosclerotic renal artery stenosis. *Nephrol Dial Transplant* 2010;**25**:813–20.
55. Hall JE, Guyton AC, Jackson TE, Coleman TG, Lohmeier TE, Trippodo NC. Control of glomerular filtration rate by renin-angiotensin system. *Am J Physiol* 1977;**233**:F366–72.
56. Palmer BF. Renal dysfunction complicating the treatment of hypertension. *N Engl J Med* 2002;**347**(16):1256–61.
57. Schoolwerth AC, Sica DA, Ballermann BJ, Wilcox CS. Renal considerations in angiotensin converting enzyme inhibitor therapy. *Circulation* 2001;**104**:1985–91.
58. Hricik DE, Browning PJ, Kopelman R, Goorno WE, Madias NE, Dzau VJ. Captopril-induced functional renal insufficiency in patients with bilateral renal-artery stenosis or renal-artery stenosis in a solitary kidney. *N Engl J Med* 1983;**308**:377–81.
59. Onuigbo MAC, Onuigbo NTC. Late onset renal failure from angiotensin blocade (LORFFAB): a prospective thirty month Mayo Health System clinic experience. *Med Sci Monit* 2005;**11**: CR462–C469.
60. Ahmed A. Use of angiotensin-converting enzyme inhibitors in patients with heart failure and renal insufficiency: how concerned should we be by the rise in serum creatinine? *J Am Geriatr Soc* 2003;**50**:1297–300.
61. Cheung CM, Wright JR, Shurrab AE, Mamtora H, Foley RN, O'Donoghue DJ, et al. Epidemiology of renal dysfunction and patient outcome in atherosclerotic renal artery occlusion. *J Am Soc Nephrol* 2002;**13**:149–57.
62. Muray S, Martin M, Amoedo ML, Garcia C, Jomet AR, Vera M, et al. Rapid decline in renal function reflects reversibility and predicts the outcome after angioplasty in renal artery stenosis. *Am J Kidney Dis* 2002;**39**:60–6.
63. Brown LC, Brown EA, Greenhalgh RM, Powell JT, Thompson SG, et al. Renal function and abdominal aortic aneurysm. The impact of different management strategies on long-term renal function in the UK endovascular aneurysm repair trials. *Ann Surg* 2010;**251**: 966–75.
64. Textor SC, Misra S, Oderich G. Percutaneous revascularization for ischemic nephropathy: the past, present and future. *Kidney Int* 2013;**83**(1):28–40.
65. Greenberg RK, Chuter TA, Lawrence-Brown M, Haulon S, Nolte L. Analysis of renal function after aneurysm repair with device using suprarenal fixation (Zenith AAA endovascular graft) in contrast to open repair. *J Vasc Surg* 2004;**39**:1219–28.
66. Cooper CJ, Murphy TP, Matsumoto A, Steffes M, Cohen DJ, Jaff M, et al. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: rationale and design of the CORAL trial. *Am Heart J* 2006;**152**:59–66.
67. Radermacher J, Chavan A, Bleck J, Vitzthum A, Stoess B, Gebel MJ, et al. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. *N Engl J Med* 2001; **344**:410–7.
68. Zeller T, Frank U, Muller C, Burgelin K, Sinn L, Bestehorn HP, et al. Predictors of improved renal function after percutaneous stent-supported angioplasty of severe atherosclerotic ostial renal artery stenosis. *Circulation* 2003;**108**:2244–9.
69. Herrmann SMS, Textor SC. Diagnostic criteria for renovascular disease: where are we now? *Nephrol Dial Transplant* 2012;**27**(7): 2657–63.
70. Prasad PV, Edelman RR, Epstein FH. Non-invasive evaluation of intrarenal oxygenation with BOLD MRI. *Circulation* 1996;**94**: 3271–5.
71. Textor SC, Glockner JF, Lerman LO, Misra S, McKusick MA, Riederer SJ, et al. The use of magnetic resonance to evaluate tissue oxygenation in renal artery stenosis. *J Am Soc Nephrol* 2008;**19**(4): 780–8.
72. Pruijm M, Mendichovszky IA, Liss P, Van der Niepen P, Textor SC, Lerman LO, et al. Renal blood oxygenation level-dependent magnetic resonance imaging to measure renal tissue oxygenation: a statement paper and systematic review. *Nephrol Dial Transplant* 2018;**33**(Suppl. 2):ii22–8.
73. Textor SC, Abumoawad A. BOLD Measures to evaluate renovascular disease: where are we now? *NephSAP* 2018;**17**(1):1–7.
74. Chrysochou C, Mendichovszky IA, Buckley DL, Cheung CM, Jackson A, Kalra PA. BOLD imaging: a potential predictive biomarker of renal functional outcome following revascularization in atheromatous renovascular disease. *Nephrol Dial Transplant* 2012;**27**(3):1013–9.
75. Ebrahimi B, Gloviczki M, Woollard JR, Crane JA, Textor SC, Lerman LO. Compartmental analysis of renal BOLD MRI data: introduction and validation. *Invest Radiol* 2012;**47**(3):175–82.

76. Wright JR, Duggal A, Thomas R, Reeve R, Roberts IS, Kalra PA. Clinicopathological correlation in biopsy-proven atherosclerotic nephropathy: implications for renal functional outcome in atherosclerotic renovascular disease. *Nephrol Dial Transplant* 2001;**16**: 765–70.
77. Rule AD, Amer H, Cornell LD, Taler SJ, Cosio FG, Kremers WK, et al. The association between age and nephrosclerosis on renal biopsy among healthy adults. *Ann Intern Med* 2010;**152**(9): 561–7.
78. Meyrier A, Hill GW, Simon P. Ischemic renal diseases: new insights into old entities. *Kidney Int* 1998;**54**:2–13.
79. Krishnamurthi V, Novick AC, Myles JL. Atheroembolic renal disease: effect on morbidity and survival after revascularization for atherosclerotic renal artery stenosis. *J Urol* 1999;**161**: 1093–6.
80. Cheung CM, Hegarty J, Kalra PA. Dilemmas in the management of renal artery stenosis. *Br Med Bull* 2005;**73–74**:35–55.
81. Chrysochou C, Foley RN, Young JF, Khavandi K, Cheung CM, Kalra PA. Dispelling the myth: the use of renin-angiotensin blockade in atheromatous renovascular disease. *Nephrol Dial Transplant* 2012;**27**(4):1403–9.
82. Hackam DG, Spence JD, Garg AX, Textor SC. Role of renin-angiotensin system blockade in atherosclerotic renal artery stenosis and renovascular hypertension. *Hypertension* 2007;**50**(6): 998–1003.
83. Hackam DG, Duong-Hua ML, Mamdani M, Li P, Tobe SW, Spence JD, et al. Angiotensin inhibition in renovascular disease: a population-based cohort study. *Am Heart J* 2008;**156**:549–55.
84. Losito A, Gaburri M, Errico R, Parente B, Cao PG. Survival of patients with renovascular disease and ACE inhibition. *Clin Nephrol* 1999;**52**:339–43.
85. Caps MT, Perissinotto C, Zierler RE, Poissar NL, Bergelin RO, Tullis MJ, et al. Prospective study of atherosclerotic disease progression in the renal artery. *Circulation* 1998;**98**:2866–72.
86. Caps MT, Zierler RE, Polissar NL, Bergelin RO, Beach KW, Cantwell-Gab K, et al. Risk of atrophy in kidneys with atherosclerotic renal artery stenosis. *Kidney Int* 1998;**53**:735–42.
87. Textor SC. Ischemic nephropathy: where are we now? *J Am Soc Nephrol* 2004;**15**(8):1974–82.
88. Textor SC, McKusick MM, Misra S, Glockner J. Timing and selection for renal revascularization in an era of negative trials: what to do? *Prog Cardiovasc Dis* 2009;**52**(3):220–8.
89. Oskin TC, Hansen KJ, Deitch JS, Craven TE, Dean RH. Chronic renal artery occlusion: nephrectomy versus revascularization. *J Vasc Surg* 1999;**29**:140–9.
90. Bax L, Woittiez AJ, Kouwenberg HJ, Mali PTM, Buskens E, Beek FJA, et al. Stent Placement in Patients with atherosclerotic renal artery stenosis and impaired renal function. *Ann Int Med* 2009;**150**:840–8.
91. Herrmann SM, Saad A, Textor SC. Management of atherosclerotic renovascular disease after cardiovascular outcomes in renal atherosclerotic lesions (CORAL). *Nephrol Dial Transplant* 2015; **30**(3):366–75.
92. Weight SC, Bell PRF, Nicholson ML. Renal ischaemia-reperfusion injury. *Br J Surg* 1996;**83**:162–70.
93. Chien CT, Lee PH, Chen CF, Ma MC, Lai MK, Hsu SM. De novo demonstration and co-localization of free radical production and apoptosis formation in rat kidney subjected to ischemia/reperfusion. *J Am Soc Nephrol* 2001;**12**:973–82.
94. Szeto HH, Liu S, Soong Y, Wu D, Darrah SF, Cheng FY, et al. Mitochondria-targeted peptide accelerates ATP recovery and reduces ischemic kidney injury. *J Am Soc Nephrol* 2011;**22**: 1041–52.
95. Eirin A, Li Z, Xhang X, Krier JD, Woollard JR, Zhu XY, et al. A mitochondrial permeability transition pore inhibitor improves renal outcomes after revascularization in experimental atherosclerotic renal artery stenosis. *Hypertension* 2012;**60**:1242–9.
96. Saad A, Herrmann SMS, Eirin A, Ferguson CM, Glockner JF, Bjarnason H, et al. Phase 2a clinical trial of mitochondrial protection (elamipretide) during stent revascularization in patients with atherosclerotic renal artery stenosis. *Circ Cardiovasc Interv* 2017; **10**(9).
97. Chade AR, Zhu X, Lavi R, Krier JD, Pislaru S, Simari RD, et al. Endothelial progenitor cells restore renal function in chronic experimental renovascular disease. *Circulation* 2009;**119**: 547–57.
98. Eirin A, Zhu X-Y, Krier JD, Tang H, Jordan KL, Grande JP, et al. Adipose tissue-derived mesenchymal stem cells improve revascularization outcomes to restore renal function in swine atherosclerotic renal artery stenosis. *Stem Cell* 2012;**30**(5): 1030–41.
99. Saad A, Dietz AB, Herrmann SMS, Hickson LJ, Glockner JF, McKusick MA, et al. Autologous mesenchymal stem cells increase cortical perfusion in renovascular disease. *J Am Soc Nephrol* 2017;**28**(2):2777–85.
100. Rocha-Singh KJ, Eisenhauer AC, Textor SC, Cooper CJ, Tan WA, Matsumoto AH, et al. Atherosclerotic peripheral vascular disease symposium II: intervention for renal artery disease. *Circulation* 2008;**118**:2873–8.
101. Warner L, Glockner JF, Woollard J, Textor SC, Romero JC, Lerman LO. Determinations of renal cortical and medullary oxygenation using blood oxygen level-dependent magnetic resonance imaging and selective diuretics. *Invest Radiol* 2011;**46**(1): 41–7.

QUESTIONS AND ANSWERS

Question 1

A 73-yr-old man is identified having a 70% stenosis of his right renal artery during CT angiography for abdominal pain. The left was normal. He has two-vessel coronary disease, for which stents were placed a month earlier. His cardiologist recommends that he must undergo renal artery stenting after six months of clopidogrel therapy.

He has hypertension for 15 yr and now feels well. His current medications include an ACE inhibitor, a beta blocker, an alpha blocker, a diuretic, clopidogrel, and aspirin.

BP: 145/74 mm Hg, P: 65
Chest clear, no edema
Labs: CBC normal, S[Cr] 1.4 mg/dL (eGFR: 49 mL/min/1.73 m^2), sodium 140 mEq/L, and potassium 4.6 mEq/L

Which of the following most accurately describes the likely results of renal artery stenting for this individual?

A. Lower antihypertensive drug requirements
B. Improved kidney function
C. Reduced angina
D. Regression of left ventricular hypertrophy
E. Lower mortality

Answer: A

Several studies demonstrate that antihypertensive medication requirements are lower, but usually not withdrawn after revascularization, making (A) most likely. Other potential benefits including changes in kidney function rarely occur, especially with unilateral disease (making (B) incorrect). Most importantly, no mortality benefits have been observed (E). (C) and (D) sometimes are benefits with effective BP control but are not directly related to stenting. These points have been underscored in several trials including ASTRAL, STAR, and CORAL.[12,13,90]

Question 2

A 69-yr-old woman returns after a recent hospitalization with congestive heart failure (EF 40%) and a rise in creatinine from 1.2 to 2.6 mg/dL. An ultrasound examination identifies a small right kidney (7.4 cm) and normal sized left kidney (10.8 cm). Doppler ultrasound demonstrates no flow to the right kidney. The left has a PSV of 425 cm/sec and estimated more than 70% stenosis.

Blood pressure was 180/80 mm Hg initially, but fell to 130/80 after treatment with ramipril, amlodipine, and furosemide. Creatinine 2.7 mg/dL, sodium 139 mEq/L, and potassium 4.9 mEq/L.

Which of the following is most likely to stabilize kidney function and fluid status for this patient?

A. Laparoscopic nephrectomy of the right kidney
B. Withdrawal of ramipril
C. Addition of spironolactone
D. Transition to an angiotensin receptor blocker
E. Endovascular stent placement

Answer: E

This individual has both impaired cardiac pump function and reduced GFR with a solitary functioning kidney. In this situation, hospitalization for recurrent CHF can be reduced by renal revascularization[19,54] taking (E) the best choice. Option (A) would have no effect on kidney function. One might withdraw ramipril (B), but this would impair cardiac function and allow higher BP, making it less correct. No benefits in this situation to a transition to ARB (same effect as doing nothing) or spironolactone (C).

Question 3

Which of the following is most probable for an 81-yr-old man with recently identified, high-grade renal arterial stenosis (S[Cr] 1.5 mg/dL) and a small abdominal aortic aneurysm (3.2 cm) over the next 2 yr?

A. Cerebrovascular event (stroke, TIA)
B. Congestive cardiac failure
C. End-stage kidney disease
D. Aneurysm rupture
E. Development of angina

Answer: E

Patients with atherosclerotic renal artery stenosis are at highest risk for developing new cardiovascular symptoms. New angina and coronary symptoms (E) are most common, as directly reflected from Figure 47.2 from the Medicare Claims review of Kalra et al.[11] End-stage disease (C) and aneurysm rupture (D) are distinctly less probable, whereas congestive heart failure (B) and CNS symptoms (A) are intermediate.

Question 4

A 65-yr-old woman is referred for CKD stage 3. Two years ago, she developed a rise in blood pressure to 170/95 mm Hg during a routine examination. Previous BP levels always had been below 140/90. Current medications include losartan, amlodipine, and indapamide.

BP: 134/70 mm Hg, P: 74 bpm trace edema. BMI: 27 kg/m^2

S[Cr] 1.5 mg/dL (CKD EPI eGFR: 36 mL/min/1.73 m^2)

Doppler ultrasound identified high velocities (310 cm/sec) to the left kidney (9.0 cm) and normal velocities (85 cm/sec) to the right kidney (10.8 cm).

Which of the following MOST accurately describes the state of the left kidney?

A. Despite reduced blood flow, cortical oxygenation is preserved
B. Progressive medullary hypoxia is inevitable
C. Reduced GFR magnifies medullary oxygen deprivation
D. Angiotensin receptor blockade limits renin release
E. Restoring renal blood flow will reverse cortical inflammation

Answer: A

Experimental and human studies indicate that moderate RVD is associated with a loss of blood flow and volume, but well-preserved cortical oxygenation, in part because the cortex receives a large excess of oxygenated blood, making (A) correct.[25] Functional and tissue biopsy information indicates that medullary hypoxia can be stable, in part because reduced GFR lowers oxygen consumption related to solute transport, making (B) and (C) incorrect.[101] Blockade of the renin–angiotensin system tends to stimulate renin release (opposite of (D)), and when inflammatory pathways become activated, restoring blood flow alone fails to abrogate that process, making (E) incorrect.

Question 5

You are asked to evaluate resistant hypertension and azotemia in a 56-yr-old woman with atherosclerotic RVD. S[Cr] had been 1.7 mg/dL during therapy with losartan, which had lowered BP to 130/70 mm Hg. She had undergone renal artery angioplasty a year previously, after which her angiotensin receptor blocker had been withdrawn.

Current medications: carvedilol, amlodipine, and furosemide.

BP: 180/98 mm Hg. Well-appearing. Audible epigastric bruit.

Urinalysis: normal, S[Cr]: 1.4 mg/dL (CKD EPI eGFR: 42 mL/min/1.73 m^2)., S[K]: 3.4 mEq/L.

CT angiography demonstrates two normal sized kidneys with residual stenosis in both renal arteries.

Which of the following MOST accurately describes the role of renin–angiotensin blockade in this patient?

A. ACE inhibition should be avoided due to bilateral RVD
B. A direct renin inhibitor (aliskiren) would be the preferred agent
C. Administration of losartan would likely lower BP
D. An angiotensin receptor blocker should be started only after repeat angioplasty

Answer: C

The vast majority of patients (92%) with RVD (either atherosclerotic or fibromuscular in origin) tolerate blockade of the renin–angiotensin system, including bilateral disease (78%).[81] The finding of recurrent hypertension and lower S[K] is consistent with activation of the renin–angiotensin system and likely would respond to blockade, making (C) the preferred answer. It is incorrect to infer that these agents should be avoided, as long-term outcomes and mortality appear to be improved with RAAS blockade,[83] making (A) incorrect. The role of aliskiren is not precisely defined, but has no advantage. If azotemia worsens, repeat revascularization may be considered, but should not be a necessary first step to therapy, making (D) less correct.

CHAPTER

48

Polycystic Kidney Disease

Gregory G. Germino[a], Lisa M. Guay-Woodford[b]

[a]National Institute of Diabetes and Digestive and Kidney Disease, National Institutes of Health, Bethesda, MD, United States; [b]The George Washington University, Center for Translational Science, Clinical and Translational Institute at Children's National, Children's National Health System, Washington, DC, United States

Abstract

Polycystic kidney disease (PKD) results from single-gene defects transmitted as either autosomal dominant or autosomal recessive traits. Different ages of onset, variability in kidney disease progression, and a diverse array of extrarenal manifestations distinguish these disorders. In autosomal dominant PKD (ADPKD), defects in either of two causative genes, *PKD1* or *PKD2*, can initiate cyst formation resulting from a germline mutation in one allele and a somatic mutation in the second allele. The respective protein products, polycystin-1 and polycystin-2, form a receptor-channel complex that is variably expressed in the plasma cell membrane, as well as in the primary apical cilia membrane. Autosomal recessive PKD (ARPKD) results from mutations in the *PKHD1* gene, which encodes the protein product, fibrocystin/polyductin, which is also expressed in primary cilia. Recent studies have identified atypical forms of ADPKD and ARPKD that result from mutation of other genes. This chapter considers PKD genetics, clinical and genetic diagnosis, management of organ-specific complications, and future directions for disease monitoring and potential therapies.

SCOPE OF THE PROBLEM

Polycystic kidney disease (PKD) describes a heterogeneous set of disorders that result from single-gene defects transmitted as either autosomal dominant or autosomal recessive traits. Although the development of fluid-filled cysts and progressive impairment of renal function is a common feature, these disorders are distinguished by different ages of onset, variable rates of renal disease progression, and a diverse array of extrarenal manifestations.

Autosomal dominant polycystic kidney disease (ADPKD; MIM 601313, MIM 613095) is by far the most common form of PKD, affecting between 1/500 and 1/2000 individuals. The disease is characterized by age-dependent occurrence of bilateral, multiple renal cysts, and a variety of extrarenal manifestations. The latter include cysts in the liver bile ducts, pancreatic ducts, seminal vesicles, and arachnoid membrane, as well as noncystic manifestations, such as intracranial aneurysms (ICA) and dolichoectasias, aortic root dilatation and aneurysms, mitral valve prolapse, and abdominal wall hernias[1] (Figure 48.1). Autosomal dominant polycystic liver disease (ADPLD; MIM 177060, MIM104160, MIM 611341) is a similarly common, related condition in which individuals have an age-dependent presentation of phenotypically identical liver cysts but few, if any renal cysts.[2] There are rare families that have genetically distinct, atypical forms of ADPKD that had initially been mistaken for the more common forms of the disease. One cohort has variably cystic kidneys and livers, but the kidneys are not enlarged and the disease does not progress to end-stage renal disease (ESRD).[3] Another set of families had chronic interstitial fibrosis and mild, variably cystic kidneys that also were not enlarged, but in which the cystic disease progressed to ESRD.[4]

Autosomal recessive polycystic kidney disease (ARPKD; MIM 606702) is less common but typically has a more severe, early onset form of cystic disease affecting 1/26,500 live births.[5] Affected patients have a spectrum of clinical phenotypes arising from cystic involvement of the renal collecting ducts and biliary tract.[6] Their parents may have mild liver cystic disease, which can be mistaken for mild forms of PLD.[7,8] The basic defects observed in ARPKD suggest defects in the terminal differentiation of the renal collecting duct and intrahepatic biliary ducts (Figures 48.2 and 48.3). There is also a very rare form of ARPKD that presents in childhood with enlarged kidneys and progressive

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00048-6

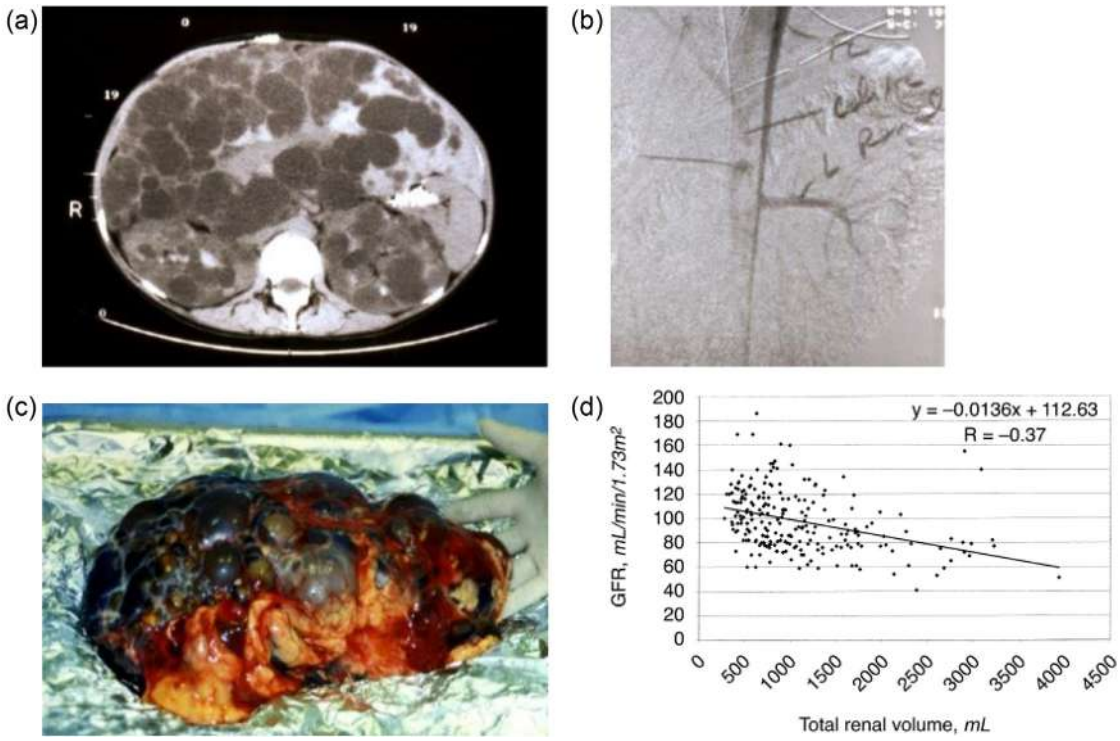


FIGURE 48.1 **Autosomal dominant polycystic kidney disease (ADPKD) clinical features.** (a) CT scan of a woman in her 40s with severe polycystic liver and kidney disease. This example highlights the observation that women tend to have more severe cystic liver disease than men. (b) Arteriogram of a 27-year-old man with a prior history of ADPKD, hypertension, and subarachnoid hemorrhage, who presented with severe back and chest pain and was found to have a dissecting aortic aneurysm. Dye is seen in the false lumen (*arrow*). This is an extreme example of the vascular abnormalities that are sometimes associated with ADPKD. (c) Typical autosomal dominant polycystic kidney. Note the grossly distorted architecture from bulging fluid-filled cysts, many of which are hemorrhagic. Normal kidney size is approximately 130 grams and 4–5 inches in length. The largest ADPKD kidney seen by the authors weighed almost 20 kg. (d) GFR–Volume Relationship in ADPKD. Relationship between GFR and age-adjusted mean renal volume in 241 participants in the CRISP study at baseline.[9] *(c) Adapted from reference 10 and used with the permission of Elsevier. (d) From reference 9 and used with permission of Elsevier.*

renal dysfunction, but which is both clinically and genetically distinct in that there is no clinical evidence of hepatic fibrosis. The disease results from mutations in *DZIPL1* (MIM 617570).[11]

Major advances in understanding the pathogenesis of human polycystic diseases have included the discovery of the mutated genes and their novel protein products by positional cloning, the understanding that multiple somatic mutations are implicated in the molecular pathogenesis of ADPKD, the recognition that there are a number of recessively transmitted disorders that can mimic the renal expression of ARPKD, and the emergence of a once disregarded organelle, the primary apical cilium, as the focus of investigation not just in renal cystic diseases but in a broad spectrum of biological processes (reviewed in reference 1); and recent evidence indicating that alterations in cell metabolism are a hallmark of the disease.[12] These specific advances, coupled with broader investigations in the field, have led to improved understanding of the clinical disease and the phenotypic variations; resulted in a steady increase in the number of therapeutic clinical trials in patients; and culminated in the first therapy approved by regulatory authorities (the US Food and Drug Administration [FDA] and the European Medicines Agency [EMA]) that may slow progression of disease in those most at risk.[13] And yet, the goal of identifying targeted treatment that arrests disease progression remains a work in progress.

PATHOPHYSIOLOGY

ADPKD

Molecular Basis of Disease: PKD1 and PKD2

Mutations of *PKD1* account for approximately 85% of ADPKD cases and mutations of *PKD2* for most of the remainder.[1] *PKD1* mutations are more common because *PKD1* is much larger than *PKD2*, and its sequence is more mutable. DNA testing methods can identify mutations in up to approximately 93% of affected individuals.[14] *De novo* mutations account for up to 10% of cases, although at least one study suggests a lower frequency.[15] The high mutability of *PKD1* likely explains

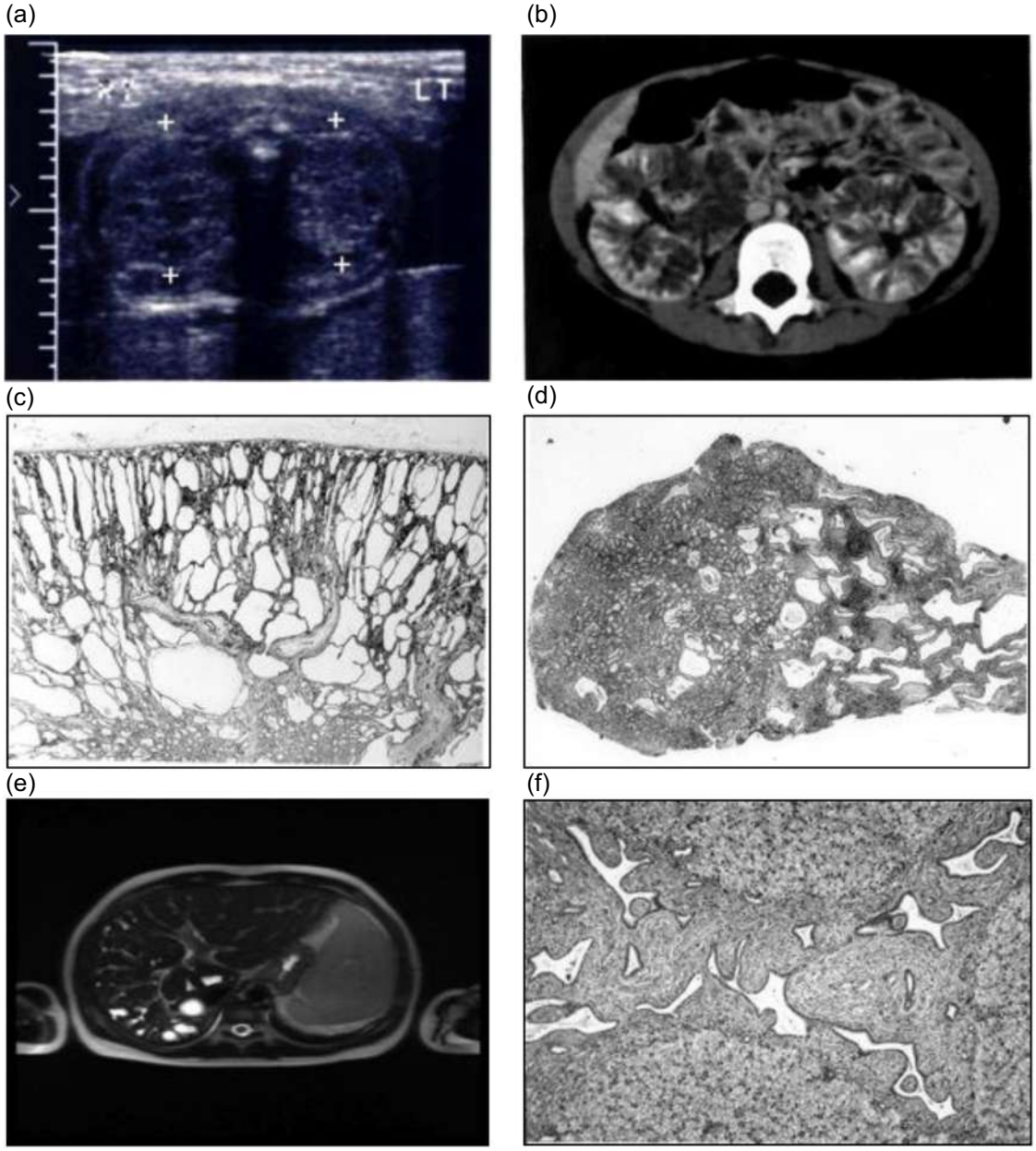


FIGURE 48.2 **Radiologic findings and pathologic features associated with autosomal recessive polycystic kidney disease (ARPKD).** (a) Neonatal sonography with nephromegaly and increased echogenicity. (b) Contrast-enhanced CT in a symptomatic 4-year-old girl reveals a striated nephrogram and prolonged corticomedullary contrast retention. (c) Light microscopy: ARPKD kidney from a 1-year-old child reveals discrete medullary cysts and dilated collecting ducts, H&E × 10. (d) Light microscopy: later-onset ARPKD kidney with prominent medullary ductal ectasia, H&E × 10. (e) Coronal heavily T2-weighted image of the abdomen in an 8-year-old boy reveals marked cystic and fusiform dilatation of the intrahepatic biliary system. (f) Light microscopy: congenital hepatic fibrosis with extensive fibrosis of the portal area, ectatic, tortuous bile ducts and hypoplasia of the portal vein, H&E × 40. *H&E*, hematoxylin/eosin.

why *de novo* mutations arise much more frequently in *PKD1* than in *PKD2* and why private mutations (i.e. unique to a single family) in *PKD1* are more abundant than in *PKD2*.[16,17]

One characteristic feature of ADPKD is its clinical variability. Even within a family, the pattern or presence of extrarenal manifestations and the severity of cystic liver and kidney disease can vary markedly. The hypervariability is perhaps most dramatic on an individual level, since only a small fraction of renal and biliary tubules within a PKD patient's organs give rise to cysts (Figure 48.4). This characteristic provided a clue to the molecular basis of disease. Although the disease is transmitted as an autosomal dominant trait, it is recessive on a cellular level.[18,19] In other words, ADPKD is genetically a "two-hit" disease analogous to what has

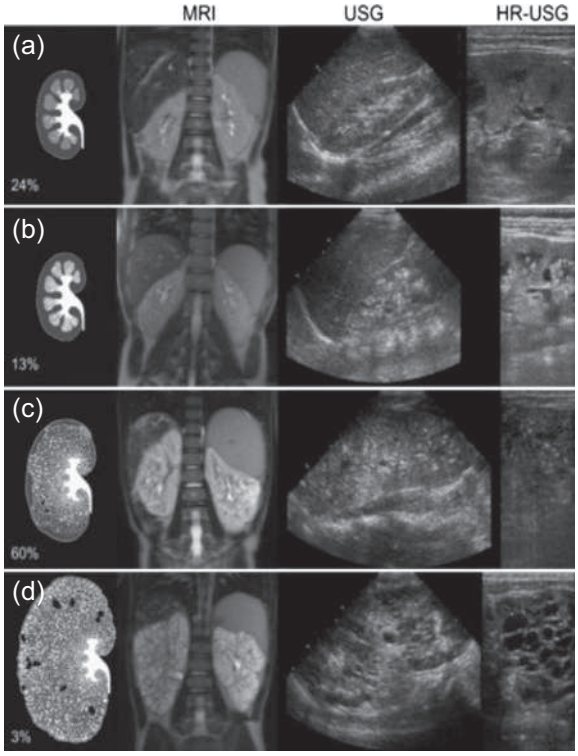


FIGURE 48.3 **Spectrum of kidney abnormalities in Autosomal recessive polycystic kidney disease (ARPKD).** Artist's rendering, MRI, standard ultrasound (USG), and high-resolution ultrasound (HR-USG) images showing the spectrum of kidney abnormalities in a cohort of 62 patients with ARPKD. Percentages refer to the frequency of each pattern within their population. (a) Normal-sized kidneys with medullary hyperechogenicity and some visibly dilated ducts; (b) Mildly enlarged kidneys with more extensive medullary hyperechogenicity and ductal dilations, with cortical sparing; (c) Enlarged kidneys with diffuse hyperechogenicity and ductal dilatation, with only partial cortical sparing and few macrocysts; (d) Massively enlarged kidneys with complete involvement of medulla and cortex and multiple macrocysts. *From Gunay-Aygun et al.[20] with permission from the American Society of Nephrology.*

been described for tumor suppressor genes like *Rb* (retinoblastoma). Cysts form only when both copies of the gene are mutated or the activity level of the complex somehow otherwise compromised.

The molecular recessive nature of ADPKD indicates that *PKD1* and *PKD2* mutations reduce gene function. This observation suggests a threshold model to explain cyst initiation[21–23] (Figure 48.5). Cysts arise when the combined effects of a germline and acquired PKD mutation reduce PKD gene activity below the threshold. The cellular threshold is not known but likely differs in cells of different nephron segments and may even change over time depending on developmental stage or other genetic or cellular factors. Genetic modifiers or other stimuli that alter the activity of critical upstream or downstream factors also could change the threshold.[23]

With this information, one can explain much of the observed clinical variability. Intraindividual variability occurs because cysts arise only from cells where PKD gene function has fallen below the threshold. Intrafamilial variability is explained in part by the same mechanism. Somatic mutation is a stochastic process. The timing, location, and frequency of the second hits determine the severity of disease. Other genetic modifying loci segregating randomly within a family also may alter the cyst-initiation threshold or the rate of cyst growth/fluid secretion once the threshold is breached.[23] Interfamilial differences mostly can be explained by the nature of the germline mutation. Families with particularly severe germline mutations are more likely to have multiple individuals with more severe clinical disease. Conversely families with germline mutations of *PKD2* generally have less severe disease than those with mutation of *PKD1*, probably because *PKD2* is less mutable.[24] Variants at modifying loci also likely play a role.[25]

It is likely that the same "two-hit" process accounts for the high prevalence of simple cysts in the general population as it ages. Although no studies have directly examined this thesis, the large population of cells at risk (all renal epithelial cells), the long duration of risk (lifetime), and the documented somatic instability of the loci make the probability of acquiring two somatic hits in either *PKD1* or *PKD2* very high.

ADPKD, ADPLD, and ADTKD—Overlapping Phenotypes and Genotypes

In individuals with classic ADPKD and ADPLD, there usually is little question about the underlying diagnosis, as renal cysts are the predominant manifestation in one and liver cysts in the other. With increased availability of genetic testing, however, it has become clear that there is a very small number of families with slightly atypical presentations who initially had been diagnosed as having ADPKD but instead were found to have mutations in genes other than *PKD1* or *PKD2*. In one example, seven families were reported with variably cystic kidneys and livers in which the cystic renal disease met the clinical criteria for ADPKD, but in them, the kidneys did not become enlarged or the disease progress to ESRD. DNA studies identified heterozygous pathogenic missense or truncating mutations in *GANAB*, which encodes the catalytic alpha subunit of glucosidase II (GII), an endoplasmic reticulum (ER)–resident enzyme involved in glycosylation.[3] Mutations of the same gene were additionally found in families with a more typical presentation of ADPLD.[3,8] Mutations of *PRKCSH*, which encodes the noncatalytic β subunit of GII, also cause ADPLD. In another example of ADPKD/ADPLD overlap, where some family members had typical ADPLD but others presented with mostly renal cysts, inactivating mutations were found in *ALG8*, which encodes α-1,3-glucosyltransferase, an ER integral membrane protein involved in glycosylation.[8]

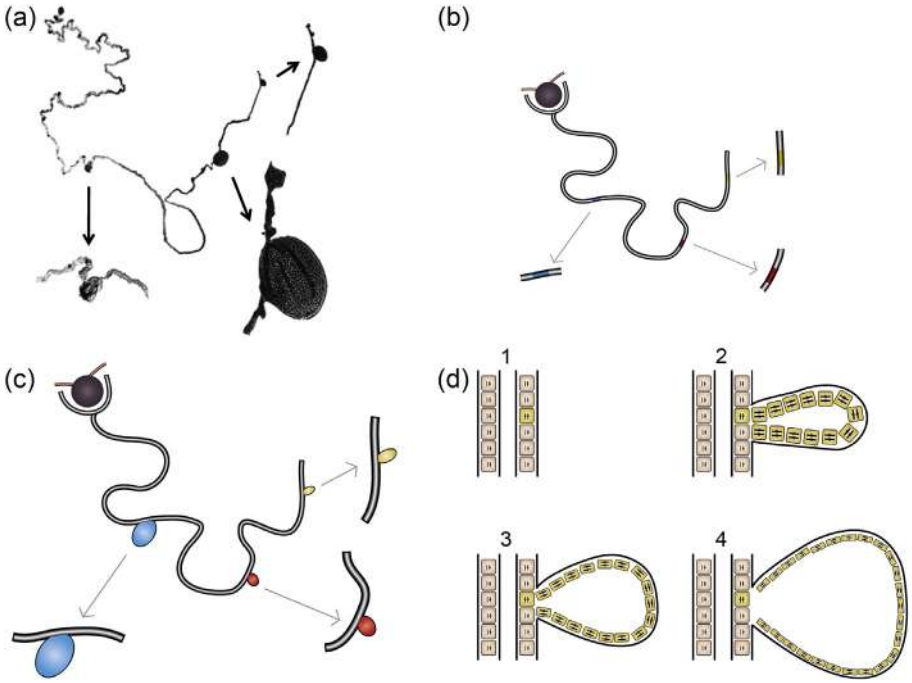


FIGURE 48.4 **Autosomal dominant polycystic kidney disease (ADPKD) cysts are focal.** (a) Microdissected nephron from a woman in her 30s with early ADPKD. The section contains a glomerulus, proximal tubule, and the loop of Henle and shows three small cysts. This elegant study clearly showed that cysts arise as localized outgrowths, initially connected[26] to nephrons, from all parts of the nephron and the collecting ducts. (b) Schematic of the same nephron but how it would have appeared prior to cyst growth. The colored areas identify locations where tubule epithelial cells will acquire a somatic mutation and initiate future cyst growth. (c) The nephron after cells with "two-hits" has begun clonal expansion. (d) Schema illustrates the different stages of cyst initiation and growth as predicted by the "two-hit" model. The first event is an acquired somatic mutation that reduces the activity of the previously normal allele (1). The "second hit" activates growth pathways which result in clonal expansion (2). As the clone expands, the cells begin to flatten and at late stages they pinch off from the tubule and lose some of their nephron-segment specific properties (3,4). *(a) Adapted from reference 26 and used with the permission of Elsevier.*

The mechanism by which mutations of *GANAB* and *ALG* cause disease has not been definitively established, but it is likely to be similar to what has been reported for *PKD1*, *PKD2*, and the ADPLD genes, *PRKCSH* and *SEC63*.[27,28] As in these other conditions, families with *GANAB* and *ALG* mutations have heterozygous variants that are either pathogenic missense substitutions or protein-truncating. The latter suggest loss of function effects.

A recent report described another small set of families initially mistaken for ADPKD that was found to have mutations in *DNAJB11* instead of *PKD1* or *PKD2*.[4] On closer inspection, the ADPKD was somewhat atypical, with variably cystic kidneys that were not enlarged and in fact often became atrophic over time, with histologic evidence of interstitial fibrosis. One family was also noted to have recurrent gout in association with the condition. Together, the presentation was more similar to Medullary Cystic Kidney Disease (OMIM 162000), a form of Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) that is clinically and genetically distinct and caused by mutations in *UMOD*, the gene that encodes Tamm–Horsfall protein (uromodulin).

Pathobiology

The decades-long interval between diagnosis and ESRD affords ample opportunity for therapeutic intervention based on a firm understanding of the pathobiology of disease. It is well established that increased cell proliferation, fluid secretion, and loss of normal renal parenchyma are key elements that together contribute to loss of renal function. The genetic origin of disease offers a unique opportunity to determine the altered signaling pathways responsible for these properties. Much of the effort over the past two decades has been focused on understanding how loss of either *PKD1* or *PKD2* triggers these changes. With the genes in hand, investigators have characterized the proteins in tissues and cell culture systems and have made genetically faithful murine models that recapitulate many aspects of the disease as well as revealing new, unsuspected functions of the proteins. A comprehensive review of this topic is beyond the scope of this chapter and is a fast-evolving science. Interested readers are referred to several recent reviews for more detailed discussions.[12,21,29–31]

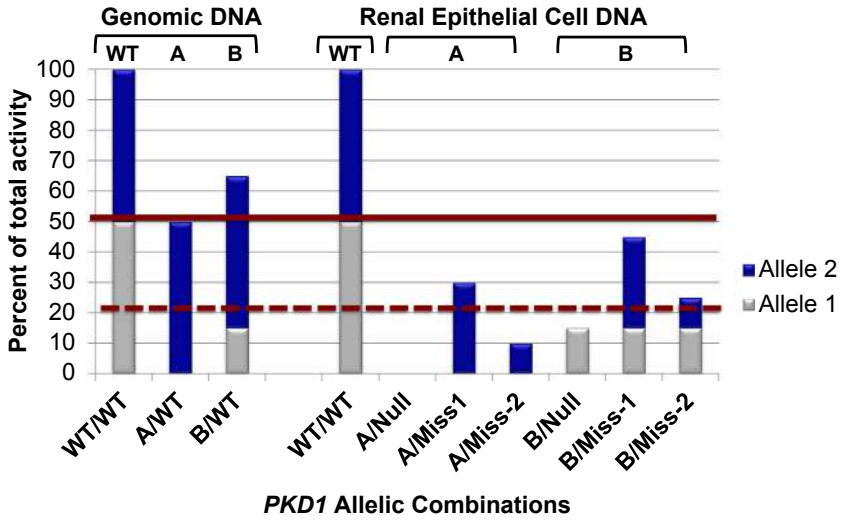


FIGURE 48.5 **The threshold model predicts that a critical level of PC1 (or PC2) is required to suppress cyst formation.** Consider two individuals (A, B) whose germline, inherited mutations have very different effects on the function of their respective mutant parental *PKD1* alleles. (A) The germline mutation results in complete loss of *PKD1* function from that parental allele ("allele 1"). This leaves the combined *PKD1* activity of the mutant and wild-type alleles at 50% as a starting point ("Genomic DNA"). (B) The germline mutation is a missense change that reduces the mutant parental *PKD1* allele's activity ("allele 1") by 70%, leaving the cell with a total of 65% *PKD1* activity. In this example, the *solid line* at 50% indicates the maximum functional *PKD1* activity of an individual that is heterozygous for a *PKD1* null mutation and the threshold that triggers cyst formation is below this level (*dotted line* at 20%). On the right, the samples are from individual renal epithelial cells of the same individuals. For (A) and (B), three "cells" that have acquired unique mutations are shown. "Miss1" and "Miss2" identify acquired missense mutations (allele 2) that reduce allelic function to 60% and 20% of normal (NL), respectively. "Null" identifies an acquired fully inactivating mutation (allele 2). In this example, (A) has two samples that fall below the 20% threshold. In contrast, (B) will only have one sample below the 20% line. In sum, individuals who have more severe germline mutations are more likely to have severe cystic disease because more types of acquired mutations will reduce total gene activity below the threshold.

The *PKD1* gene encodes a membrane receptor (Polycystin-1; PC1) and *PKD2* a nonselective cation channel (Polycystin-2; PC2), which together function as a receptor-channel complex on the cell surface, and possibly at the attachment site of the endoplasmic reticulum to mitochondria.[21,29–34] Although initial studies suggested that PC2 was most likely a calcium channel, recent studies have called this into question, suggesting the channel has higher preference for monovalent cations such as potassium or sodium, and that its activity is instead regulated by calcium.[35–38] The complex localizes to the primary cilia, a microtubule-based structure that projects from the apical surface of most cells. Cilia are thought to function primarily as cellular environmental sensors and signaling organelles. The primary cilium has emerged as a major player in the cystic field. Almost every cystoprotein (i.e. a protein encoded by a gene whose mutation results in renal cystic disease in humans or other species) has been localized to the primary cilium or the associated protein networks that regulate its formation and function (Figure 48.6).

Until recently, the prevailing model had been that primary cilia normally signal to suppress cyst formation, and the ciliary PC1/PC2 complex plays a key role in this. The polycystin complex was postulated to function as a flow sensor that signaled by triggering release of intracellular calcium stores and regulating other signaling pathways.[39,40] A recent mouse study has revealed unexpected complexities in the relationship between ciliary function and the PC1/PC2 complex. Specifically, primary cilia signaling can either suppress or promote cyst growth, depending on context.[41] This will likely complicate efforts to manipulate ciliary signaling as an approach to therapy.

The PC1/PC2 complex is thought to cap a cascade of intersecting signaling pathways that cooperate to regulate cellular growth, fluid secretion, and tubular morphology. Although a number of pathways have been directly linked to PC1 or PC2, such as mTORC1, canonical and noncanonical WNT, JAK-STAT, and heterotrimeric G-proteins, there is no consensus regarding which if any are functionally important. Although it is generally assumed that the calcium second messenger pathway is an important immediate downstream target of polycystins, how this links to the pathophysiology of cystic disease remains undefined.

Multiple other signaling pathways whose activities have not yet been directly linked to PC1 and PC2 have also been implicated in the disease. These include SRC kinase, the mitogen-activated protein kinase/extracellular regulated kinase (MAPK/ERK) cascade, and cAMP.[29,30] Alterations in level of intracellular calcium,

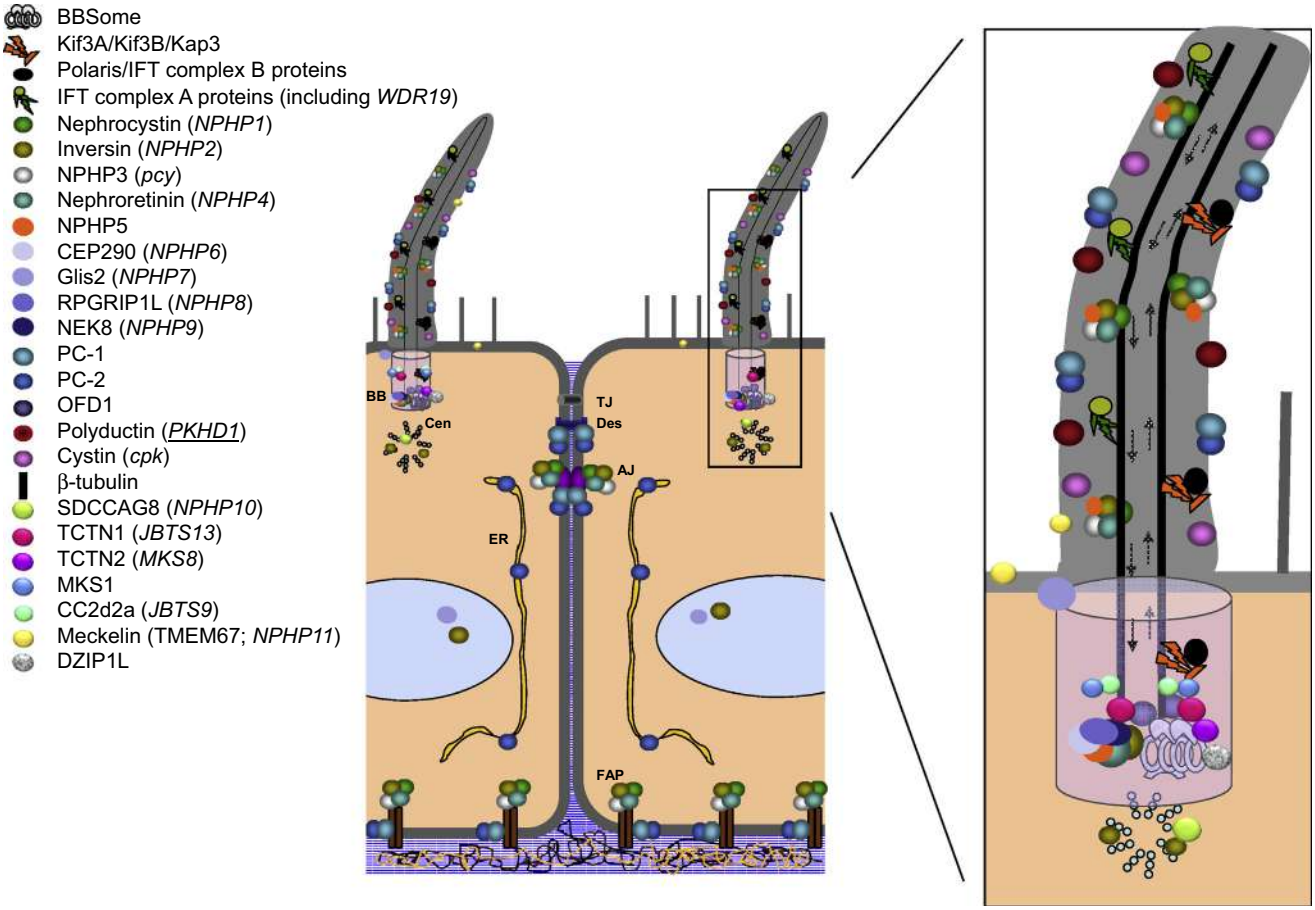


FIGURE 48.6 **Subcellular localization of cystoproteins.** Over 60 cystoproteins have been localized to the primary cilium/basal body complex (legend on top left) but many also map to other intracellular domains. The majority of genes that encode these proteins have been reported to cause a ciliopathy or cystic phenotype in both humans and rodents when mutated. Mutations in several of the genes result in a wide variety of related conditions with distinct findings (nephronopthisis [NPHP], Senior-Loken Syndrome, Joubert [JBTS], and Meckel–Gruber [MKS]). *AJ*, adherens junction; *BB*, basal body; *Cen*, centriole; *ER*, endoplasmic reticulum; *FAP*, focal adhesion plaque; *TJ*, tight junction. *Adapted from reference 29 and used with permission of Elsevier.*

resulting from decreased PC1/PC2 activity, may play a role in activating some of these systems. There has been considerable interest in these pathways, as there are FDA-approved therapies that target them.

The cAMP signaling system has been of particular interest. Its higher level of activity in cystic epithelia is thought to drive CFTR-dependent fluid secretion and increase cellular proliferation *via* the B-Raf/MEK/extracellular signal-regulated kinase pathway.[42,43] The effects on B-Raf are thought to result from the altered cytoplasmic calcium activity present specifically within cystic epithelial cells. Dysregulated calcium signaling also is thought to increase cAMP levels through opposite effects on calcium-sensitive phosphodiesterases and adenylate cyclases that are responsible for degrading and boosting cAMP levels, respectively.

These observations prompted investigators to evaluate whether interventions that reduced cAMP activity had any effects on cyst growth. They found that genetic, dietary, and pharmacologic interventions that reduced vasopressin-2 receptor (V2R) activity reduced the rate of cyst growth and the decline of renal function.[30,44] Because increased cAMP activity is thought to also drive biliary cyst growth where V2R is not expressed, investigators postulated that activation of the somatostatin receptor, which increases Gαi activity and decreases cAMP, might also be beneficial. Pilot studies of humans with severe polycystic liver disease treated with octreotide, a somatostatin receptor agonist, reported modest benefit.[45]

Finally, several recent studies suggest a role for dysregulated metabolic pathways in cyst formation and growth.[12] PC1 reportedly binds to tuberin, the gene product of the *Tuberous Sclerosis 2* (*TSC2*) locus, a known regulator of mTOR signaling.[46,47] Several studies have reported increased mTOR activity in cystic tissue, and inhibitors such as rapamycin slow cystic growth.[46,48] Other studies suggest that the activity of AMPK, both

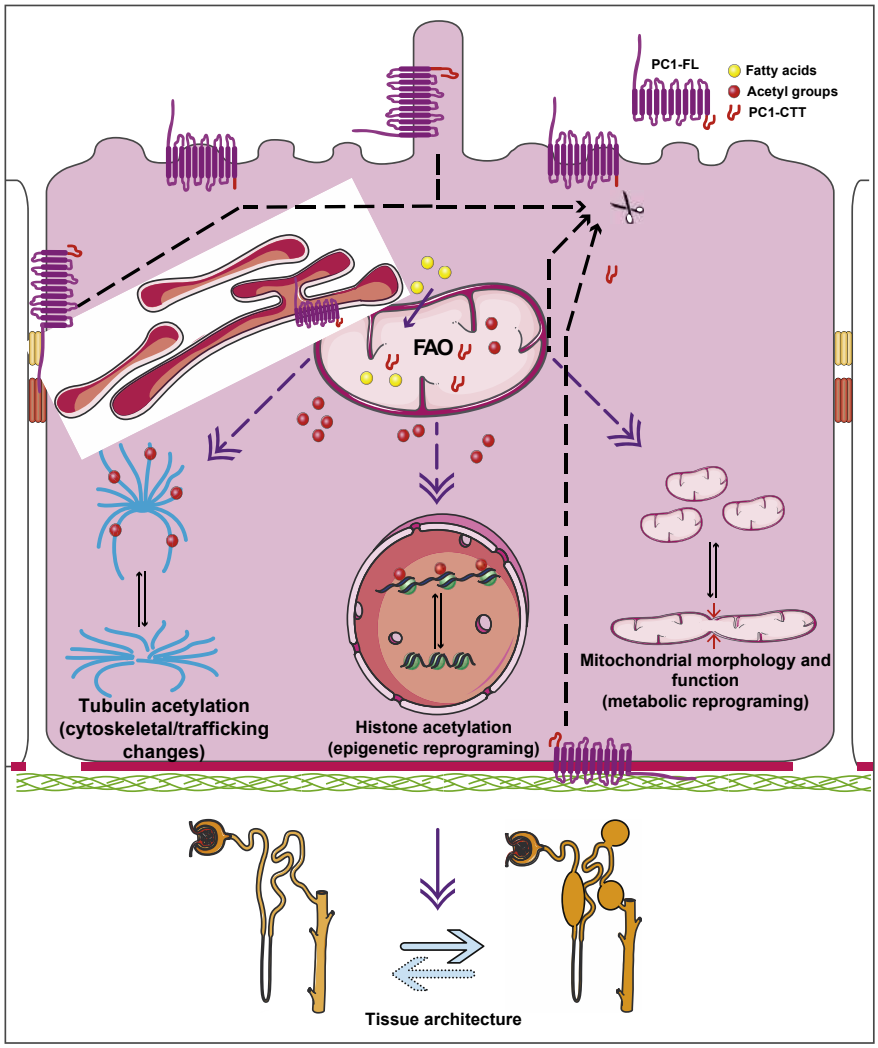


FIGURE 48.7 **Model of how PC1 signaling could regulate nephron architecture.** PC1 could respond to ligand binding or mechanical stimuli (from cilia, cell−cell or cell—matrix interactions) by modulating mitochondria activity and acid oxidation (FAO). Altered FAO could change the pool of acetyl-CoA (and possibly reactive oxygen species and NAD+/NADH), with effects on tubulin acetylation (affecting trafficking and cytoskeleton) and histone acetylation (possibly with global gene expression reprogramming), processes previously linked to PKD. A similar cascade was observed in lymphangiogenesis and planar cell polarity, processes previously linked to *Pkd1* function.[49] *Used under Copyright Commons License 4.0.*

a nutrient-sensitive kinase and regulator of CFTR, is decreased in cystic kidneys. Treatment of rodents with metformin, a known activator, slowed cyst growth.[50] Clinical trials are underway testing this thesis in humans (NCT02656017, NCT02903511). Transcriptomic and metabolomic analyses of normal and cystic murine kidneys suggest that multiple metabolic pathways, including glycolysis and fatty acid metabolism are dysregulated in cystic tissue, and that manipulation of these pathways with drugs, diet, or genetic manipulations can slow renal growth.[51−55] Moderate to large caloric restriction in rodents also has been shown to be highly effective in slowing progression, even reversing disease.[56,57]

Recent studies suggest mitochondrial dysfunction might play a central role in the pathogenesis of disease. Human and mouse cystic kidneys have abnormal mitochondria structure.[49,58] A portion of PC1 is reported to localize to the mitochondria, where it may regulate mitochondrial network structure and calcium uptake.[34,49]

Figure 48.7 presents one model of how PC1, acting through cellular metabolism, could result in changes in nephron tubular structure. PC1 may detect mechanical or other signals at cilia, cell−cell and/or cell−matrix sites of interaction and transmit this information to mitochondria through release of a cleavage product. The latter may regulate mitochondrial function and affect cellular redox activity, NAD+/NADH levels, and acetyl-CoA levels. Loss of PC1 activity could result in metabolic reprogramming and alterations in acetyl-CoA levels, which can, in turn, mediate epigenetic or

cytoskeletal changes. Collectively, these effects could disrupt the normal activity of the many signaling pathways that maintain cellular structure and function under homeostatic conditions and result in the cystic phenotype that is characterized by numerous dysfunctional signaling pathways.[49]

ARPKD

Molecular Basis of Disease—PKHD1

All typical forms of ARPKD are caused by mutations in *PKHD1*, a large ~500 kb gene with a complex splicing pattern.[59,60] Mutations have been identified along the entire length of the *PKHD1* gene, and multiple mutation types have been described as pathogenic. To date, more than 700 pathogenic mutations have been cataloged in the ARPKD Mutation Database (http://www.humgen.rwth-aachen.de),[61] of which approximately half are missense changes. The most common mutation overall is a missense mutation in exon 3, c.107C>T (p.Thr36Met), which accounts for approximately 20% of all mutated alleles.[62] Aside from this mutation, which has been observed in a large number of unrelated patients, there do not appear to be any mutational hotspots. Indeed, a large proportion of mutations are unique to a single pedigree.[63]

Multiple studies have examined ARPKD cohorts for potential genotype–phenotype correlations. Given the diversity of *PKHD1* mutations, most patients are compound heterozygotes, and the functional effect of any particular mutant allele can be difficult to discern. Nevertheless, some broad themes have emerged. Notably, patients with two truncating mutations typically have a severe phenotype leading to perinatal or neonatal mortality.[63] However, there are notable exceptions, e.g. a child who is homozygous for a large *PKHD1* deletion surviving well past the neonatal period.[64] Moreover, not all missense mutations lead to a more benign outcome. A number of missense mutations result in severe phenotypes when present with a truncating mutation or in homozygous form.[63] Genetic modifiers likely also play a significant role in disease expression, as illustrated by significant phenotypic variability in subsets of families. For example, in a study of 126 unrelated families, 20 sibships showed widely discordant phenotypes (perinatal lethality in one sibling and survival into childhood in the other).[62]

Taken together, these genetic features pose particular challenges for genetic counseling of ARPKD families.

Atypical ARPKD and Phenocopy Disorders

Although ARPKD is generally considered a genetically homogeneous disease, a recent report described seven children from four unrelated, consanguineous families with an atypical form of ARPKD that results from mutations in a second gene, *DZIP1L*.[11] The children presented with hypertension and large, cystic kidneys; some had progressed to ESRD. A distinguishing feature of this ARPKD phenotype is the more moderate renal disease and the absence of clinically apparent liver disease.

The *DZIP1L* gene spans about 53 kb and encodes a 767 amino acid ciliary transition zone protein, DAZ interacting protein 1-like (DZIP1L). Among the four reported families, two families had different homozygous missense changes predicted to be pathogenic, while the other two had distinct, homozygous truncating mutations. While the function of DZIP1L is largely unknown, it is implicated in hedgehog signaling and ciliogenesis.

ARPKD is the prototype of the hepatorenal fibrocystic diseases (HRFDs), a subset of recessively transmitted cilia-related disorders, or ciliopathies, which are characterized by renal cystic disease and can be associated with congenital hepatic fibrosis and/or Caroli syndrome as well as extrarenal manifestations.[65] These rarer disorders in which the kidney disease can phenocopy ARPKD include nephronophthisis (MIM 256100), Joubert syndrome (MIM 213300), Bardet–Biedl syndrome (MIM 209900), Meckel–Gruber syndrome (MIM 249000), and oro-facial-digital syndrome I (MIM 311200). As with FPC and DZIP1L, the proteins disrupted in these disorders are critical in the structure/function of the primary apical cilium.[66]

Finally, a form of PKD that can mimic either ARPKD or ADPKD and is associated with hyperinsulinic hypoglycaemia (HIPKD) has been described in 11 pedigrees, who had biallelic mutations in *PMM2*, which encodes phosphomannomutase 2.[67] PMM2 is a key enzyme in N-linked glycosylation. Recessive mutations in *PMM2* are usually associated with congenital disorder of glycosylation type 1a (CDG1A), which has a severe, pleiotropic phenotype.

Pathobiology

The product of the *PKHD1* gene, fibrocystin/polyductin (FPC), is a 4074 amino acid, single-membrane spanning protein with a long extracellular N-terminus and short cytoplasmic C-terminus, which appears to have multiple isoforms.[60] During fetal development, *PKHD1* is expressed widely and is found in the neural tube, bronchi, primordial gut, early ureteric bud, mesonephric tubules, adrenal cortex, and immature hepatocytes, suggesting a role in organ development and tubular morphogenesis. In adult tissues, it is expressed predominantly in the kidney (mostly in collecting ducts and thick ascending loops of Henle), liver (localized to bile ducts), and pancreas.[68,69] In renal tubular and biliary epithelial cells, FPC localizes to the apical membranes, as well as to the primary cilia/basal

body[60,68,70] and mitotic spindle.[71] A subset of membrane-bound FPC appears to undergo Notch-like proteolytic processing, with shedding of the extracellular domain into the tubular lumen and nuclear translocation of the C-terminus, where it may play a role in downstream signaling.[68,69,72] However, predictions regarding the nuclear function of the cytoplasmic C-terminus are confounded by a recently reported mouse model that was engineered to lack most of the C-terminus and is phenotypically normal, without renal or hepatic disease even when aged.[69]

The function of FPC remains unclear. In animal studies, mice-harboring mutations in both *Pkhd1* and either of the ADPKD genes (*Pkd1* or *Pkd2*) display cystic phenotypes much more severe than those seen with either mutation alone, suggesting genetic interaction *in vivo*.[27,73] However, a direct physical interaction between FPC and PC1 has not been demonstrated. The functional significance of the reported interaction of FPC with PC2[73] is uncertain, because *Pkhd1* mutant mice lacking the FPC–PC2 interaction domain are phenotypically normal.[69]

A recent study suggests that FPC may indirectly regulate the function of the C2-WWW-HECT domain E3 family of ubiquitin ligases, by affecting the subcellular localization of NDFIP2, a protein implicated in regulating the trafficking and function of the E3 ubiquitin ligase family.[74] This protein family includes SMURFs and NEDD4, which are known to regulate the activity of RhoA, TGF-β signaling, and ENaC activity, all of which have been reported to be upregulated in ARPKD renal and biliary epithelial cells. Although these data provide a unifying explanation for the observed changes in cytoskeletal structure, increased fibrosis, and enhanced sodium absorption and hypertension, the mechanism through which FPC modulates NDFIP2 function remains unknown.

The reported localization of FPC to the basal body/primary cilium provides another intriguing but incomplete insight into its function. As noted, FPC, DZIP1L, and other proteins associated with HRFD (e.g. ADPKD, nephronophthisis, and Meckel, Joubert, and Bardet–Biedl syndromes) also localize to these structures (Figure 48.6). Taken together, these data suggest a central role for the primary cilium in the development and maintenance of renal tubular architecture, perhaps *via* mechanisms such as flow sensing and establishment of planar cell polarity, but the specific function of FPC in any of these processes remains undefined.

As in ADPKD, the cAMP signaling system is activated in ARPKD,[75] as is the mTOR pathway.[76,77] Yet, efforts to translate these findings to human clinical trials have been complicated by incongruities between human disease and animal models, and the lack of noninvasive markers to track disease progression and assess outcomes. For example, although agents that target cAMP activation have been shown to be effective in attenuating cystic disease progression in the *pck* rat (orthologous ARPKD model),[78] mTOR inhibition in this rat model failed to impact progression of kidney and liver disease.[79] Thus, current research efforts are focused on optimizing the preclinical studies with targeted therapeutics in experimental models and developing noninvasive markers for human clinical trials, which assess progression endpoints and are acceptable to regulatory agencies.

DIAGNOSIS

ADPKD

Renal sonography is the diagnostic mainstay in ADPKD. It is widely available, relatively low cost, with good patient tolerance, and lack of known toxicity. The criteria used to assign a diagnosis, i.e. number of renal cysts, have been defined in studies of large cohorts of genetically well-defined families (Table 48.1). The diagnostic threshold is age-dependent, reflecting the age-dependent penetrance of disease. The original Ravine criteria, established in the 1990s, have been revised in recognition of the milder disease course typical of patients with *PKD2*-linked disease.[80,81]

In evaluating individuals presenting with renal cystic disease, a detailed family history is required, both to guide the decision process and to alert the clinician about risk for comorbidities, such as ICA. If a family history of ADPKD is established, there are well-defined standards for clinical management.[80,81]

Even with the clinical introduction of enhanced imaging techniques, there remain a significant subset of individuals for whom the diagnosis is uncertain. They may lack family history, have a borderline number of cysts, have kidneys that are not enlarged, or express other atypical features, such as asymmetric cystic disease, which increase diagnostic uncertainty. This diagnostic uncertainty is particularly problematic in evaluating at-risk family members less than 30 years old with truncating *PKD1* mutations or less than 40 years old with other classes of *PKD1* or *PKD2* mutations as potential transplant donors, because a normal renal ultrasound does not exclude ADPKD with certainty. Ultrasound is also less sensitive for individuals with large BMI. Rarely, high-resolution ultrasound may yield false positive diagnoses.[82] Contrast CT scans or noncontrast MRI may provide better sensitivity and specificity, particularly in young at-risk individuals. In one small study of 110 at-risk individuals aged 16–40 years from families with known genetic mutations (73 affected, 37 at-risk unaffected, 45 unrelated controls), a threshold of greater than 10 cysts by

TABLE 48.1 Sonographic Criteria for Diagnosing and Excluding Autosomal Dominant Polycystic Kidney Disease in Individuals With Positive Family History but Unknown Genotype

Age Group (yr)	Diagnostic Criterion	PPV (SEN)	NPV (SPEC)
15–29	>1 renal cyst	0.966 (89.3%)	0.908 (97.1%)
	>2 renal cysts[a]	0.992 (84.8%)	0.877 (99.4%)
	>3 renal cysts[a]	1.00 (81.7%)	0.855 (100%)
	>2 renal cysts in each kidney	1.00 (82.8%)	0.875 (100%)
	>1 renal cyst	0.94 (98%)	0.983 (94.8%)
30–39	>2 renal cysts[a]	0.979 (96.4%)	0.970 (98.3%)
	>3 renal cysts[a]	1.00 (95.5%)	0.964 (100%)
	>2 renal cysts in each kidney	1.00 (90%)	0.948 (100%)
	>1 renal cyst	0.897, (100%)	1.00 (93.9%)
40–59	>2 renal cysts[a]	0.967 (100%)	1.00 (98.2%)
	>3 renal cysts[a]	0.965 (97%)	0.984 (98.1%)

NPV, negative predictive value; *PPV*, positive predictive value; *SEN*, sensitivity; *SPEC*, specificity.
[a]*One or both kidneys.*
Adapted from Pei et al.[81,82]

MRI was found to be 100% sensitive and specific. This threshold, however, has not yet been validated in large cohorts or diverse populations.[82] At present, in most situations, the two best options for the clinician are to provide standard clinical management with periodic repeat imaging or DNA testing.

Differential Diagnosis of ADPKD

The most common diagnostic challenge in considering ADPKD is determining whether an individual lacking a family history has simple cysts or a genetic cause. The proportion of the population with simple cysts increases with age, from a few percent in individuals below age 30 years to 25% of those >70 years. The latter cohort often has at least one cyst in each kidney but rarely more than three per kidney.

Some individuals have few or no kidney cysts but prominent liver cystic disease. In many cases, these patients have a family history consistent with an autosomal dominant pattern of inheritance. These individuals have ADPLD, a genetically heterogeneous disorder that results from mutation of at least six distinct genes: *PRKCSH*,[83] *SEC63*,[84] *SEC61B*,[8] *LRP5*,[85] *GANAB*,[3] and *PKHD1*.[8] The liver cystic disease is clinically indistinct from that associated with ADPKD. The two conditions are primarily distinguished by the presence or absence of significant renal cystic disease. In the unusual cases where individuals with ADPLD present with many renal cysts, the kidneys are not enlarged and they do not progress to ESRD.

Although ADPKD and ARPKD usually have distinct clinical presentations, there is a subset of the latter that presents in late childhood or adulthood with significant liver disease and focal cystic renal disease.[86] Moreover, congenital hepatic fibrosis is occasionally expressed in ADPKD.[87] ARPKD should be suspected if imaging studies indicate both biological parents are clinically unaffected.

Numerous other conditions are associated with renal cysts, including both nongenetic and genetic disorders. Those transmitted as dominant traits are typically distinguished from ADPKD by their extrarenal manifestations (Table 48.2). The majority of other renal cystic diseases are recessive disorders and thus distinguished from ADPKD by their mode of inheritance (Table 48.3).

Genetic Testing in ADPKD

Given the advances in sequencing technologies and the dramatic decrease in cost, DNA-based testing could soon emerge as the most effective and definitive diagnostic method. There are a number of important caveats, however. First, as indicated above, there are multiple *PKD1* homologues, i.e. pseudogenes, with nearly identical sequence to *PKD1*, and these sequences must be distinguished from that of the actual gene.[88] Until recently, multiple enrichment steps were required to isolate *PKD1*-specific gene fragments prior to sequencing,[89] making the method technically challenging. However, recent developments in next generation sequencing (NGS) may have overcome this problem.[90–92]

TABLE 48.2 Renal Cystic Diseases That can Mimic Autosomal Dominant Polycystic Kidney Disease

Disorder	MIM	Gene(s) Protein(s)	Inheritance	Distinct Clinical Features
Simple Cysts	Not applicable	None	None	Normal kidney size; isolated cysts, usually no more than 4/kidney at age 60
Acquired Cystic Disease	Not applicable	None	None	Develops in individuals with chronic kidney disease from other cause; kidneys usually small; can progress to renal cell carcinoma
Tuberous Sclerosis Complex	191100 613254	*TSC1*, *TSC2* Tuberin1, Tuberin2	AD	Associated with a wide variety of other clinical features involving the kidney (angiomyolipoma, renal cell carcinoma), skin (hypomelanotic macules, facial angiofibromas, shagreen patches, fibrous facial plaques, ungula fibromas), brain (cortical tubers, subependymal nodules, subependymal giant cell astrocytomas, seizures, intellectual disability), heart (rhabdomyoma, arrhythmias), lung (lymphangioleiomyomatosis)
Oro-facial-digital Type 1 syndrome	311200 300170	*CXORF5* OFD1	X-linked dominant	Lethal in males; families have female-to-female transmission. Characterized by malformations of the face (widely spaced eyes, hypoplasia of the alae nasi, micrognathia, cleft, or pseudocleft lip), oral cavity (lobed tongue, hamartomas, or lipomas of the tongue, dental abnormalities, cleft palate) and digits (duplicated hallux, polydactyly, brachydactyly, syndactyly, clinodactyly), brain (intellectual disability, agenesis of corpus callosum or cerebellum, intracerebral cysts, intracerebral cysts)
Autosomal Recessive PKD	263200 606702 617610	*PKHD1*, *DZIP1L* Fibrocystin/polyductin, DZIP1L	AR	Congenital hepatic fibrosis with hypersplenism and other signs of portal hypertension. Very early onset ADPKD (1−2% of affected children) may be clinically indistinguishable from ARPKD.
Polycystic Liver Disease	174050 608648 177060	*PRKCSH*, Glucosidase II, β subunit *GANAB*, Glucosidase II, α subunit *SEC63*, Translocation Protein SEC63 *SEC61B*, Translocation Protein SEC61b *ALG8*, α-1, 3-glucosyltransferase *PKHD1*, Fibrocystin	AD	Age-dependent expression of numerous hepatic cysts; few if any renal cysts.
Renal Cysts and Diabetes Syndrome (Maturity-Onset Diabetes of the Young Type 5)	137920	*TCF2* HNF1β	AD	Exocrine pancreatic failure and pancreatic atrophy; maturity-onset type diabetes of the young; abnormalities of the genitourinary system; hyperuricemia common. Associated with a broad range of renal abnormalities.
Von Hippel Lindau syndrome	193300 608537	*VHL* VHL	AD	Pheochromocytomas, papillary cystadenoma, renal tumors and renal cell carcinoma, hemangioblastomas of the retina, and central nervous system.

AD, autosomal dominant; *AR*: autosomal recessive; *MIM*, Mendelian inheritance in man.

TABLE 48.3 Hepato-renal Fibrocystic Diseases

Disease	Gene(s)	Renal Disease	Hepatic Disease	Associated Features
ARPKD	*PKHD1; DZIP1L*	Collecting duct dilatation	CHF*; Caroli disease	Growth retardation
ADPKD	*PKD1; PKD2; GANAB*	Cysts along entire nephron	Biliary cysts; CHF	Minimal in children
Nephronophthisis (NPHP)	*NPHP1—NPHP20*	Cysts at the corticomedullary junction	CHF	Tapetoretinal degeneration; situs inversus
Joubert syndrome (JBTS)	*JBTS1—JBTS35*	Cystic dysplasia; NPHP	CHF; Caroli disease	Cerebellar vermis hypo/aplasia with episodic hyperpnea; abnormal eye movements; intellectual disability
Bardet—Biedl syndrome (BBS)	*BBS1—BBS21*	Cystic dysplasia; NPHP	CHF	Retinal degeneration; obesity; postaxial polydactyly; hypogonadism in males; intellectual disability
Meckel—Gruber syndrome (MKS)	*MKS1—MKS13*	Cystic dysplasia	CHF	Occipital encephalocele; polydactyly
Oral-facial-digital syndrome, Type I	*CXORF5*	Glomerular cysts	CHF (rare)	Malformations of the face, oral cavity, and digits
Glomerulocystic disease	*PKD1; TCF2; UMOD*	Enlarged; normal or hypoplastic kidneys	CHF (with *PKD1* mutations)	Diabetes; hyperuricemia
Jeune syndrome (short-rib thoracic dystrophy [SRTD])	*SRTD1—SRTD20*	Cystic dysplasia	CHF; Caroli disease	Short stature; skeletal dysplasia; small thorax; short limbs; polydactyly; hypoplastic pelvis
Renal-hepatic-pancreatic dysplasia (RHPD)	*NPHP3; NEK8*	Cystic dysplasia	Intrahepatic biliary dysgenesis	Pancreatic cysts, dysplasia, and/or fibrosis; splenic abnormalities; situs inversus
Zellweger syndrome	*PEX1—3;5—7;10—14;16;19;26*	Renal cortical microcysts	Intrahepatic biliary dysgenesis	Hypotonia; seizures; agenesis/hypoplasia of corpus callosum; characteristic facies; skeletal abnormalities; neonatal death

* *CHF, congenital hepatic fibrosis.*
Adapted from O'Connor et al.[66]

Second and more clinically relevant, DNA testing is reliable in identifying sequence variants in a gene of interest, but it is less effective in predicting the disease-causing potential of these sequence changes. For variants predicted to cause a truncated or absent protein, the molecular diagnosis is readily established. However, in about half of the cases, missense changes predicted to result in amino acid substitutions, small in-frame deletions, or no variants are identified.[16,17,92] Even with current bioinformatic tools, the likely pathogenicity of such variants is not clear, and a definitive DNA diagnosis is not possible.

The final challenge with current DNA testing is that it is not a good predictive tool. Although certain types of mutations are statistically associated with more severe disease (e.g. mutations in *PKD1*, and truncating changes, especially those nearer the 5′ end of *PKD1*), there is considerable heterogeneity and this information is of limited use for counseling purposes.[24]

Despite the limitations, there are circumstances where a DNA-based diagnosis may be advantageous:

- Living related donor evaluation: For younger, at-risk candidate donors whose disease status is unknown, imaging studies may yield nondiagnostic results and DNA testing can help guide decision-making.[93] In this case, the recipient is tested first to identify a definitive mutation, and if positive, then a directed test can be performed in the potential donor to determine whether the mutation is present.
- Diagnostic uncertainty: Examples include individuals with borderline clinical findings, renal dysfunction out of proportion to the degree of cystic disease, suspected *de novo* disease, and atypical disease presentations.
- Prenatal or preimplantation testing: As with pretransplant testing, this method is used only when a pathogenic mutation is identifiable in the donor of the egg or sperm.
- Early and severe disease or very large intrafamilial disease discordance: A form of very early onset ADPKD occurs in 1−2% of affected children and may be clinically indistinguishable from ARPKD.[94] These severe ADPKD cases can result from a combination of mutations in *PKD1* and hypomorphic (limited loss of function) alleles of other genes that cause cystic kidney disease.[95] Therefore, genetic testing should be considered to evaluate the contribution of other "cystogenes" to the clinical disease expression.

Diagnostic Screening in Individuals At-risk for ADPKD

In the absence of target therapy for PKD, a conservative approach has traditionally been preferred in asymptomatic at-risk individuals because there was little direct benefit in establishing a specific diagnosis, and there were practical risks regarding insurability for life, disability, and until recently in the US, health care. However, the approach differed somewhat by health system. In Europe, presymptomatic testing was relatively common. In the US it was not, with clinicians typically monitoring at-risk individuals for hypertension and pursuing diagnostic studies only after the onset of symptoms. Even in the US, there were important exceptions, where establishing the diagnosis might change clinical management (e.g. athletes participating in high-impact contact sports, individuals with a positive family history of ADPKD and aneurysms, and individuals interested in serving as a transplant donor for an affected family member) or where at-risk individuals wanted to know their status. This conservative approach, however, has been predicated on the assumption that there was little to offer other than symptomatic care. The recent approval of tolvaptan for individuals most at risk for progression changes the risk−benefit calculation, and clinicians should consider this factor when deciding whether to test.

Diagnostic screening in asymptomatic children is controversial due to the limited sensitivity of ultrasonography, particularly in children less than 5 years of age,[96] and the ethical concerns about screening asymptomatic minors. Renal imaging should be pursued primarily in at-risk children with hypertension, hematuria, and/or proteinuria. Screening for extrarenal features of the disease is not recommended during childhood.

In sum, the decision of when and how to screen asymptomatic individuals must be customized to the individual/family-specific circumstances.

ARPKD

Imaging

ARPKD is typically first detected on routine prenatal ultrasound. Suggestive features in a fetus include symmetrically enlarged, echogenic kidneys (due to multiple microscopic cysts) with loss of corticomedullary differentiation due to medullary hyperechogenicity[97] (Figures 48.2 and 48.3). Discrete cysts are sometimes evident.[98] Oligohydramnios may be present due to poor fetal urine output.[6,97] However, normal sonographic findings do not necessarily exclude a diagnosis of ARPKD because abnormalities may not be evident until late in the second trimester (or beyond), even in infants who go on to manifest a severe phenotype at birth.[6,97,99] In addition, the presence or absence of oligohydramnios does not always correlate with disease severity or degree of pulmonary insufficiency.[99]

ARPKD can often be distinguished on fetal imaging from other HRFD[65] (Table 48.3), as well as ADPKD. ARPKD kidneys *in utero* are typically hyperechogenic and display *decreased* corticomedullary differentiation due to the hyperechogenic medulla. With high-resolution ultrasound, the radial array of dilated collecting ducts may be imaged. Although the other HRFD are characterized by large, echogenic kidneys in the fetus and neonate, they can often be distinguished from ARPKD by the presence of extrarenal manifestations (e.g. central nervous system abnormalities, eye defects, and/or polydactyly).[98] In comparison, ADPKD kidneys *in utero* tend to be moderately enlarged with a hyperechogenic cortex and relatively hypoechogenic medulla causing *increased* corticomedullary differentiation.[100]

A recent International Working Group Consensus Statement recommends ultrasonography as the method of choice for assessing renal cystic disease in children, with selected indications for MRI and contrast-enhanced ultrasound. Ultrasonography yields essential diagnostic information in most cases, and in patients with ARPKD or other HRFD, abdominal ultrasonography is a useful tool for screening for and diagnosis of portal hypertension.[101] There is broad consensus that CT should be avoided in children whenever possible because of the exposure to ionizing radiation.

In children with ARPKD, kidney size typically peaks at 1–2 years of age, then gradually declines relative to the child's body size and stabilizes by 4–5 years.[102] As patients age, there is increased medullary echogenicity with scattered small cysts, measuring less than 2 cm in diameter. These cysts and progressive fibrosis can alter the usual kidney contour, causing ARPKD in some older children to be mistaken for ADPKD.[103] Contrast-enhanced MRI can be useful in delineating the renal architecture in these children. Bilateral pelvicaliectasis and renal calcifications have been reported in 25% and 50% of ARPKD patients, respectively.[86,104] In adults with medullary ectasia alone, the cystic lesion may be confused with medullary sponge kidney (Figure 48.3).

The liver may be either normal in size or enlarged. Prominent intrahepatic bile duct dilatation suggests associated Caroli syndrome. With age, the portal fibrosis tends to progress. In older children, ultrasound typically shows hepatosplenomegaly and a patchy increase in hepatic echogenicity.[105,106]

Genetic Testing in ARPKD

Molecular diagnostic analysis is rapidly becoming the gold standard for diagnosing ARPKD and distinguishing this disorder from the large number of phenocopying disorders or syndromes.[107] In practice, screening a panel of genes rather than analysis of *PKHD1* alone has become the preferred diagnostic approach.[108] Advances in NGS now enable simultaneous analysis of a large group of genes in a single test at relatively low cost. While whole exome or whole genome-based screening may become the mainstay for genetic testing in the near future, at present, targeted NGS panel testing is the most efficient diagnostic approach. Whichever methodology is used, the testing strategy should be designed to detect copy number variations such as heterozygous deletions (for example, in *HNF1B*) and to cover complex genomic regions, such as *PKD1*.

Clinical genetic testing laboratories are summarized at the NIH-sponsored Genetic Testing Registry, www.ncbi.nlm.nih.gov/gtr.

Preimplantation Genetic Diagnosis

In families who have had a previous child with severe ARPKD, preimplantation genetic diagnosis (PGD) offers an alternative to prenatal diagnosis in a current pregnancy. The procedure requires prospective identification of the *PKHD1* mutations transmitted from each parent. The couple then must undergo *in vitro* fertilization. The resulting embryo is biopsied, with removal of 1–2 embryonic cells for genetic testing.[109] PGD has guided the birth of unaffected infants in at-risk families.[110,111]

MANAGEMENT AND TREATMENT

Until recently, the clinical management of individuals with ADPKD was focused on treating disease complications, reducing the risk of cardiovascular disease, and providing genetic counseling. The hope had been that ongoing research would one day identify new therapies that slowed or even prevented cyst growth and progression to ESRD. This section will first review the current status of therapies that hold the potential to alter the disease course and then, discuss symptomatic management for ADPKD and ARPKD.

Slowing Disease Progression

The discovery of the PKD genes and the generation of genetically faithful mouse models have provided important tools and insights into disease pathobiology. The weight of the evidence strongly indicates that cell proliferation is a key step in disease pathogenesis. Presumably, if one could stop cystic epithelial cell division, one could prevent cyst expansion. Unfortunately, the very slow, progressive nature of ADPKD poses real challenges for treatment. In ARPKD, the very early disease onset poses different, but equally vexing changes. Therapies will likely have to be given for decades, they must be able to selectively inhibit cystic epithelial cells, and they must have minimal off-target effects.

In addition to the biological hurdles, there is the challenge of establishing clinical trial designs that can measure clinically significant changes in outcome in a timeline compatible with pharmaceutical industry requirements. The usual acceptable study endpoints, e.g. doubling of S[Cr] or development of ESRD, occur very late in PKD patients, typically after much of the kidney architecture has already been destroyed. It is widely recognized that therapies need to be evaluated earlier in the course of the disease. The major challenge is defining endpoints for clinical trials that are acceptable to regulatory agencies.

Although suitable predictive markers remain elusive in ARPKD, total kidney volume (TKV) is now widely accepted as an early predictor of ADPKD progression, based on the findings of the NIH-sponsored CRISP study.[9,112] This ongoing longitudinal study has carefully characterized the kidney volume and rates of increase using highly reproducible MRI imaging and correlated these variables with changes in renal function.[9] The investigators found an imperfect inverse relationship between changes in renal/cyst volume and renal function at baseline (Figure 48.1), but showed they could detect progressive changes in function that correlated with volume in the largest cystic kidneys. The Polycystic Kidney Disease Outcomes Consortium, a collaboration between the Critical Path Institute (C-Path) and several leading academic medical centers, pharmaceutical companies, patient organizations, and international regulatory agencies, recently succeeded in having TKV qualified as a prognostic biomarker with both the US Food and Drug Administration and the European Medicines Agency.[113]

Advances in knowledge about disease pathophysiology, clinical trial design, and regulatory policies culminated in approval by regulatory authorities in Japan, Canada, Europe, and the US of the first treatment for slowing disease progression. The TEMPO 3:4 study tested tolvaptan, a V2R antagonist, in 1445 ADPKD patients with well-preserved renal function (eGFR >60 mL/min/1.73 m^2) but large renal volume (>750 mL). They found the treatment modestly reduced the rate of kidney growth (from 5.5% to 2.8% per year) and eGFR decline (from −3.81 mL/min/1.73 m^2 to −2.61 mL/min/1.73 m^2 per year). Participants taking tolvaptan experienced fewer and less severe pain episodes.[13] The REPRISE study subsequently showed that tolvaptan slowed eGFR decline by a similar amount in 1370 participants with later stage ADPKD (CKD stages 2–4) randomized to placebo or study drug.[114] The drug was generally well-tolerated, with the principal side effects being polydypsia and polyuria due to the aquaretic effects of the medication. A small number (~5%) of participants also developed reversible liver function abnormalities. Several participants however met Hy's law criteria, indicating a 10% risk of developing liver failure. Based on its acceptable risk/benefit ratio, tolvaptan was approved for treatment of adults with preserved GFR at risk of rapidly progressing ADPKD with regular monitoring of liver function.

Various approaches have been proposed to identify those most likely to benefit from tolvaptan treatment. They include measurements of TKV adjusted for height, rates of change of eGFR or renal volume over time, and adjustments for age, genotype, and family history.[115–118] The Mayo Imaging Classification, based on a one-time measurement of TKV adjusted for height and age, is one of the simplest and most commonly used in the US[115] (Figure 48.8). Several groups have published practical guides that can be used to decide who to treat and then how to manage them once they start therapy.[119,120]

This begins a new chapter in the management of ADPKD. For the first time, there is something to offer those with the highest risk of severe disease that may slow progression and reduce pain. This information should be considered when counseling individuals known to be at-risk for ADPKD because of family history about presymptomatic testing. Finally, it should be noted that ultimate beneficial impact of tolvaptan will only be known in time. Follow-up of 97 individuals who had participated in the various tolvaptan trials suggests sustained and cumulative benefit for up to 11 years and models suggest that treatment may delay progression to ESRD by up to 7 years.[120] In contrast, several rodent studies found the benefits to attenuate over time.[121–123]

Whether this reflects different species effects or overly optimistic projections based on a relatively small number of people is not known. If, however, the drug is widely utilized and truly provides long-lasting benefits, we will see for the first time a change in the age-dependent incidence of renal replacement therapy (RRT).[124]

Symptomatic Care—ADPKD

Most ADPKD patients are asymptomatic for the majority of their lives, with only intermittent clinical issues. Management is focused on five aspects of care.

Hypertension and Cardiovascular Health

Most PKD patients develop hypertension, more than the proportion that develops ESRD. Cardiovascular disease is the leading cause of death. Therefore, blood pressure control and management of standard cardiovascular risk factors are paramount in caring for PKD patients. There currently are no PKD-specific recommendations for preventing or treating cardiovascular disease. For hypertension, angiotensin converting

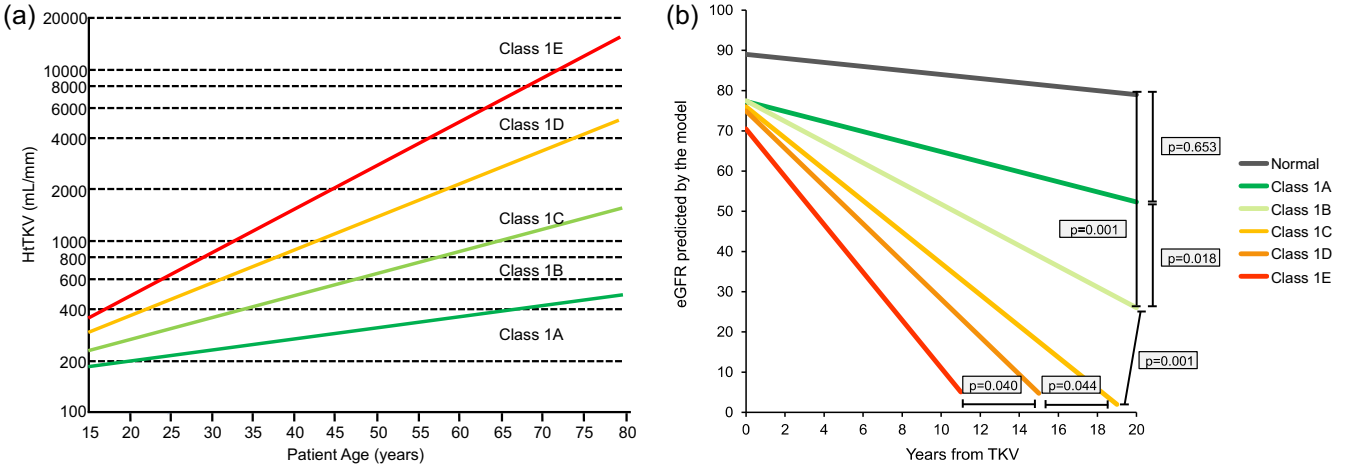


FIGURE 48.8 **The Mayo Image Classification can predict the change in renal volume and eGFR over time based on a one-time measurement of total kidney volume adjusted for height (HtTKV) and age in individuals with class 1 disease.** (a) This plot estimates the predicted increase in renal volume over time based on the class a single MRI measurement places an individual: 1A: <1.5%/year; 1B 1.5–3.0%/year; 1C 3.0–4.5%/year; 1D 4.5–6.0%/year, and 1E >6.0%/year. Note that these estimates only apply to individuals with class 1 disease, which is characterized by bilateral and diffuse cysts (i.e. typical autosomal dominant polycystic kidney disease [ADPKD] presentation). Class 2 disease has unusual features such as unilateral, segmental, or grossly asymmetric localization of cysts or renal atrophy. (b) Predicted slopes of eGFR decline in men with class 1 ADPKD vs. normal kidney donors. The estimated slopes (mL/min per 1.73 m^2/year) by subclass are −0.23, −1.33, −2.63, −3.48, and −4.78. The corresponding slopes for women are 0.03, −1.13, −2.43, −3.29, and −4.58 for women (not plotted). *(a and b) Modified and used with permission of the American Society of Nephrology.*[115]

enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are most commonly used because the angiotensin system is thought to be upregulated in cystic tissue. There had been hope that combining therapies to block both the ACE and ARB pathways might better preserve renal function, but the NIH-funded HALT trial found no added benefit of dual therapy.[125] One arm of the study did find, however, that intensive treatment to a target of 95–110/60–75 mm Hg compared to a standard target of 120–130/70–80 mm Hg in younger patients with preserved GFR resulted in slower renal growth, greater reduction in urinary albumin excretion, and a greater decline in the left ventricular mass index, although no overall benefit with respect to the estimated GFR was detected.[126] Given that cardiovascular disease is the primary cause of death of people with ADPKD, aggressive BP control to this lower target might have long-term health benefits, but this has not yet been shown in this patient population, and this lower target can be difficult to achieve in practice.

Infections

Although most infections are easily treated, cyst infections can be particularly difficult to diagnose and treat. Imaging studies can sometimes be helpful. ^{18}F-fluorodeoxyglucose positron emission tomography scanning, where available, is the most sensitive method, but persistent fever or high clinical suspicion is sometimes the only clues[127] that an infection is present. Antibiotics that penetrate cysts well include trimethoprim-sulfamethoxazole, fluoroquinolones, clindamycin, vancomycin, and metronidazole.

Abdominal and Back Pain

The evaluation and management of abdominal or back pain in PKD patients can be challenging.[128,129] Diagnostic considerations for acute episodes include cyst rupture, cyst infection, nephrolithiasis, cyst hemorrhage, diverticulitis, and the usual causes that affect the general population. Treatment is directed at the underlying diagnosis. Chronic pain is a much more vexing syndrome. Chronic pain correlates poorly with renal size and like most other types of chronic pain can be difficult to manage. After excluding acute events, nonnarcotic-based treatments are the preferred approach. Several groups have reported that acupuncture and other nonpharmacologic approaches can provide reasonable relief. Early referral to pain management specialists also may be helpful.

Screening for Aneurysms

ICA are reported to be between two and five times more common in PKD patients than in the general population, cluster in families, and are one of the most feared extrarenal manifestations of ADPKD.[31] ICAs often present at an earlier age in ADPKD patients than in the general population and are reported to rupture at a smaller size. ICA rupture can sometimes be the presenting symptom for otherwise asymptomatic

individuals.[130] Fortunately, only a small fraction (~8%) of PKD patients develop this problem. Standard practice has been to reserve screening for a small subset of individuals: those with symptoms suggestive of ICA, members of families with a known history of ICA and PKD, patients who have had a previous ICA rupture, individuals in high-risk professions where a sudden catastrophic event could impact the lives of many others (such as commercial airplane pilots), or individuals whose life quality is compromised by the uncertainty of not knowing.

Counseling

Genetic diseases pose special challenges for patients and their care-providers. On the one hand, they offer an opportunity for early, presymptomatic diagnosis, with the potential for intervention before complications arise. For some individuals, however, a genetic diagnosis is perceived as deterministic of an ill-fated future. Part of the health care provider's role is to both educate the individual and family about the disease and its natural history and to provide treatment. Counseling must be tailored to the specific situation, but common themes include explaining genetic risk and genetic tests, counseling regarding when to test, sharing information with other family members, and discussing prognosis.

Symptomatic Care—ARPKD

A recent study using national statistics from the US calculated a 21% perinatal mortality rate in ARPKD patients, primarily due to respiratory compromise.[5] One-year survival rates of 92–98% have been reported in patients who survive the first month of life.[6,131] Clinical management should attend to several key issues.

Neonatal Pulmonary Hypoplasia

This is a major cause of respiratory compromise and neonatal mortality, although the proportion of infants requiring mechanical ventilation is not well established.[132] Pneumothoraces are relatively common, likely a consequence of the pulmonary hypoplasia. In addition to ventilatory support, aggressive management strategies have been reported, including unilateral or bilateral nephrectomy to improve ventilation and nutrition. However, while, unilateral nephrectomy can avoid the immediate need for dialysis, it may not provide adequate decompression in infants with massive renal enlargement. At present, the optimal approach for neonatal management is not well established, given that the evidence base is limited to case reports and case series and well-controlled trials have not been done.[133]

Renal Function

Most ARPKD patients progress to ESRD, but the age at onset is highly variable, depending in part on the age at initial presentation. In a recent, large European study, 9.4% of patients who presented in the perinatal period required RRT in the first year of life.[134] In older children, a case-controlled study in the Chronic Kidney Disease in Children cohort found that overall rates of GFR decline did not differ significantly in ARPKD subjects vs. CKD controls.[135] A recent study found that among patients who presented after the perinatal period, only 25% required RRT by age 32 years.[20]

Systemic Hypertension

The prevalence of hypertension in various cohorts reportedly ranges from 55 to 75%. The onset typically precedes a decline in GFR. In ARPKD patients the severity of hypertension decreases as renal function declines. The underlying mechanism in ARPKD-related hypertension remains elusive. The data, particularly regarding the role of renin–angiotensin–aldosterone system (RAAS) activation, are controversial. Studies in the *pck* rat model found a significant increase in intrarenal, but not systemic, RAAS activation.[136] This finding may explain why previous human studies had not detected increased plasma renin levels. ACEIs and ARBs are very effective as therapeutic agents, but combination therapy is not advised.[133] Multiagent therapy is often required.

The multicenter ESCAPE trial (i.e. Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of Chronic Renal Failure in Pediatric Patients) demonstrated that in children with CKD stages 2–4, aggressive blood pressure control (target 24-hour mean arterial blood pressure below the 50th percentile for age, height, and sex) may slow progression to ESRD.[137] However, although this study may have relevance for children with renal cystic disease, the specific BP target for ARPKD patients has not been established.

Other Renal Morbidities

Hyponatremia occurs in up to 25% of neonates and may be due to an inability to maximally dilute the urine. Children with ARPKD appear to be at higher risk for urinary tract infections (UTIs), possibly due to urinary stasis within the cystic, dilated collecting ducts. UTIs have been reported at rates of around 20–50% in various cohorts and are more common in females. Renal calcifications are reportedly more common in older children with ARPKD and may be related to hypocitraturia and a defect in urine acidification due to renal failure.[138]

Hepatobiliary Manifestations

ARPKD is invariably associated with congenital hepatic fibrosis, the result of a developmental defect in ductal plate development. In a subset of patients, the associated progressive portal tract fibrosis causes portal hypertension and associated complications of hypersplenism and varices.[105] Platelet counts, prothrombin time, and spleen volume have been correlated with the severity portal hypertension.[106] Liver transaminases are generally normal, with abnormalities in serum alkaline phosphatase and γ-glutamyltransferase evident in only a fraction of patients. Ascending cholangitis is another important complication, especially for patients with associated Caroli syndrome, and it is a leading cause of morbidity and mortality in ARPKD patients. In one cohort, about 7% of long-term survivors required liver transplantation, with primary indications being portal hypertension that is refractory to medical management or recurrent cholangitis.[6] The relationship between renal and hepatic disease severity in ARPKD is unclear, with most studies demonstrating no significant correlation.[139] A subset of patients with late-onset ARPKD can present with a liver-predominant phenotype with few or no manifestations of kidney disease.[86]

Transplantation

Infants with ESRD can be managed with either peritoneal dialysis or hemodialysis. Renal transplantation is limited by body size, but in experienced pediatric centers, children with a minimum weight of 10 kg can successfully receive renal grafts.[140] Rejection rates and survival beyond 3 years of age are not different in ARPKD patients compared with those with other renal diseases who undergo transplant surgery.[141] However, biliary sepsis is a significant cause of morbidity and mortality in ARPKD patients after renal transplantation.[142] Combined kidney and liver transplantation can be effective for select ESRD patients who have substantial bile duct dilatation and episodes of recurrent cholangitis.[143]

Growth Impairment

Review of the recent literature indicates that a disease-specific effect of ARPKD on growth is controversial.[6,131] Assertive nutritional support, including gastrostomy tube insertion, is often required to optimize linear growth.[144] If growth impairment occurs, treatment with growth hormone can be considered.[145]

Intracranial Aneurysms

Several case reports indicate that ARPKD patients have a low but nonnegligible incidence of ruptured intracranial aneurysms.[146] Given the potential for catastrophic outcomes of subarachnoid hemorrhage in young patients, a low threshold for early radiographic screening may be warranted.

CONCLUSIONS

Spring 2019 marks the 25th anniversary of the identification of the *PKD1* gene, which was followed over the next several years by identification of the *PKD2* and *PKHD1* genes. These discoveries heralded an era of exciting progress in our understanding of the pathogenesis of PKD, accelerated the development of clinical tools to assess disease and track progression, and spurred efforts to identify factors that predict prognosis. Therefore, the stage has been set for the next chapter, in which the efficacy of therapeutic agents that target key pathogenic pathways can be rigorously evaluated in human clinical trials. Although the studies to date have not yet yielded a cure for any of these conditions, they have established an exciting paradigm and have produced a therapy that may slow progression. Building on this paradigm, future clinical trials, using newer study design methodologies, additional predictive markers, and perhaps combinations of targeted therapeutic agents, are positioned to achieve the ultimate goal of identifying disease-specific therapies that prevent or at least arrest the inexorable progression of PKD-related morbidities.

Acknowledgements

GGG is supported by the NIDDK Intramural Research Program (ZIA DK075042).
LGW is supported by the University of Alabama at Birmingham Hepato-Renal Fibrocystic Disease Core Center {NIDDK P30 DK074038} and the Clinical and Translational Science Institute at Children's National (CTSI-CN) (NIH National Center for Advancing Translational Sciences, UL1TR000075). The views expressed in this chapter reflect the personal opinions of the authors and not those of their respective organizations.

References

1. Bergmann C, Guay-Woodford LM, Harris PC, Horie S, Peters DJM, Torres VE. Polycystic kidney disease. *Nat Rev Dis Primers* 2018;**4**(1):50.
2. van de Laarschot LFM, Drenth JPH. Genetics and mechanisms of hepatic cystogenesis. *Biochim Biophys Acta (BBA) − Mol Basis Dis* 2018;**1864**(4 Pt B):1491−7.
3. Porath B, Gainullin VG, Cornec-Le Gall E, et al. Mutations in GANAB, encoding the glucosidase IIalpha subunit, cause autosomal-dominant polycystic kidney and liver disease. *Am J Hum Genet* 2016;**98**(6):1193−207.
4. Cornec-Le Gall E, Olson RJ, Besse W, et al. Monoallelic mutations to DNAJB11 cause atypical autosomal-dominant polycystic kidney disease. *Am J Hum Genet* 2018;**102**(5):832−44.
5. Alzarka B, Morizono H, Bollman JW, Kim D, Guay-Woodford LM. Design and implementation of the hepatorenal fibrocystic disease core center clinical database: a centralized resource for

characterizing autosomal recessive polycystic kidney disease and other hepatorenal fibrocystic diseases. *Front Pediatr* 2017;**5**:80.
6. Guay-Woodford LM, Desmond RA. Autosomal recessive polycystic kidney disease: the clinical experience in North America. *Pediatrics* 2003;**111**(5 Pt 1):1072–80.
7. Gunay-Aygun M, Turkbey BI, Bryant J, et al. Hepatorenal findings in obligate heterozygotes for autosomal recessive polycystic kidney disease. *Mol Genet Metabol* 2011;**104**(4):677–81.
8. Besse W, Dong K, Choi J, et al. Isolated polycystic liver disease genes define effectors of polycystin-1 function. *J Clin Investig* 2017;**127**(5):1772–85.
9. Chapman AB, Guay-Woodford LM, Grantham JJ, et al. Renal structure in early autosomal-dominant polycystic kidney disease (ADPKD): the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) cohort. *Kidney Int* 2003;**64**(3): 1035–45.
10. Boletta A, Germino GG. Role of polycystins in renal tubulogenesis. *Trends Cell Biol* 2003;**13**(9):484–92.
11. Lu H, Galeano MCR, Ott E, et al. Mutations in DZIP1L, which encodes a ciliary-transition-zone protein, cause autosomal recessive polycystic kidney disease. *Nat Genet* 2017;**49**(7):1025–34.
12. Padovano V, Podrini C, Boletta A, Caplan MJ. Metabolism and mitochondria in polycystic kidney disease research and therapy. *Nat Rev Nephrol* 2018;**14**(11):678–87.
13. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012;**367**(25):2407–18.
14. Heyer CM, Sundsbak JL, Abebe KZ, et al. Predicted mutation strength of nontruncating PKD1 mutations aids genotype-phenotype correlations in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2016;**27**(9):2872–84.
15. Reed B, McFann K, Kimberling WJ, et al. Presence of de novo mutations in autosomal dominant polycystic kidney disease patients without family history. *Am J Kidney Dis* 2008;**52**(6):1042–50.
16. Garcia-Gonzalez MA, Jones JG, Allen SK, et al. Evaluating the clinical utility of a molecular genetic test for polycystic kidney disease. *Mol Genet Metabol* 2007;**92**(1–2):160–7.
17. Rossetti S, Consugar MB, Chapman AB, et al. Comprehensive molecular diagnostics in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2007;**18**(7):2143–60.
18. Qian F, Watnick TJ, Onuchic LF, Germino GG. The molecular basis of focal cyst formation in human autosomal dominant polycystic kidney disease type I. *Cell* 1996;**87**(6):979–87.
19. Tan AY, Zhang T, Michaeel A, et al. Somatic mutations in renal cyst epithelium in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2018;**29**(8):2139–56.
20. Gunay-Aygun M, Font-Montgomery E, Lukose L, et al. Correlation of kidney function, volume and imaging findings, and PKHD1 mutations in 73 patients with autosomal recessive polycystic kidney disease. *Clin J Am Soc Nephrol* 2010;**5**(6):972–84.
21. Gallagher AR, Germino GG, Somlo S. Molecular advances in autosomal dominant polycystic kidney disease. *Adv Chron Kidney Dis* 2010;**17**(2):118–30.
22. Hopp K, Ward CJ, Hommerding CJ, et al. Functional polycystin-1 dosage governs autosomal dominant polycystic kidney disease severity. *J Clin Investig* 2012;**122**(11):4257–73.
23. Rossetti S, Kubly VJ, Consugar MB, et al. Incompletely penetrant PKD1 alleles suggest a role for gene dosage in cyst initiation in polycystic kidney disease. *Kidney Int* 2009;**75**(8):848–55.
24. Cornec-Le Gall E, Audrezet MP, Chen JM, et al. Type of PKD1 mutation influences renal outcome in ADPKD. *J Am Soc Nephrol* 2013; **24**(6):1006–13.
25. Bergmann C, von Bothmer J, Ortiz Bruchle N, et al. Mutations in multiple PKD genes may explain early and severe polycystic kidney disease. *J Am Soc Nephrol* 2011;**22**(11):2047–56.
26. Baert L. Hereditary polycystic kidney disease (adult form): a microdissection study of two cases at an early stage of the disease. *Kidney Int* 1978;**13**:519–25.
27. Fedeles SV, Tian X, Gallagher AR, et al. A genetic interaction network of five genes for human polycystic kidney and liver diseases defines polycystin-1 as the central determinant of cyst formation. *Nat Genet* 2011;**43**(7):639–47.
28. Janssen MJ, Salomon J, Te Morsche RH, Drenth JP. Loss of heterozygosity is present in SEC63 germline carriers with polycystic liver disease. *PLoS One* 2012;**7**(11):e50324.
29. Menezes LF, Germino GG. Polycystic kidney disease, cilia, and planar polarity. *Methods Cell Biol* 2009;**94**:273–97.
30. Torres VE, Harris PC. Polycystic kidney disease in 2011: connecting the dots toward a polycystic kidney disease therapy. *Nat Rev Nephrol* 2012;**8**(2):66–8.
31. Somlo S, Guay-Woodford L. Polycystic kidney disease. In: Lifton R, Somlo S, Giebisch G, Seldin D, editors. *Genetic diseases of the kidney.* 1st ed. Elsevier; 2009. p. 393–424.
32. Hanaoka K, Qian F, Boletta A, et al. Co-assembly of polycystin-1 and -2 produces unique cation-permeable currents. *Nature* 2000; **408**(6815):990–4.
33. Vassilev PM, Guo L, Chen XZ, et al. Polycystin-2 is a novel cation channel implicated in defective intracellular Ca(2+) homeostasis in polycystic kidney disease. *Biochem Biophys Res Commun* 2001; **282**(1):341–50.
34. Padovano V, Kuo IY, Stavola LK, et al. The polycystins are modulated by cellular oxygen-sensing pathways and regulate mitochondrial function. *Mol Biol Cell* 2017;**28**(2):261–9.
35. Arif Pavel M, Lv C, Ng C, et al. Function and regulation of TRPP2 ion channel revealed by a gain-of-function mutant. *Proc Natl Acad Sci USA* 2016;**113**(17):E2363–72.
36. Grieben M, Pike AC, Shintre CA, et al. Structure of the polycystic kidney disease TRP channel Polycystin-2 (PC2). *Nat Struct Mol Biol* 2017;**24**(2):114–22.
37. Wilkes M, Madej MG, Kreuter L, et al. Molecular insights into lipid-assisted Ca(2+) regulation of the TRP channel polycystin-2. *Nat Struct Mol Biol* 2017;**24**(2):123–30.
38. Liu X, Vien T, Duan J, Sheu SH, DeCaen PG, Clapham DE. Polycystin-2 is an essential ion channel subunit in the primary cilium of the renal collecting duct epithelium. *eLife* 2018;**7**.
39. Nauli SM, Alenghat FJ, Luo Y, et al. Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. *Nat Genet* 2003;**33**(2):129–37.
40. Low SH, Vasanth S, Larson CH, et al. Polycystin-1, STAT6, and P100 function in a pathway that transduces ciliary mechanosensation and is activated in polycystic kidney disease. *Dev Cell* 2006; **10**(1):57–69.
41. Ma M, Tian X, Igarashi P, Pazour GJ, Somlo S. Loss of cilia suppresses cyst growth in genetic models of autosomal dominant polycystic kidney disease. *Nat Genet* 2013;**45**(9):1004–12.
42. Belibi FA, Reif G, Wallace DP, et al. Cyclic AMP promotes growth and secretion in human polycystic kidney epithelial cells. *Kidney Int* 2004;**66**(3):964–73.
43. Yamaguchi T, Nagao S, Wallace DP, et al. Cyclic AMP activates B-Raf and ERK in cyst epithelial cells from autosomal-dominant polycystic kidneys. *Kidney Int* 2003;**63**(6):1983–94.
44. van Gastel MDA, Torres VE. Polycystic kidney disease and the vasopressin pathway. *Ann Nutr Metab* 2017;**70**(Suppl. 1): 43–50.
45. Hogan MC, Masyuk TV, Page LJ, et al. Randomized clinical trial of long-acting somatostatin for autosomal dominant polycystic kidney and liver disease. *J Am Soc Nephrol* 2010;**21**(6): 1052–61.
46. Shillingford JM, Murcia NS, Larson CH, et al. The mTOR pathway is regulated by polycystin-1, and its inhibition reverses renal

cystogenesis in polycystic kidney disease. *Proc Natl Acad Sci USA* 2006;**103**(14):5466–71.
47. Kleymenova E, Ibraghimov-Beskrovnaya O, Kugoh H, et al. Tuberin-dependent membrane localization of polycystin-1: a functional link between polycystic kidney disease and the TSC2 tumor suppressor gene. *Mol Cell* 2001;**7**(4):823–32.
48. Shillingford JM, Piontek KB, Germino GG, Weimbs T. Rapamycin ameliorates PKD resulting from conditional inactivation of Pkd1. *J Am Soc Nephrol* 2010;**21**(3):489–97.
49. Lin CC, Kurashige M, Liu Y, et al. A cleavage product of Polycystin-1 is a mitochondrial matrix protein that affects mitochondria morphology and function when heterologously expressed. *Sci Rep* 2018;**8**(1):2743.
50. Takiar V, Nishio S, Seo-Mayer P, et al. Activating AMP-activated protein kinase (AMPK) slows renal cystogenesis. *Proc Natl Acad Sci USA* 2011;**108**(6):2462–7.
51. Menezes LF, Zhou F, Patterson AD, et al. Network analysis of a Pkd1-mouse model of autosomal dominant polycystic kidney disease identifies HNF4alpha as a disease modifier. *PLoS Genetics* 2012;**8**(11):e1003053.
52. Rowe I, Chiaravalli M, Mannella V, et al. Defective glucose metabolism in polycystic kidney disease identifies a new therapeutic strategy. *Nat Med* 2013;**19**(4):488–93.
53. Menezes LF, Lin CC, Zhou F, Germino GG. Fatty acid oxidation is impaired in an orthologous mouse model of autosomal dominant polycystic kidney disease. *EBioMedicine* 2016;**5**:183–92.
54. Podrini C, Rowe I, Pagliarini R, et al. Dissection of metabolic reprogramming in polycystic kidney disease reveals coordinated rewiring of bioenergetic pathways. *Commun Biol* 2018;**1**:194.
55. Hajarnis S, Lakhia R, Yheskel M, et al. microRNA-17 family promotes polycystic kidney disease progression through modulation of mitochondrial metabolism. *Nat Commun* 2017;**8**:14395.
56. Warner G, Hein KZ, Nin V, et al. Food restriction ameliorates the development of polycystic kidney disease. *J Am Soc Nephrol* 2016; **27**(5):1437–47.
57. Kipp KR, Rezaei M, Lin L, Dewey EC, Weimbs T. A mild reduction of food intake slows disease progression in an orthologous mouse model of polycystic kidney disease. *Am J Physiol Renal Physiol* 2016;**310**(8):F726–31.
58. Ishimoto Y, Inagi R, Yoshihara D, Kugita M, Nagao S, Shimizu A, Takeda N, Wake M, Honda K, Zhou J, Nangaku M. Mitochondrial abnormality facilitates cyst formation in autosomal dominant polycystic kidney disease. *Mol Cell Biol* 2017;**37**:e00337-17.
59. Onuchic LF, Furu L, Nagasawa Y, et al. PKHD1, the polycystic kidney and hepatic disease 1 gene, encodes a novel large protein containing multiple immunoglobulin-like plexin-transcription-factor domains and parallel beta-helix 1 repeats. *Am J Hum Genet* 2002;**70**(5):1305–17.
60. Menezes LF, Cai Y, Nagasawa Y, et al. Polyductin, the PKHD1 gene product, comprises isoforms expressed in plasma membrane, primary cilium, and cytoplasm. *Kidney Int* 2004;**66**(4): 1345–55.
61. Aachen University R. *Mutation database autosomal recessive polycystic kidney disease (ARPKD/PKHD1)*. 2013.
62. Bergmann C, Kupper F, Dornia C, Schneider F, Senderek J, Zerres K. Algorithm for efficient PKHD1 mutation screening in autosomal recessive polycystic kidney disease (ARPKD). *Hum Mutat* 2005;**25**(3):225–31.
63. Rossetti S, Harris PC. Genotype-phenotype correlations in autosomal dominant and autosomal recessive polycystic kidney disease. *J Am Soc Nephrol* 2007;**18**(5):1374–80.
64. Zvereff V, Yao S, Ramsey J, Mikhail FM, Vijzelaar R, Messiaen L. Identification of PKHD1 multiexon deletions using multiplex ligation-dependent probe amplification and quantitative polymerase chain reaction. *Genet Test Mol Biomark* 2010;**14**(4): 505–10.
65. Kerkar N, Norton K, Suchy FJ. The hepatic fibrocystic diseases. *Clin Liver Dis* 2006;**10**(1):55–71 [v-vi].
66. O'Connor A, Guay-Woodford L. The polycystic kidney diseases and other hepato-renal fibrocystic diseases: clinical phenotypes, molecular pathobiology, and variation between mouse and man. In: Little M, editor. *Kidney development, repair, and regeneration*. Elsevier; 2015. p. 241–64.
67. Cabezas OR, Flanagan SE, Stanescu H, et al. Polycystic kidney disease with hyperinsulinemic hypoglycemia caused by a promoter mutation in phosphomannomutase 2. *J Am Soc Nephrol* 2017;**28**(8): 2529–39.
68. Bakeberg JL, Tammachote R, Woollard JR, et al. Epitope-tagged Pkhd1 tracks the processing, secretion, and localization of fibrocystin. *J Am Soc Nephrol* 2011;**22**(12):2266–77.
69. Outeda P, Menezes L, Hartung EA, et al. A novel model of autosomal recessive polycystic kidney questions the role of the fibrocystin C-terminus in disease mechanism. *Kidney Int* 2017;**92**(5): 1130–44.
70. Ward CJ, Yuan D, Masyuk TV, et al. Cellular and subcellular localization of the ARPKD protein; fibrocystin is expressed on primary cilia. *Hum Mol Genet* 2003;**12**(20):2703–10.
71. Zhang J, Wu M, Wang S, Shah JV, Wilson PD, Zhou J. Polycystic kidney disease protein fibrocystin localizes to the mitotic spindle and regulates spindle bipolarity. *Hum Mol Genet* 2010;**19**(17): 3306–19.
72. Kaimori JY, Nagasawa Y, Menezes LF, et al. Polyductin undergoes notch-like processing and regulated release from primary cilia. *Hum Mol Genet* 2007;**16**(8):942–56.
73. Kim I, Fu Y, Hui K, et al. Fibrocystin/polyductin modulates renal tubular formation by regulating polycystin-2 expression and function. *J Am Soc Nephrol* 2008;**19**(3):455–68.
74. Kaimori JY, Lin CC, Outeda P, et al. NEDD4-family E3 ligase dysfunction due to PKHD1/Pkhd1 defects suggests a mechanistic model for ARPKD pathobiology. *Sci Rep* 2017;**7**(1):7733.
75. Yamaguchi T, Hempson SJ, Reif GA, Hedge AM, Wallace DP. Calcium restores a normal proliferation phenotype in human polycystic kidney disease epithelial cells. *J Am Soc Nephrol* 2006;**17**(1): 178–87.
76. Fischer DC, Jacoby U, Pape L, et al. Activation of the AKT/mTOR pathway in autosomal recessive polycystic kidney disease (ARPKD). *Nephrol Dial Transplant* 2009;**24**(6):1819–27.
77. Becker JU, Opazo Saez A, Zerres K, et al. The mTOR pathway is activated in human autosomal-recessive polycystic kidney disease. *Kidney Blood Press Res* 2010;**33**(2):129–38.
78. Wang X, Gattone 2nd V, Harris PC, Torres VE. Effectiveness of vasopressin V2 receptor antagonists OPC-31260 and OPC-41061 on polycystic kidney disease development in the PCK rat. *J Am Soc Nephrol* 2005;**16**(4):846–51.
79. Renken C, Fischer DC, Kundt G, Gretz N, Haffner D. Inhibition of mTOR with sirolimus does not attenuate progression of liver and kidney disease in PCK rats. *Nephrol Dial Transplant* 2011;**26**(1): 92–100.
80. Ravine D, Gibson RN, Donlan J, Sheffield LJ. An ultrasound renal cyst prevalence survey: specificity data for inherited renal cystic diseases. *Am J Kidney Dis* 1993;**22**(6):803–7.
81. Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol* 2009;**20**(1):205–12.
82. Pei Y, Hwang YH, Conklin J, et al. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2015;**26**(3):746–53.
83. Li A, Davila S, Furu L, et al. Mutations in PRKCSH cause isolated autosomal dominant polycystic liver disease. *Am J Hum Genet* 2003;**72**(3):691–703.
84. Davila S, Furu L, Gharavi AG, et al. Mutations in SEC63 cause autosomal dominant polycystic liver disease. *Nat Genet* 2004; **36**(6):575–7.

85. Cnossen WR, te Morsche RH, Hoischen A, et al. Whole-exome sequencing reveals LRP5 mutations and canonical Wnt signaling associated with hepatic cystogenesis. *Proc Natl Acad Sci USA* 2014; **111**(14):5343–8.
86. Adeva M, El-Youssef M, Rossetti S, et al. Clinical and molecular characterization defines a broadened spectrum of autosomal recessive polycystic kidney disease (ARPKD). *Medicine* 2006; **85**(1):1–21.
87. O'Brien K, Font-Montgomery E, Lukose L, et al. Congenital hepatic fibrosis and portal hypertension in autosomal dominant polycystic kidney disease. *J Pediatr Gastroenterol Nutr* 2012;**54**(1):83–9.
88. Harris PC, Rossetti S. Molecular diagnostics of ADPKD coming of age. *Clin J Am Soc Nephrol* 2008;**3**(1):1–2.
89. Phakdeekitcharoen B, Watnick TJ, Germino GG. Mutation analysis of the entire replicated portion of PKD1 using genomic DNA samples. *J Am Soc Nephrol* 2001;**12**(5):955–63.
90. Eisenberger T, Decker C, Hiersche M, et al. An efficient and comprehensive strategy for genetic diagnostics of polycystic kidney disease. *PLoS One* 2015;**10**(2):e0116680.
91. Trujillano D, Bullich G, Ossowski S, et al. Diagnosis of autosomal dominant polycystic kidney disease using efficient PKD1 and PKD2 targeted next-generation sequencing. *Mol Genet Genomic Med* 2014;**2**(5):412–21.
92. Lanktree MB, Iliuta IA, Haghighi A, Song X, Pei Y. Evolving role of genetic testing for the clinical management of autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant* 2018: gfy261. https://doi.org/10.1093/ndt/gfy261.
93. Huang E, Samaniego-Picota M, McCune T, et al. DNA testing for live kidney donors at risk for autosomal dominant polycystic kidney disease. *Transplantation* 2009;**87**(1):133–7.
94. Boyer O, Gagnadoux MF, Guest G, et al. Prognosis of autosomal dominant polycystic kidney disease diagnosed in utero or at birth. *Pediatr Nephrol* 2007;**22**(3):380–8.
95. Bergmann C, Bruchle NO, Frank V, Rehder H, Zerres K. Perinatal deaths in a family with autosomal dominant polycystic kidney disease and a PKD2 mutation. *N Engl J Med* 2008;**359**(3):318–9.
96. Reed B, Nobakht E, Dadgar S, et al. Renal ultrasonographic evaluation in children at risk of autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 2010;**56**(1):50–6.
97. Reuss A, Wladimiroff JW, Niermeyer MF. Sonographic, clinical and genetic aspects of prenatal diagnosis of cystic kidney disease. *Ultrasound Med Biol* 1991;**17**(7):687–94.
98. Chaumoitre K, Brun M, Cassart M, et al. Differential diagnosis of fetal hyperechogenic cystic kidneys unrelated to renal tract anomalies: a multicenter study. *Ultrasound Obstet Gynecol* 2006;**28**(7): 911–7.
99. Luthy DA, Hirsch JH. Infantile polycystic kidney disease: observations from attempts at prenatal diagnosis. *Am J Med Genet* 1985;**20**(3):505–17.
100. Brun M, Maugey-Laulom B, Eurin D, Didier F, Avni EF. Prenatal sonographic patterns in autosomal dominant polycystic kidney disease: a multicenter study. *Ultrasound Obstet Gynecol* 2004; **24**(1):55–61.
101. Gimpel C, Avni EF, Breysem L, et al. Imaging of kidney cysts and cystic kidney diseases in children: an international working group consensus statement. *Radiology* 2018:181243.
102. Hartung EA, Guay-Woodford LM. Autosomal recessive polycystic kidney disease: a hepatorenal fibrocystic disorder with pleiotropic effects. *Pediatrics* 2014;**134**(3):e833–45.
103. Nicolau C, Torra R, Badenas C, et al. Sonographic pattern of recessive polycystic kidney disease in young adults. Differences from the dominant form. *Nephrol Dial Transplant* 2000;**15**(9):1373–8.
104. Capisonda R, Phan V, Traubuci J, Daneman A, Balfe JW, Guay-Woodford LM. Autosomal recessive polycystic kidney disease: outcomes from a single-center experience. *Pediatr Nephrol* 2003; **18**(2):119–26.
105. Srinath A, Shneider BL. Congenital hepatic fibrosis and autosomal recessive polycystic kidney disease. *J Pediatr Gastroenterol Nutr* 2012;**54**(5):580–7.
106. Gunay-Aygun M, Font-Montgomery E, Lukose L, et al. Characteristics of congenital hepatic fibrosis in a large cohort of patients with autosomal recessive polycystic kidney disease. *Gastroenterology* 2013;**144**(1):112–121 e2.
107. Bergmann C. ARPKD and early manifestations of ADPKD: the original polycystic kidney disease and phenocopies. *Pediatr Nephrol* 2015;**30**(1):15–30.
108. Bergmann C. Genetics of autosomal recessive polycystic kidney disease and its differential diagnoses. *Front Pediatr* 2017; **5**:221.
109. Thornhill AR, DeDie-Smulders CE, Geraedts JP, et al. ESHRE PGD Consortium 'Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)'. *Hum Reprod* 2005;**20**:35–48.
110. Gigarel N, Frydman N, Burlet P, et al. Preimplantation genetic diagnosis for autosomal recessive polycystic kidney disease. *Reprod Biomed Online* 2008;**16**(1):152–8.
111. Lau EC, Janson MM, Roesler MR, Avner ED, Strawn EY, Bick DP. Birth of a healthy infant following preimplantation PKHD1 haplotyping for autosomal recessive polycystic kidney disease using multiple displacement amplification. *J Assist Reprod Genet* 2010; **27**(7):397–407.
112. Grantham JJ, Chapman AB, Torres VE. Volume progression in autosomal dominant polycystic kidney disease: the major factor determining clinical outcomes. *Clin J Am Soc Nephrol* 2006;**1**(1): 148–57.
113. Perrone RD, Mouksassi MS, Romero K, et al. Total kidney volume is a prognostic biomarker of renal function decline and progression to end-stage renal disease in patients with autosomal dominant polycystic kidney disease. *Kidney Int Rep* 2017;**2**(3): 442–50.
114. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med* 2017;**377**(20):1930–42.
115. Irazabal MV, Rangel LJ, Bergstralh EJ, et al. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. *J Am Soc Nephrol* 2015;**26**(1): 160–72.
116. Cornec-Le Gall E, Audrezet MP, Rousseau A, et al. The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2016; **27**(3):942–51.
117. Soroka S, Alam A, Bevilacqua M, et al. Assessing risk of disease progression and pharmacological management of autosomal dominant polycystic kidney disease: a Canadian expert consensus. *Can J Kidney Health Dis* 2017;**4**. 2054358117695784.
118. McEwan P, Bennett Wilton H, Ong ACM, et al. A model to predict disease progression in patients with autosomal dominant polycystic kidney disease (ADPKD): the ADPKD Outcomes Model. *BMC Nephrol* 2018;**19**(1):37.
119. Gansevoort RT, Arici M, Benzing T, et al. Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice. *Nephrol Dial Transplant* 2016;**31**(3):337–48.
120. Chebib FT, Perrone RD, Chapman AB, et al. A practical guide for treatment of rapidly progressive ADPKD with tolvaptan. *J Am Soc Nephrol* 2018;**29**(10):2458–70.
121. Meijer E, Gansevoort RT, de Jong PE, et al. Therapeutic potential of vasopressin V2 receptor antagonist in a mouse model for autosomal dominant polycystic kidney disease: optimal timing and dosing of the drug. *Nephrol Dial Transplant* 2011;**26**(8): 2445–53.

122. Roix J, Saha S. TNF-alpha blockade is ineffective in animal models of established polycystic kidney disease. *BMC Nephrol* 2013;**14**(1): 233.
123. Zittema D, Versteeg IB, Gansevoort RT, et al. Dose-titrated vasopressin V2 receptor antagonist improves renoprotection in a mouse model for autosomal dominant polycystic kidney disease. *Am J Nephrol* 2016;**44**(3):194–203.
124. Spithoven EM, Kramer A, Meijer E, et al. Analysis of data from the ERA-EDTA Registry indicates that conventional treatments for chronic kidney disease do not reduce the need for renal replacement therapy in autosomal dominant polycystic kidney disease. *Kidney Int* 2014;**86**(6):1244–52.
125. Torres VE, Abebe KZ, Chapman AB, et al. Angiotensin blockade in late autosomal dominant polycystic kidney disease. *N Engl J Med* 2014;**371**(24):2267–76.
126. Schrier RW, Abebe KZ, Perrone RD, et al. Blood pressure in early autosomal dominant polycystic kidney disease. *N Engl J Med* 2014;**371**(24):2255–66.
127. Suwabe T, Ubara Y, Sumida K, et al. Clinical features of cyst infection and hemorrhage in ADPKD: new diagnostic criteria. *Clin Exp Nephrol* 2012;**16**(6):892–902.
128. Bajwa ZH, Sial KA, Malik AB, Steinman TI. Pain patterns in patients with polycystic kidney disease. *Kidney Int* 2004;**66**(4): 1561–9.
129. Hogan MC, Norby SM. Evaluation and management of pain in autosomal dominant polycystic kidney disease. *Adv Chron Kidney Dis* 2010;**17**(3):e1–16.
130. Kanne JP, Talner LB. Autosomal dominant polycystic kidney disease presenting as subarachnoid hemorrhage. *Emerg Radiol* 2004; **11**(2):110–2.
131. Bergmann C, Senderek J, Windelen E, et al. Clinical consequences of PKHD1 mutations in 164 patients with autosomal-recessive polycystic kidney disease (ARPKD). *Kidney Int* 2005;**67**:829–48.
132. Beaunoyer M, Snehal M, Li L, Concepcion W, Salvatierra Jr O, Sarwal M. Optimizing outcomes for neonatal ARPKD. *Pediatr Transplant* 2007;**11**(3):267–71.
133. Guay-Woodford LM, Bissler JJ, Braun MC, et al. Consensus expert recommendations for the diagnosis and management of autosomal recessive polycystic kidney disease: report of an international conference. *J Pediatr* 2014;**165**(3):611–7.
134. Burgmaier K, Kunzmann K, Ariceta G, et al. Risk factors for early dialysis dependency in autosomal recessive polycystic kidney disease. *J Pediatr* 2018;**199**:22–8.
135. Dell KM, Matheson M, Hartung EA, Warady BA, Furth SL. Kidney disease progression in autosomal recessive polycystic kidney disease. *J Pediatr* 2016;**171**:196–201.e1.
136. Goto M, Hoxha N, Osman R, Dell KM. The renin-angiotensin system and hypertension in autosomal recessive polycystic kidney disease. *Pediatr Nephrol* 2010;**25**(12):2449–57.
137. Group ET, Wühl E, Trivelli A, et al. Strict blood-pressure control and progression of renal failure in children. *N Engl J Med* 2009; **361**:1639–50.
138. Lucaya J, Enriquez G, Nieto J, Callis L, Garcia Pena P, Dominguez C. Renal calcifications in patients with autosomal recessive polycystic kidney disease: prevalence and cause. *Am J Roentgenol* 1993;**160**(2):359–62.
139. Wehrman A, Kriegermeier A, Wen J. Diagnosis and management of hepatobiliary complications in autosomal recessive polycystic kidney disease. *Front Pediatr* 2017;**5**:124.
140. Weitz M, Laube GF, Schmidt M, et al. Outcome of renal transplantation in small infants: a match-controlled analysis. *Pediatr Nephrol* 2018;**33**(6):1057–68.
141. Smith JM, Martz K, Blydt-Hansen TD. Pediatric kidney transplant practice patterns and outcome benchmarks, 1987-2010: a report of the North American Pediatric Renal Trials and Collaborative Studies. *Pediatr Transplant* 2013;**17**(2):149–57.
142. Davis ID, Ho M, Hupertz V, Avner ED. Survival of childhood polycystic kidney disease following renal transplantation: the impact of advanced hepatobiliary disease. *Pediatr Transplant* 2003;**7**(5):364–9.
143. Mekahli D, van Stralen KJ, Bonthuis M, et al. Kidney versus combined kidney and liver transplantation in young people with autosomal recessive polycystic kidney disease: data from the European society for pediatric nephrology/European renal association-European dialysis and transplant (ESPN/ERA-EDTA) registry. *Am J Kidney Dis* 2016;**68**(5):782–8.
144. Burgmaier K, Brandt J, Shroff R, et al. Gastrostomy tube insertion in pediatric patients with autosomal recessive polycystic kidney disease (ARPKD): current practice. *Front Pediatr* 2018; **6**:164.
145. Lilova M, Kaplan BS, Meyers KE. Recombinant human growth hormone therapy in autosomal recessive polycystic kidney disease. *Pediatr Nephrol* 2003;**18**:57–61.
146. Chalhoub V, Abi-Rafeh L, Hachem K, Ayoub E, Yazbeck P. Intracranial aneurysm and recessive polycystic kidney disease: the third reported case. *JAMA Neurol* 2013;**70**(1):114–6.

QUESTIONS AND ANSWERS

Question 1

A 65-year-old man with ADPKD has an eGFR of 15 mL/min/1.73 m^2 and is asymptomatic. He is medically cleared for transplantation and has a 29-year-old son who is willing to be considered a potential donor candidate. The son is healthy, normotensive, has a normal eGFR, and an unremarkable urinalysis. Which of the following would be an acceptable next step, and why? (More than one answer may be correct.)

A. Decline further work-up since the son has a 50% risk of having the disease
B. Renal ultrasound
C. Abdominal CT scan with contrast
D. Abdominal MRI
E. DNA testing

Answer: B, D

While it is true that the son is at 50% risk of having the disease, there are well-established diagnostic tests and criteria that can be used to determine his true risk. If studies can determine that he does not have ADPKD, then he is a perfectly acceptable donor if other standard conditions are met. The renal ultrasound is usually the preferred initial diagnostic screening tool because it is of low cost, requires no contrast or ionizing radiation, and is the method that was used to establish the diagnostic criteria that have been validated with the largest datasets. The presence of one or more cysts in an at-risk individual less than 30 years of age makes it highly likely he has inherited the disease. A T2-weighted MRI is another acceptable screening alternative. Although it usually costs more, it provides more detailed anatomic information, greater sensitivity, and possibly better specificity for patients less than 40 years old than ultrasound.[82] Using a total of >10 cysts as the diagnostic threshold for this age group, a recent study found that MRI provided 100% sensitivity and specificity. Although the authors note that a total of <10 cysts can generally be considered sufficient for disease exclusion, they recommended a more stringent threshold of <5 total cysts in at-risk individuals.

An abdominal CT scan with contrast is another sensitive modality frequently used by transplant centers to screen at-risk individuals. It should be noted that diagnostic criteria have not yet been well established.

DNA testing is presently not the preferred initial test since it is expensive, requires analysis of both the recipient and donor, and sometimes yields ambiguous results. In DNA testing, the recipient is first screened to determine whether a definitive pathogenic mutation (i.e. protein-terminating [PT] due to stop codons, deletions that change the reading frame, or splice site mutations that disrupt reading frame or delete exons) is identifiable. If so, the test is highly reliable in determining the genetic risk of a potential donor, and the donor's DNA is then screened in a directed way for that same mutation. If the donor lacks the pathogenic mutation found in the recipient, then he is declared free of disease and is an acceptable potential donor. If the donor has the same pathogenic mutation, he is diagnosed as having the disease and thus excluded as a donor. Unfortunately, in a number of cases, the DNA test results are nondiagnostic, i.e. the test identifies variants of uncertain pathogenicity or the test fails to find any changes that are predicted to alter the DNA sequence in a meaningful way.

In sum, DNA testing is helpful when definitive (50−80%) but is more expensive and more often yields nondiagnostic results. It can be a useful second-level test, however, in situations where the ultrasound or other imaging study is nondiagnostic and the candidate donor is either the best match or the only available potential living donor. For example, the positive predictive value of ultrasound in identifying ADPKD is 100% if an individual has three or more cysts, but the negative predictive value is only 91% if no cysts are detected. This is too high a false-negative rate for most centers, so the choice is either to exclude the possible donor or pursue more definitive testing.

Question 2

A 32-year-old woman is thinking about having a child, but knows that she is at risk for ADPKD because of a positive family history. She consults you to find out whether she has the disease and if so, is it the more (*PKD1*) or less (*PKD2*) severe form. In reviewing her history, you learn that she has had occasional UTIs since becoming sexually active, rare episodes of crampy abdominal pain she attributes to menstrual cramps, but has otherwise been healthy without hypertension. Her mother was diagnosed as having ADPKD in her 50s as an incidental finding while being worked up for suspected cholelithiasis. Her mother has since progressed to ESRD at age 68. In reviewing her outside records you find that an ultrasound done by a trusted radiology practice revealed that her kidneys are on the upper end of normal for her size and she has a single cyst on the left. A CT scan with contrast detected one additional very small cyst in the left kidney and two very small cysts on the right. What do you tell her?

A. She has >99% probability of having ADPKD because she has >3 cysts in both kidneys and should consider adoption
B. She does not have ADPKD because she does not have multiple cysts in both kidneys by ultrasound.

C. She has >90% probability of having ADPKD because she has 1 cyst by ultrasound
D. If she has ADPKD, she will not develop ESRD until her late 60s because that is when her mother developed it
E. Choice "D" with either Choice "A" or Choice "C"

Answer: C

The prior probability of her having the disease is 50% because of her family history but with one cyst detected by renal ultrasound the posttest probability increases to approximately 95%. Simple cysts can be detected in 1–2% of the general population by this age, so one cannot exclude this possibility in her, but the odds of her having the disease far exceed the likelihood that this is a false positive. The reason "A" is not correct is because the diagnostic significance of the additional, small cysts seen only by CT scan with contrast is not known. If one wants to make a more definitive diagnosis, one can either rescan in a year to see if she develops additional cysts detectable by ultrasound (3> is 100% predictive), obtain an MRI, or perform genetic testing. Regardless of whether the individual is ultimately determined to have ADPKD, there is no compelling medical reason to advise this 32-year-old to forego having a child. She has normal renal function and is at low risk of having a complication (94). The reason "E" is not the best choice is because of the intrafamilial variability of its course. The fact that she does not have hypertension, proteinuria, or severe cystic disease at age 32 suggests that she is at lower risk for rapid progression to ESRD, but one cannot state with any confidence whether she will develop ESRD and if so, when.

Question 3

A 30-year-old mother of two presents with a history of occasional UTI, an unremarkable physical examination, a negative pregnancy test, and a urinalysis that was unremarkable except for microhematuria. She had been referred for an abdominal ultrasound because of intermittent abdominal pain. The ultrasound report describes increased echogenicity in the liver, splenomegaly, and several cysts in each kidney. Kidneys were slightly large for the patient's size. The patient reports that she is not aware of anyone else in the family having kidney cysts. Which of the following is the best answer?

A. Tell the patient that she has ADPKD and counsel her about the implications of having an autosomal dominant trait for other family members and her children
B. Tell the patient she has ARPKD, explain the clinical implications of the diagnosis, and reassure her that her children are unlikely to develop the disease given its recessive inheritance pattern
C. Request scans of the young woman's mother and father, and if not available or they are unwilling to be scanned, consider testing for mutations in *PKD1*, *PKD2*, and *PKHD1*

Answer: C

Although the patient technically meets the criteria for a diagnosis of ADPKD because she has bilateral cystic disease with >2 cysts in each kidney, it is important to note that these criteria are most appropriately applied in the setting of a positive family history. This individual lacks a known positive family history. So does this mean she cannot have ADPKD? Certainly not. It is quite common for individuals with ADPKD to be unaware of the health status of other family members because many affected individuals are asymptomatic until quite late in the disease. It is still possible that she could have ADPKD even if imaging studies of her 60+-year-old parents are negative because *de novo* disease accounts for 5–10% of all ADPKD.

But there is another confounding factor that also makes Choice "A" not optimal. She has hyperechogenicity in the liver and hypersplenism, indicating that she likely has hepatic congenital fibrosis (CHF) and portal hypertension. CHF is typically seen with ARPKD, and given her negative family history one might suspect this as the likely diagnosis (Choice "B"). Although historically ARPKD has been viewed almost exclusively as a disease of infants and young children, it is now appreciated that there is a wide range of severity with respect to the renal disease. Presentation in adulthood with predominantly liver disease and mild kidney involvement has been reported.[74] However, the combination of CHF and cystic disease does occur uncommonly in ADPKD, as well as in a number of other ciliopathies including Joubert syndrome, Bardet–Biedl syndrome, nephronophthisis, and COACH syndrome. Therefore, one cannot simply assume that she must have ARPKD because she has CHF and lacks a positive family history. This makes Choice "B" not optimal.

So how should one move ahead with making a more definitive diagnosis? The presence of large kidneys and the absence of other clinical features typically associated with other ciliopathies make ADPKD or ARPKD the likeliest diagnosis. The most definitive approach is to evaluate her parents and look for renal and hepatic cysts. If either parent has classic changes of ADPKD, one can be confident that she has ADPKD, and she can forego more testing given the extended Ravine criteria. Note that the CHF is not an invariant finding within an ADPKD family, so the lack of this finding in other family members is not informative. Genetic modifiers are thought to account for its variable presentation.

If the scans are negative, inconclusive (i.e. a few cysts in one or both parents) or if the parents are unavailable for testing, one can obtain DNA testing of either the ADPKD genes (*PKD1*, *PKD2*) or ARPKD (*PKHD1*) as the next step. If the test is negative, then one could evaluate the other gene. As DNA testing becomes cheaper, it is quite likely that this step-wise approach will be replaced by a single test of all PKD genes.

Question 4

A 22-year-old previously healthy primigravida presents for routine obstetrical sonography at 20-weeks gestation. Her male fetus is noted to have large echogenic kidneys; there is no evidence of other major malformations. There is no known family history of perinatal demise, individuals with renal cystic disease, or individuals requiring RRT. Follow-up maternal renal sonography revealed normal-sized kidneys with normal echo pattern. One cyst (<1 cm) was evident in her right kidney. The maternal grandparents were willing to be screened and neither had evidence of renal cysts. What do you tell the patient?

A. She has ~90% probability of having ADPKD because she has a renal cyst on ultrasound
B. Her son has >99% probability of having ADPKD because she has a kidney cyst
C. Choice "A" and "B"
D. Her son has ARPKD because he has large, echogenic kidneys *in utero*
E. The diagnosis in her son is likely to be ARPKD, but he should undergo further testing when he is born

Answer: E

Although the mother has evidence for one renal cyst, there is no family history to support the diagnosis of ADPKD. Simple cysts can be detected in 1–2% of the general population in early adulthood. Given that the mother does not meet the sonographic criteria for ADPKD, this diagnosis cannot be immediately inferred in her fetus. That said, spontaneous mutations do occur in the ADPKD genes with an estimated frequency from 1–2% to as high as 10% of affected individuals. Enlarged echogenic kidneys *in utero* are a common manifestation of ARPKD. However, this presentation can be phenocopied by very early onset ADPKD (in this case reflecting a spontaneous mutation in the fetus), as well as numerous other hepato-renal fibrocystic diseases. Therefore, the diagnostic approach once this child is born should include a careful physical examination (to exclude syndromic features) and further imaging studies.

If genetic testing is considered, the phenotypic overlap between ARPKD with syndromic HRFD must be considered. Screening a panel of genes using NGS is rapidly becoming the most efficient diagnostic approach and soon will be the most cost-effective. In the near future, it is likely that single-gene testing will become the exception rather than the rule, especially for genetically heterogeneous disorders with a broad phenotypic spectrum such as PKD.

Question 5

A 32-year-old woman presents for prenatal consultation. She and her husband have had two previous children who died shortly after birth due to respiratory insufficiency associated with severe renal cystic disease. The parents were told that both children had ARPKD based on autopsy findings in the kidney and liver. No DNA is available for either child. The parents are interested in pursuing preimplantation genetic diagnosis (PGD) for the next pregnancy. What can you advise them?

A. Because they have had two children with ARPKD, the likelihood is quite low that they would have a third affected child
B. Ultrasound is quite sensitive in detecting ARPKD early in a pregnancy and thus, imaging studies in the first trimester should demonstrate whether the current fetus is affected
C. Without documented *PKHD1* mutations in a previously affected child, PGD is impractical for future pregnancies
D. In the context of a future pregnancy, DNA extracted from tissue blocks taken at the time of autopsy in the previous children and from amniocentesis in the current pregnancy can be used for linkage studies to determine the affectation status of the current fetus
E. The parents can undergo *PKHD1* testing, and if likely pathogenic mutations are identified in each, PGD is feasible to guide the implantation of an unaffected embryo

Answer: E

In recessive disorders, every pregnancy has a 25% chance of yielding an affected child. In ARPKD, prenatal sonography can detect affected kidneys as early as 20-weeks gestation. However, normal sonographic findings do not necessarily exclude a diagnosis of ARPKD because abnormalities may not be evident until late in the second trimester (or beyond), even in infants who go on to manifest a severe phenotype at birth. Linkage studies (or haplotype analysis) have been a useful diagnostic tool for families with more than one affected child when no *PKHD1* mutations have been identified. However, this approach means testing a current pregnancy, with the attendant complexities of how to proceed if

the testing indicates that the current fetus is affected. PGD offers an alternative to prenatal diagnosis in a current pregnancy. This methodology requires the prospective identification of the *PKHD1* mutations transmitted from each parent. Thus, in the current situation, PGD is feasible if the likely pathogenic allele is identified in each parent.

Question 6

A 16-year-old girl presents for evaluation after passing tarry stool. She had an uneventful delivery and neonatal course. Her childhood has been similarly uneventful. On physical examination, she is well-grown and normotensive. Other notable findings include a liver edge palpable 3 cm below her right costal margin and a palpable spleen tip. Sonography reveals that her kidney length is within the normal limits for her age and the echotexture is normal. Her liver has a heterogeneous echo pattern and evidence of dilated bile ducts. There is no known family history of perinatal demise, individuals with renal cystic disease, or individuals requiring RRT. What do you tell the patient and her parents?

A. She likely has ARPKD
B. Her diagnosis is uncertain and she should undergo *PKHD1* genetic testing
C. She does not have PKD because there are no renal cysts evident on ultrasound
D. She may have polycystic liver disease

Answer: A

The patient's presentation with tarry stools indicates low-grade GI bleeding. In the context of her physical examination and liver sonographic findings, a variceal source is likely. A subset of patients with ARPKD can present exclusively with liver disease related to portal hypertension and no evidence of renal cystic disease. MRI studies would be a useful next diagnostic step to further evaluate the patient's kidneys and liver, as well as the extent of the bile duct dilatation. Endoscopy should be considered to identify and manage the likely varices. With the advent of NGS, a targeted gene panel that includes *PKHD1*, as well as *PKD1*, would enhance the diagnostic certainty.

In patients with congenital hepatic fibrosis (an invariant feature of ARPKD), and sonographic evidence of bile duct dilatation, the term Caroli syndrome is used to describe the liver lesion. This lesion is architecturally distinct from ADPLD, which involves gross liver cysts and is much less commonly associated with portal hypertension. Therefore, screening the genes associated with ADPLD is not likely to be informative.

CHAPTER

49

Lupus Nephritis

Brad Rovin[a], *Samer Mohandes*[a], *Andrew Bomback*[b], *Jai Radhakrishnan*[b]

[a]Division of Nephrology, Department of Internal Medicine, Ohio State University Wexner Medical Center, Columbus, OH, United States; [b]Division of Nephrology, Department of Medicine, Columbia University Irving Medical Center, New York, NY, United States

Abstract

Lupus nephritis (LN) is clinically evident in 50–75% of lupus patients and is a significant cause of end-stage renal disease. Although LN is a paradigm of immune complex–mediated renal injury, its pathogenesis is complex, involving abnormalities in multiple components of the immune system including B and T cells, the complement cascade (especially the alternative pathway), and tissue enzymes that clear denatured DNA. The diagnosis of LN still hinges on the renal biopsy, with glomerular changes being the predominant feature in the classification of LN. The prognostic role of interstitial inflammation has recently been demonstrated. Treatment regimens for severe proliferative LN consist of combination therapy using corticosteroids with cyclophosphamide or antimetabolites (mycophenolate). After remission is achieved, maintenance therapy with a tapering dose of corticosteroids is combined with an antimetabolite (mycophenolate or azathioprine). LN may be refractory to standard regimens in up to 50% of patients and B-cell therapies, calcineurin inhibitors, immunomodulators, and complement inhibitors have been used in this setting with varying success.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect multiple organs, including the skin, joints, brain, peripheral nervous system, heart, gastrointestinal tract, and kidneys. Renal involvement in SLE, generally termed lupus nephritis (LN), is a major contributor to disease morbidity and mortality. Up to 50% of SLE patients will have clinically evident kidney disease at presentation. During follow-up, renal involvement occurs in up to 75% of patients, with an even greater representation among children and young adults. LN has been shown to impact clinical outcomes in SLE both directly, *via* target organ damage, and indirectly, through complications of therapy.

THE PATHOGENESIS OF KIDNEY INJURY IN LUPUS NEPHRITIS

Immune complex accumulation in the glomeruli of patients with SLE appears to be the earliest step in the development of LN, initiating a series of events that result in renal inflammation and kidney injury. Glomerular immune complex accumulation may be due to deposition of preformed circulating immune complexes, kidney-specific nephritogenic autoantibodies directed against intrinsic glomerular basement membrane (GBM) proteins (antilaminin and anti-α-actinin), or *in situ* formation of immune complexes between antichromatin antibodies and extracellular glomerular chromatin derived from apoptotic kidney cells. Kidney-specific autoantibodies are not found in glomerular immune complexes, and circulating levels do not correlate with LN clinical activity.[1–4]

Glomerular immune deposits do contain extracellular chromatin with nicked DNA suggestive of an apoptotic origin,[1,5] and kidney cell apoptosis has been demonstrated in lupus-prone mice.[1] Chromatin derived from apoptotic kidney cells could accumulate along the GBM because the major kidney endonuclease responsible for chromatin degradation (Dnase1) is downregulated in LN, and positively charged histones bind to the negatively charged GBM with high affinity.[5,6] Although autoantibodies found in the LN kidney are generally considered to originate from the circulation, T and B cells can form aggregates, and in some cases germinal centers in the kidney interstitium. Interstitial plasma cells appear to produce antibodies in a clonally restricted fashion, suggesting kidney-relevant autoantibodies may be produced locally.[7,8]

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00049-8

The expression of autoantibodies and clearance of immune complexes in LN patients are under genetic control. For example, the HLA DR3 allele (DRB1 *0301) is associated with anti-dsDNA antibodies and with LN.[9,10] Genetic variants of immune complex clearance proteins, such as the immunoglobulin heavy chain receptors that result in higher-affinity interactions with IgG, are associated with protection against LN in SLE patients.[11,12]

Anti-dsDNA autoantibodies are predominantly IgG1 and IgG3,[13,14] the most proinflammatory IgG subtypes due to their ability to activate complement and engage leukocyte Fc receptors for IgG (FcγR). Complement-mediated kidney damage has been demonstrated directly in experimental models of LN.[15–20] These experiments indicate that the alternative pathway of complement activation is probably the effector arm of complement within the lupus kidney, a conclusion also applicable to renal injury in human LN.[21] Blocking the classical complement pathway may actually worsen LN,[18] likely because complement is not only proinflammatory but also important in clearing apoptotic debris.[22,23] Thus, if complement is to be targeted therapeutically in human LN, drugs that attenuate alternative pathway activation will probably be more successful.[24]

Complement-mediated kidney injury may occur by direct cellular damage through formation of the membrane attack complex C5b-9,[25] or more indirectly through recruitment of leukocytes to the kidney by the chemotactic complement fragments C3a and C5a. These complement fragments, along with immune complex ligation of leukocyte FcyR, can activate infiltrating leukocytes to produce proinflammatory cytokines and chemokines.[26,27] Immune complexes and complement can also induce cytokine and chemokine expression by intrinsic kidney cells. Several cytokines are known to be upregulated in LN kidneys, including monocyte chemoattractant protein-1 and macrophage inflammatory protein-1-α, IL-6, IL-10, IL-12, IL-17, IL-18, IFN-γ, TNF-α, and Eta-1/osteospontin.[28–35] The contribution of individual cytokines to kidney injury in LN has been assessed by genetically deleting or neutralizing specific cytokines in murine models and observing the effect on disease activity and kidney pathology.[36–40] These experiments provide a rationale for therapeutic targeting of individual cytokines and chemokines in human LN. Given the intrinsic redundancy of cytokine effects, finding a single cytokine target with robust therapeutic potential is likely to be challenging.

An exception may be interferon-α (IFN-α).[41] Plasmacytoid dendritic cells (pDCs) are the major source of IFN-α following engagement of their endosomal toll-like receptors 7 and 9 (TLR7, TLR9) by nucleic acids.[42,43] During LN pDCs leave the circulation and accumulate in glomeruli.[44,45] This influx is mediated in part by IL-18 and IL-18 receptor. Human diffuse proliferative LN is associated with an IL-18 promoter polymorphism that causes increased IL-18 expression.[46] The effects of IFN-α on the immune response include driving maturation of conventional dendritic cells into potent antigen presenting cells,[47] inducing B-cell differentiation to plasma cells,[48] and contributing to the development of CD4 helper T cells,[49] and CD8 central memory T cells.[50] Peripheral blood cell levels of IFN-inducible genes are associated with LN,[51,52] and a genetic variant that increases STAT4, a secondary messenger for IFN-α signaling, is overexpressed in LN.[53,54] It is plausible that the presence of glomerular immune complexes could drive pDCs to produce IFN-γ, amplifying the autoimmune response to local kidney antigens and contributing to the formation of local germinal centers. Studies in mouse models also generally support a role for IFN-γ in LN pathogenesis. Experimental LN is reduced by deletion of the IFN-γ receptor or by administration of TLR7 or TLR9 antagonists, whereas LN is worsened by administration of an IFN-α–producing vector or an agonist of TLR7 or TLR9.[55] Clinical trials of IFN-α antagonists are currently underway in SLE.

Intrarenal cytokine and chemokine production amplifies the kidney inflammatory response by recruiting leukocytes to the kidney. Neutrophils and monocytes/macrophages can damage the kidney directly through secretion of oxygen radicals and proteolytic enzymes. Neutrophils may also contribute to LN as they die and release neutrophil extracellular traps (NETS), which are chromatin structures that can bind autoantigens.[56–58] NETs stimulate IFN-α secretion from dendritic cells,[56] amplifying the intrarenal autoimmune response.

Kidney-infiltrating T cells tend to exhibit a Th1 cytokine expression profile, including IL-12, IL-18, and IFN-γ; however this is not exclusive and some Th2 cytokines, such as IL-10, also increase. Overall the Th1/Th2 ratio is increased[30,33,34,59] and correlates with histologic activity. Th1 cytokines are associated with activated macrophages and with the production of immunoglobulins that can activate complement and FcyR pathways, further amplifying renal inflammation. IL-17, from Th17 cells and $CD4^{-}CD8^{-}$ T cells, is found in the kidney in LN.[35] In addition to IL-17's role in mediating inflammation,[60–62] this cytokine may also represent a shift away from natural regulatory T cells capable of suppressing immune responses.[63]

Human regulatory T cells (Treg) attenuate immune responses, particularly autoantibody production.[64–67] In murine lupus models, adoptive transfer of Tregs can suppress LN.[68,69] Some human studies have described lower circulating levels of Tregs in SLE,[65,70] but their role in human LN remains to be determined.

CLINICAL MANIFESTATIONS OF LUPUS NEPHRITIS[71]

Clinical Presentation

Most patients with SLE have laboratory evidence of kidney involvement at some point in their disease. In about one-third of SLE patients, renal involvement first manifests with proteinuria and/or microhematuria on urinalysis. This is a harbinger of eventual progression to reduction in kidney function. However, early in the course of disease, it is unusual for patients to present with decreased kidney function (i.e. elevated S[Cr] and reduced eGFR), with the exception of very aggressive cases of LN, some of which present as rapidly progressive glomerulonephritis. Instead, patients often present initially with evidence of nonrenal organ involvement, such as malar rash, arthritis, and oral ulcers. After a diagnosis of SLE is confirmed with appropriate laboratory tests, evidence of kidney disease, if present, usually emerges within the first 3 years after diagnosis.

The symptoms of kidney involvement tend to correlate with laboratory abnormalities. For example, patients with nephrotic range proteinuria often present with edema of the lower extremities and, if severe, periorbital edema in the morning. When kidney function is impaired, as is the case with progressive forms of LN, elevated blood pressure is a common clinical finding. The rare development of dark or tea-colored urine is a sign of gross hematuria. A number of tools, such as the SLE Disease Activity Index and the British Isles Lupus Assessment Group Index, have been developed to assess the systemic severity of lupus symptoms. Although these questionnaires are primarily used to codify symptoms for clinical trial settings, they also can be very helpful to elicit a detailed history from a patient with SLE.

Laboratory Findings

The American College of Rheumatology has listed 11 diagnostic criteria for SLE: antinuclear antibodies (ANA), arthritis, immunologic disorders (including antidouble strand DNA antibody, antiphospholipid antibody, or anti-Smith antibody), malar rash, discoid rash, photosensitivity, oral ulcers, serositis, hematologic disorder, neurologic disorder, and renal disorder. Ideally, four or more of these criteria should be present to make the diagnosis of SLE, including laboratory findings of a positive ANA and/or antidouble strand DNA antibody. In addition to the ANA and double-strand DNA antibody, serum complements (C3, C4, CH50) should be checked whenever kidney involvement is suspected because these are often low when disease is active, as is usually the case with any severe proliferative LN. Antiphospholipid and anticardiolipin antibodies are useful in gauging the risk for clotting abnormalities that can accompany SLE.

Laboratory testing is used both to diagnose kidney involvement and to assess response to therapy in patients with SLE. Traditional parameters, such as S[Cr] and urinary protein excretion (quantified by either 24-hour collection or first morning urine protein:creatinine ratio), are supplemented by serial review of microscopic urinary sediment, changes in serum complement levels, and titers of ANA and double-strand DNA antibodies. Because cytopenias can often be seen with active SLE, complete blood counts should be checked regularly. A number of urine and serologic tests have been recently studied as biomarkers for SLE and, specifically, LN disease activity.[72] These include molecules specific to lupus (e.g. anti-C1q antibodies), mediators of chronic inflammation (e.g. TNF-like weak inducer of apoptosis), and generalized markers of kidney injury (urinary neutrophil gelatinase–associated lipocalin).[73] However, the clinical utility of this approach remains unproven, and no serum or urine disease markers are able to provide as much information as a kidney biopsy. Hence, virtually all patients with SLE with suspected kidney involvement will undergo one or more kidney biopsies at some point during their care.

Kidney Biopsy Findings

The classic pattern of LN is an immune complex–mediated glomerulonephritis; however, the pathology of LN can be quite varied and at times cause confusion with other immune complex-mediated glomerulonephritides. Particular biopsy findings are highly characteristic of LN, including: (1) glomerular deposits that stain dominantly for IgG with codeposits of IgA, IgM, C3, and C1q, the so-called "full house" immunofluorescence (IF) pattern; (2) extraglomerular immune type deposits within tubular basement membranes, the interstitium, and blood vessels; (3) the ultrastructural finding of coexistent mesangial, subendothelial, and subepithelial electron dense deposits; and (4) the ultrastructural finding of tubuloreticular inclusions (TRIs), which represent "interferon footprints" in the glomerular endothelial cell cytoplasm.

Although LN may affect all compartments of the kidney, glomerular involvement is the best-studied component and correlates well with the presentation, course, and treatment of the disease. Disease classification, therefore, is based largely on the glomerular alterations as assessed by the combined modalities of light microscopy (LM), IF, and electron microscopy (EM). The 2004 modifications in the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) Classification refine and clarify some of the deficiencies of

the older WHO classification of LN.[74] The current approach to treating LN—and studying new therapeutic modalities—has largely been guided by histologic findings (i.e. ISN Class) with appropriate consideration of presenting clinical parameters and the degree of renal impairment.

The ISN/RPS classification recognizes six different classes of immune complex-mediated lupus glomerulonephritis based on biopsy findings.[75] These classes are not static entities but may transform from one class to another, both spontaneously and after therapy. ISN/RPS class I represents the mildest possible glomerular lesion—immune deposits limited to the mesangium, without associated mesangial hypercellularity. In class II, the mesangial deposits detected by IF and/or EM are accompanied by mesangial hypercellularity of any degree. In class III, there is focal and predominantly segmental endocapillary proliferation and/or sclerosis affecting <50% of glomeruli sampled. The active endocapillary lesions typically include infiltrating monocytes and neutrophils and may exhibit necrotizing features. In class IV, the endocapillary lesions involve ≥50% of glomeruli sampled, typically in a diffuse and global distribution. Subendothelial immune deposits are a feature of the endocapillary lesion in class III and class IV, where they vary from focal and segmental (class III) to more diffuse and global (class IV). Both class III and class IV may exhibit extracapillary proliferation in the form of cellular crescents, a feature that correlates best with a rapidly progressive clinical course. Class V denotes membranous LN. Subepithelial deposits are the defining feature, usually superimposed on a base of mesangial hypercellularity and/or mesangial immune deposits. Well-developed examples of class V typically exhibit glomerular basement membrane spikes between the subepithelial deposits. In those patients with combined membranous and endocapillary lesions, a diagnosis of both class V and class III or IV is made. These mixed classes carry a worse prognosis than pure class V LN. Class VI identifies advanced chronic disease exhibiting >90% sclerotic glomeruli, without residual activity.

Unusual kidney biopsy findings in SLE patients include "lupus podocytopathy," presenting as nephrotic syndrome with diffuse foot process effacement in the absence of peripheral capillary wall immune deposits.[76] Such cases resemble minimal change disease or focal segmental glomerulosclerosis in their histopathologic findings and response to glucocorticoids. Rare cases of LN have predominant tubulointerstitial nephritis with abundant tubulointerstitial immune deposits in the absence of significant glomerular lesions. Some cases with necrotizing and crescentic features and a paucity of peripheral capillary wall immune deposits are associated with circulating antineutrophil cytoplasmic antibody (ANCA) in addition to ANA.[77] This "pauci-immune" variant is particularly common in LN class IV-S, in which there are diffuse but segmental lesions of necrosis and crescent formation. In any patient with SLE who develops thrombotic microangiopathy affecting the glomeruli and/or vessels, the possibility of a circulating lupus anticoagulant or antiphospholipid antibody should be investigated.

TREATMENT

General Treatment Concepts

The 2003 ISN/RPS classification of LN (Table 49.1) is widely accepted and forms the cornerstone for treatment decisions. Class I and II lesions do not need specific therapy; treatment if needed is directed at extrarenal lupus manifestations. The optimal regimen for treating the aggressive forms of LN is far from established in terms of efficacy and toxicity. Treatment regimens for the more aggressive forms of LN take the form of an "induction" phase where combinations of corticosteroids and either cytotoxic agents or antimetabolites have been studied in several controlled trials. This is followed by a "maintenance" phase where the doses of corticosteroids are lowered and cytotoxic agents, if used for the induction phase, are replaced by antimetabolites. The treatment for class V LN is similar to that used for idiopathic membranous nephropathy, although large controlled trials are lacking. LN has a significant relapse rate and there is considerable morbidity (and even mortality) associated with treatment. Thus, close monitoring of patients for clinical lupus activity, laboratory indices (S[Cr], proteinuria, urinary sediment and lupus serologies), and side effects (blood counts, infections, malignancies) are important.

Proliferative Lupus Nephritis: Induction Therapy

Recent clinical studies of SLE patients with renal disease, including a number of randomized controlled trials (RCTs), have clarified the therapeutic role of a variety of immunosuppressive regimens both in proliferative and membranous LN. The goal of each of these trials has been to achieve clinical efficacy with a remission of the nephritis while minimizing deleterious side effects of treatment. The greatest amount of RCT evidence in treating LN is in the induction phase of proliferative LN.

Most patients with active proliferative LN are initially treated with corticosteroids (traditionally a "pulse" of IV steroids followed by a high dose oral regimen that begins to taper at 8 weeks) used in conjunction with other immunosuppressive agents. Clinical trials over the last

TABLE 49.1 International Society of Nephrology/Renal Pathology Society Classification of Lupus Nephritis (LN) With Corresponding Treatment Strategies

Lupus Class	Treatment Strategy
Class I Minimal mesangial LN	No specific treatment for LN. Treatment dictated by extrarenal systemic lupus erythematosus (SLE) symptoms
Class II Mesangial proliferative LN	No specific treatment for LN unless significant proteinuria, e.g. >1 g/day (short course of tapering corticosteroids may be considered) Treatment dictated by extrarenal SLE symptoms
Class III Focal LN* (<50% of glomeruli) III (A): active lesions III (A/C): active and chronic lesions III (C): chronic lesions	As in Figure 49.1
Class IV Diffuse LN* (≥50% of glomeruli) Diffuse segmental (IV-S) or global (IV-G) LN IV (A): active lesions IV (A/C): active and chronic lesions IV (C): chronic lesions	As in Figure 49.1
Class V Membranous LN	Corticosteroids with calcineurin inhibitors, mycophenolate or intravenous cyclophosphamide in patients with nephrotic proteinuria
Class VI Advanced sclerosing LN (≥90% globally sclerosed glomeruli without residual activity)	Conservative management and preparation for end-stage renal failure

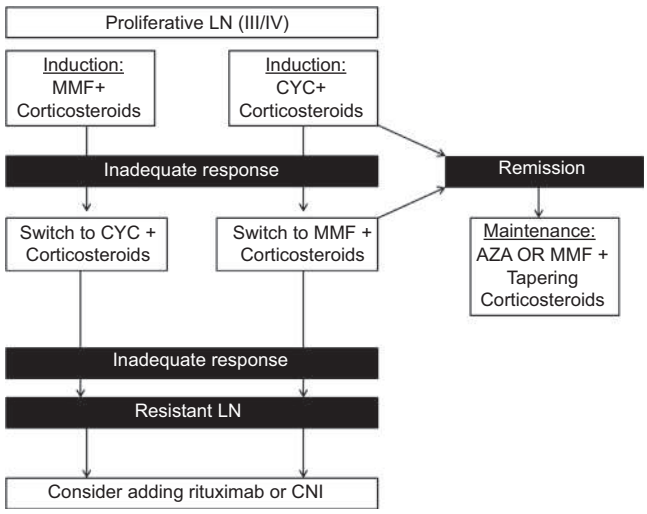


FIGURE 49.1 Suggested treatment algorithm for proliferative lupus nephritis. *AZA*, azathioprine, *CNI*, calcineurin inhibitor; *CYC*, cyclophosphamide (includes intravenous or oral regimens); *MMF*, mycophenolate mofeti.

decade have provided support for using mycophenolate mofetil (MMF) as an alternative to intravenous cyclophosphamide for induction therapy in severe LN (ISN classes IIIA, IIIA/C, IVA, and IVA/C).

Cyclophosphamide remains a reliable and effective treatment choice for inducing remission in LN. Whether oral therapy or intravenous pulses of cyclophosphamide is more effective in treating LN remains inconclusive, but intravenous therapy involves a lower cumulative exposure to cyclophosphamide, less-frequent cytopenias, enables enhanced bladder protection, and avoids problems of nonadherence. RCTs at the National Institutes of Health (NIH) in patients with severe, proliferative LN established that six pulses of intravenous cyclophosphamide (0.5–1 g/m^2) on consecutive months, followed by every third month follow-up pulses with low-dose corticosteroids, was effective and prevented relapses better than a shorter regimen limited to six doses alone. A subsequent controlled trial established that pulse cyclophosphamide, when given with monthly pulses of methylprednisolone, led to better long-term GFR than either regimen alone.[78,79] Nevertheless, side effects were significant in both therapeutic arms of this study, including ischemic and valvular heart disease, avascular necrosis, osteoporosis, and premature menopause. Major infections occurred in 33% of subjects treated with cyclophosphamide alone and 45% of subjects treated with cyclophosphamide plus steroids. Therefore, more recent studies using newer regimens have focused on achieving the high induction response rate of "NIH protocol" cyclophosphamide with fewer side effects.

A trial by the EuroLupus Group randomized 90 patients with diffuse or focal proliferative LN, or

membranous plus proliferative disease, to receive either standard six monthly pulse of cyclophosphamide (0.5–1 g/m^2) followed by every third monthly infusions or to a shorter treatment course consisting of 500 mg of intravenous cyclophosphamide every two weeks for six doses (total dose 3 g) followed by azathioprine maintenance therapy (2 mg/kg/day). Both regimens were equally effective for various renal and extrarenal outcomes. The shorter regimen had less toxicity with significantly less severe and total infections as a complication of treatment.[80] Reports from this trial with up to 10 years of follow-up continue to find no differences in outcome between treatment groups, although approximately 75% of these patients remained on some dose of steroids throughout this follow-up period. As this trial was largely performed in white subjects, questions about whether the "EuroLupus regimen" was applicable to all populations at high risk for poor renal outcomes persisted. However, a recent study examining the role of abatacept in proliferative LN added either abatacept or placebo in conjunction with the EuroLupus regimen of low-dose cyclophosphamide in 134 subjects, of whom only half (n=67) were white and almost 40% (n=52) were African American. Although this study found no benefit in using abatacept, the background response rates across all participants were high enough to lend support for using the EuroLupus regimen in nonwhite patients.[71]

Several recent controlled trials and subsequent meta-analyses have established MMF as one of the recommended, first choice regimens for inducing a remission in severe active proliferative LN. An initial report was a Chinese study of 42 patients randomized to receive either 12 months of oral MMF (2 g/day for 6 months followed by 1 g/day for 6 months) or 6 months of oral cyclophosphamide (2.5 mg/kg/day), followed by oral azathioprine (1.5 mg/kg/day) for 6 months. Both groups received concomitant tapering doses of corticosteroids. At 12 months, the rate of complete remission (81% vs. 76%), partial remission (14% vs. 14%), and relapses (15% vs. 11%) were not different between the regimens, but infections were less common in the MMF arm, and mortality was only seen in the cyclophosphamide group (0 vs. 10%).[81] Long-term follow-up of this population showed similar rates of chronic renal failure, defined as doubling of baseline S[Cr], in the MMF group (6.3%) and the cyclophosphamide-azathioprine group (10.0%), as well as similar rates of relapse and relapse-free survival. However, infection was now significantly less in the MMF group (13% vs. 40%) and mortality was still entirely in the cyclophosphamide group.[82]

A larger US induction trial, reported 5 years later in a more diverse population (over 50% African Americans), examined 140 patients with proliferative LN or membranous LN randomized to intravenous cyclophosphamide monthly pulses vs. oral MMF up to 3 g daily, each in conjunction with a fixed tapering dose of corticosteroids as induction therapy over 6 months. Although the study was powered as a noninferiority trial, complete remissions and complete plus partial remissions at 6 months were significantly more common in the MMF arm (52%) than the cyclophosphamide arm (30%).[83] Again, the side effect profile was better in the MMF group, and at 3 years, there were no significant differences in numbers of patients with renal failure, end-stage renal disease (ESRD), or mortality. Most recently, a 370-patient, international multicenter trial of induction therapy with either MMF (3 g/day) or monthly intravenous cyclophosphamide pulses showed, after 6 months of therapy, virtually identical rates of achieving complete and partial remission (56.2% of patients receiving MMF vs. 53.0% of patients receiving IV cyclophosphamide, $p = 0.58$).[84] The groups proved identical with respect to improvement of renal function (assessed by eGFR, S[Cr], proteinuria, and urine sediment) as well as nonrenal parameters (reduction in anti-DNA antibody titers, normalization of serum complement, and increase in serum albumin (S[Alb]) levels). Notably, there was no difference in mortality between the groups with a total of 14 deaths among the 370 patients. A subgroup analysis of those presenting with significant renal failure (defined as GFR <30 mL/min) found no indication that MMF was less effective than cyclophosphamide in this setting.[85]

Other agents have been explored in induction regimens, typically used in conjunction with MMF and/or steroids. Rituximab, an anti-CD20 monoclonal antibody that depletes B cells, has proven useful in inducing remissions in some patients with severe LN, including those who have failed cyclophosphamide or MMF therapy, although this strategy is not supported by data from randomized trials. The Lupus Nephritis Assessment with Rituximab (LUNAR) trial randomized 140 patients with severe LN to rituximab or placebo added to a full dose of MMF (up to 3 g/day) and tapering dose of corticosteroids.[86] Although more subjects in the rituximab group achieved complete remission or partial remission, there was no statistically significant difference in the primary clinical endpoint at Week 52. The role of rituximab remains unclear in the treatment of LN, but it may still be of use in treating resistant patients, preventing flares, or reducing the number or doses of other immunosuppressive medications.[56] For example, subgroup analyses of the LUNAR study showed higher rates of remission in African Americans and Hispanics randomized to rituximab vs. placebo, suggesting that these higher-risk populations might still receive benefit from rituximab, especially if initial induction therapy with MMF has failed to achieve sustained remission.

Another induction treatment strategy studied in small settings is to combine a calcineurin inhibitor with MMF or azathioprine plus corticosteroids. This multitargeted immunosuppressant regimen is akin to those used in protecting kidney transplants. For example, Bao and colleagues randomized 40 patients with diffuse proliferative LN superimposed on membranous LN (ISN class IV + V) to induction therapy with MMF, tacrolimus, and steroids (multitarget therapy) or intravenous cyclophosphamide plus steroids.[87] Intention-to-treat analysis revealed a higher rate of complete remission with multitarget therapy at both 6 and 9 months (50% and 65%, respectively) than with cyclophosphamide (5% and 15%, respectively). Adverse events were lower in the multitarget group. In a subsequent report using a much larger patient population drawn from 26 nephrology centers across China, this multitarget therapy at 24 weeks, compared to cyclophosphamide-based induction, also showed higher rates of complete (46% vs. 26%) and complete plus partial (84% vs. 63%) remission. The median time to overall response was shorter in the multitarget group.[88] Voclosporin, a new calcineurin inhibitor, is currently being evaluated as a treatment for proliferative LN. This agent, given in combination with MMF in a multitargeted approach similar to that used in the aforementioned Chinese studies, has shown promising results in a phase 2 study (presented in abstract form) and is now being evaluated in a larger, phase 3 study (NCT03021499).

Plasma exchange has been added to other induction therapies (e.g. cyclophosphamide) in several trials without any demonstrated clear benefit in terms of renal or patient survival.[89] Therefore, the routine use of plasma exchange is not justified in LN, although this procedure may be of value in unique individuals such as those with a refractory antiphospholipid antibody and contraindications to anticoagulation, or those with both positive lupus and ANCA serologies. For patients with life-threatening resistant disease, small pilot studies have utilized total lymphoid irradiation, and immunoablation by high dose cyclophosphamide and anti-thymocyte globulin, with or without reconstitution with autologous stem cells.[90,91] Although these approaches have led to some sustained, treatment-free remissions, they are potentially toxic and have significant treatment-related mortality. They have not been widely studied or embraced as therapy for LN.

Proliferative Lupus Nephritis: Maintenance Therapy

The two goals of maintenance therapy are provision of chronic immunosuppression after the intense induction period, and prevention of renal flares after a response has been achieved, while limiting adverse treatment effects. The main agents used for LN maintenance are MMF and AZA. If neither can be used, calcineurin inhibitors are an additional option.

The evolution of LN treatment provides context for understanding current maintenance regimens. After it was shown that cyclophosphamide plus corticosteroids was more effective than corticosteroids alone for long-term kidney health, it was found that prolonged therapy with cyclophosphamide (30 vs. 6 months) resulted in even better renal outcomes and fewer renal flares.[92] However, the toxicity of cyclophosphamide maintenance was very high. Investigating less-toxic long-term immunosuppression regimens led to the seminal clinical observation that MMF or AZA could be used instead of cyclophosphamide with similar efficacy but significantly lower morbidity and mortality.[93] This ushered in the current approach to maintenance therapy.

MMF and AZA have been compared head-to-head in two recent randomized trials to determine the drug of choice for maintenance. In the ALMS maintenance trial, after induction with either MMF or cyclophosphamide, patients who had a renal response were rerandomized to receive MMF or AZA for 3 years.[94] MMF was superior to AZA in preventing the composite treatment failure endpoint of death, renal flare, ESRD, and doubling of S [Cr]. In contrast, MMF and AZA were equivalent in preventing renal flare over more than 4 years of follow-up after induction with low-dose (Eurolupus protocol) cyclophosphamide (MAINTAIN Trial).[95,96] Although the ALMS maintenance and MAINTAIN results seem contradictory, the two trials are not strictly comparable. MAINTAIN included mainly European Caucasians, whereas ALMS maintenance followed a multiracial cohort. In summary, MMF appears to be the maintenance immunosuppressive of choice for most LN patients[97]; however, AZA can be used if MMF is not tolerated, or individual patient needs preclude its use, such as a desire to become pregnant.

The calcineurin inhibitors cyclosporine and tacrolimus provide a third option for LN maintenance therapy. Two randomized trials compared calcineurin inhibitors to AZA, and both showed that cyclosporine and tacrolimus were as effective as AZA in preventing LN flares.[98,99] Both of these trials were underpowered and had short follow-up. Calcineurin inhibitors have not yet been compared to MMF for maintenance.[97] For now, calcineurin inhibitors should be reserved for patients who cannot receive MMF or AZA. The study authors from China who reported on multitarget (MMF + tacrolimus) therapy for induction therapy have also reported an open label, multicenter study for 18 months to assess the efficacy and safety of a similar multitarget maintenance therapy in patients who had responded at 24 weeks during the induction phase.

Those induced on multitarget therapy (N = 116) remained on low-dose MMF, tacrolimus, and prednisone, whereas those induced with cyclophosphamide (N = 90) were given azathioprine plus prednisone. The multitarget and azathioprine groups had similar cumulative renal relapse rates (6% vs. 8%, respectively), and S[Cr] levels remained stable in both groups. The azathioprine group had more adverse events (44% vs. 16% for multitarget therapy).[100] The caveats for both the induction and maintenance phase of these multitarget therapy studies include (a) whether they will be generalizable beyond Asian LN populations, and (b) whether the remission rates achieved will be sustained once calcineurin inhibitors are weaned off, given the high rate of proteinuria relapse when calcineurin inhibitors have been stopped in other glomerular diseases.

The optimal duration of maintenance therapy has not been investigated by any prospective randomized clinical trial. Most patients remain on maintenance therapy for years. In a survey of several randomized clinical trials immunosuppression was continued for an average of 3.5 years (range 1.5–7 years).[80,82,92,93,101–104] LN guidelines recommend slow withdrawal of maintenance therapy beginning 1 year after a complete renal response, but continuing indefinitely in patients who only achieve a partial renal response.[105] Two small retrospective studies examined renal flares after maintenance therapy was withdrawn or tapered. One study found that patients segregated into a group that flared and a group that did not flare during a median of 17 years of follow-up after stopping maintenance therapy.[106] The nonflare group had a longer overall duration of therapy (57 vs. 30 months) and a longer duration of maintenance after remission (24 vs. 12 months). The other investigation studied timing of MMF taper after renal response. If dose reduction began within 18 months of renal remission, the risk of LN flare was several-fold higher than if the dose of MMF remained stable or was tapered after 18 months of remission.[107] Given the toxicity of long-term immunosuppression, tapering should be attempted in patients with a good clinical response. For patients who do not achieve a complete renal response, it would be reasonable to repeat the kidney biopsy to determine whether the clinical findings are due to active LN or renal scarring, in which case tapering immunosuppression is justified.

Recent data raise the possibility that with the right induction regimen maintenance therapy may not be necessary. In eight refractory lupus patients, five with LN, remissions were induced with rituximab, intravenous methylprednisolone, and intravenous cyclophosphamide, followed by a rapid oral corticosteroid taper.[108] No maintenance immunosuppressive agents were given. During an average follow-up of 36 months, only 2 had flares, 1 LN, and 1 extrarenal, at 36 and 41 months respectively.

Membranous Lupus Nephritis

Class V membranous LN is the least studied form of LN due to its relative rarity, and optimal treatment has not been established. Similar to the proliferative forms of LN, combination therapies are generally employed. A retrospective study using chlorambucil and methylprednisolone showed improved results over those achieved with corticosteroids alone.[109] In a small study using cyclosporine, there was improvement in proteinuria (decreasing from 6 to 1–2 g daily by 6 months).[110] Although repeat biopsy did not reveal cyclosporine toxicity, two patients were noted to have developed superimposed proliferative lesions. A randomized trial of 42 nephrotic patients with membranous LN found superior remission rates with cyclosporine and cyclophosphamide regimens over prednisone monotherapy.[111] However, there were more relapses after cyclosporine was withdrawn. Prednisone with azathioprine has also been studied, with 67% of patients in complete remission and 22% in partial remission at 12 years. Relapse rates were also low with 12% at 3 years and 16% at 5 years.[112] In a meta-analysis of 84 patients who had been enrolled in two similarly designed controlled trials, MMF and intravenous cyclophophamide were comparable in inducing remission at 6 months.[113] These data are somewhat similar to results in patients with idiopathic membranous nephropathy.

The treatment of membranous LN should be individualized. Patients with a good renal prognosis (subnephrotic levels of proteinuria and preserved GFR) may be treated conservatively with inhibitors of the renin–angiotensin system and statins, with perhaps a short course of a calcineurin inhibitor with low doses of steroids. For those at higher risk of progression disease (heavy proteinuria, impaired renal function), options include cyclosporine, monthly IV pulses of cyclophosphamide, MMF, or azathioprine (plus tapering doses of corticosteroids). Patients with mixed membranous and proliferative LN are treated in the same way as those with proliferative disease alone.

CONCLUSION

LN is an important cause of morbidity and ESRD in patients with LN. Rapid advances have been made in understanding the pathogenesis of this complex disease. LN is one of the best studied glomerular diseases. RCTs

have provided disease-specific data on induction and maintenance therapy, leading to impressive improvements in the care of patients with LN, resulting in diminution in mortality and progression to ESRD. However, a substantial number of patients with LN still have persistent disease despite immunosuppressive therapy. Relapse is common and is associated with side effects from prolonged immunosuppression. Therapeutic challenges underscore the need for studying targeted therapy in combination with current immunosuppressive agents, hopefully further improving the long-term prognosis for patients with this once fatal disease.

References

1. Kalaaji M, Mortensen E, Jorgensen L, Olsen R, Rekvig OP. Nephritogenic lupus antibodies recognize glomerular basement membrane-associated chromatin fragments released from apoptotic intraglomerular cells. *Am J Pathol* 2006;**168**(6):1779–92.
2. Kalaaji M, Sturfelt G, Mjelle JE, Nossent H, Rekvig OP. Critical comparative analyses of anti-alpha-actinin and glomerulus-bound antibodies in human and murine lupus nephritis. *Arthritis Rheum* 2006;**54**(3):914–26.
3. Kalaaji M, Fenton KA, Mortensen ES, et al. Glomerular apoptotic nucleosomes are central target structures for nephritogenic antibodies in human SLE nephritis. *Kidney Int* 2007;**71**(7):664–72.
4. Manson JJ, Ma A, Rogers P, et al. Relationship between anti-dsDNA, anti-nucleosome and anti-alpha-actinin antibodies and markers of renal disease in patients with lupus nephritis: a prospective longitudinal study. *Arthritis Res Ther* 2009;**11**(5):R154.
5. Fenton K, Fismen S, Hedberg A, et al. Anti-dsDNA antibodies promote initiation, and acquired loss of renal Dnase1 promotes progression of lupus nephritis in autoimmune (NZBxNZW)F1 mice. *PLoS One* 2009;**4**(12):e8474.
6. Zykova SN, Tveita AA, Rekvig OP. Renal Dnase1 enzyme activity and protein expression is selectively shut down in murine and human membranoproliferative lupus nephritis. *PLoS One* 2010;**5**(8).
7. Steinmetz OM, Velden J, Kneissler U, et al. Analysis and classification of B-cell infiltrates in lupus and ANCA-associated nephritis. *Kidney Int* 2008;**74**(4):448–57.
8. Chang A, Henderson SG, Brandt D, et al. In situ B cell-mediated immune responses and tubulointerstitial inflammation in human lupus nephritis. *J Immunol* 2011;**186**(3):1849–60.
9. Marchini M, Antonioli R, Lleo A, et al. HLA class II antigens associated with lupus nephritis in Italian SLE patients. *Hum Immunol* 2003;**64**(4):462–8.
10. Taylor KE, Chung SA, Graham RR, et al. Risk alleles for systemic lupus erythematosus in a large case-control collection and associations with clinical subphenotypes. *PLoS Genet* 2011;**7**(2):e1001311.
11. Karassa FB, Trikalinos TA, Ioannidis JP. Role of the Fcgamma receptor IIa polymorphism in susceptibility to systemic lupus erythematosus and lupus nephritis: a meta-analysis. *Arthritis Rheum* 2002;**46**(6):1563–71.
12. Karassa FB, Trikalinos TA, Ioannidis JP. The Fc gamma RIIIA-F158 allele is a risk factor for the development of lupus nephritis: a meta-analysis. *Kidney Int* 2003;**63**(4):1475–82.
13. Winkler TH, Henschel TA, Kalies I, Baenkler HW, Skvaril F, Kalden JR. Constant isotype pattern of anti-dsDNA antibodies in patients with systemic lupus erythematosus. *Clin Exp Immunol* 1988;**72**(3):434–9.
14. Devey ME, Lee SR, Le Page S, Feldman R, Isenberg DA. Serial studies of the IgG subclass and functional affinity of DNA antibodies in systemic lupus erythematosus. *J Autoimmun* 1988;**1**(5):483–94.
15. Watanabe H, Garnier G, Circolo A, et al. Modulation of renal disease in MRL/lpr mice genetically deficient in the alternative complement pathway factor B. *J Immunol* 2000;**164**(2):786–94.
16. Elliott MK, Jarmi T, Ruiz P, Xu Y, Holers VM, Gilkeson GS. Effects of complement factor D deficiency on the renal disease of MRL/lpr mice. *Kidney Int* 2004;**65**(1):129–38.
17. Bao L, Haas M, Quigg RJ. Complement factor H deficiency accelerates development of lupus nephritis. *J Am Soc Nephrol* 2011;**22**(2):285–95.
18. Sekine H, Reilly CM, Molano ID, et al. Complement component C3 is not required for full expression of immune complex glomerulonephritis in MRL/lpr mice. *J Immunol* 2001;**166**(10):6444–51.
19. Wenderfer SE, Ke B, Hollmann TJ, Wetsel RA, Lan HY, Braun MC. C5a receptor deficiency attenuates T cell function and renal disease in MRLlpr mice. *J Am Soc Nephrol* 2005;**16**(12):3572–82.
20. Sekine H, Ruiz P, Gilkeson GS, Tomlinson S. The dual role of complement in the progression of renal disease in NZB/W F(1) mice and alternative pathway inhibition. *Mol Immunol* 2011;**49**(1–2):317–23.
21. Birmingham DJ, Irshaid F, Nagaraja HN, et al. The complex nature of serum C3 and C4 as biomarkers of lupus renal flare. *Lupus* 2010;**19**(11):1272–80.
22. Korb LC, Ahearn JM. C1q binds directly and specifically to surface blebs of apoptotic human keratinocytes: complement deficiency and systemic lupus erythematosus revisited. *J Immunol* 1997;**158**(10):4525–8.
23. Pickering MC, Botto M, Taylor PR, Lachmann PJ, Walport MJ. Systemic lupus erythematosus, complement deficiency, and apoptosis. *Adv Immunol* 2000;**76**:227–324.
24. Sekine H, Kinser TT, Qiao F, et al. The benefit of targeted and selective inhibition of the alternative complement pathway for modulating autoimmunity and renal disease in MRL/lpr mice. *Arthritis Rheum* 2011;**63**(4):1076–85.
25. Biesecker G, Katz S, Koffler D. Renal localization of the membrane attack complex in systemic lupus erythematosus nephritis. *J Exp Med* 1981;**154**(6):1779–94.
26. Anderson CL. Human IgG Fc receptors. *Clin Immunol Immunopathol* 1989;**53**(2 Pt 2):S63–71.
27. Li X, Ptacek TS, Brown EE, Edberg JC. Fcgamma receptors: structure, function and role as genetic risk factors in SLE. *Genes Immun* 2009;**10**(5):380–9.
28. Rovin BH. The chemokine network in systemic lupus erythematosis nephritis. *Front Biosci* 2007;**13**:904–22.
29. Peterson KS, Huang JF, Zhu J, et al. Characterization of heterogeneity in the molecular pathogenesis of lupus nephritis from transcriptional profiles of laser-captured glomeruli. *J Clin Investig* 2004;**113**(12):1722–33.
30. Chan RW, Lai FM, Li EK, et al. Intrarenal cytokine gene expression in lupus nephritis. *Ann Rheum Dis* 2007;**66**(7):886–92.
31. Malide D, Russo P, Bendayan M. Presence of tumor necrosis factor alpha and interleukin-6 in renal mesangial cells of lupus nephritis patients. *Hum Pathol* 1995;**26**(5):558–64.
32. Herrera-Esparza R, Barbosa-Cisneros O, Villalobos-Hurtado R, Avalos-Diaz E. Renal expression of IL-6 and TNFalpha genes in lupus nephritis. *Lupus* 1998;**7**(3):154–8.
33. Uhm WS, Na K, Song GW, et al. Cytokine balance in kidney tissue from lupus nephritis patients. *Rheumatology* 2003;**42**(8):935–8.
34. Masutani K, Akahoshi M, Tsuruya K, et al. Predominance of Th1 immune response in diffuse proliferative lupus nephritis. *Arthritis Rheum* 2001;**44**(9):2097–106.
35. Crispin JC, Oukka M, Bayliss G, et al. Expanded double negative T cells in patients with systemic lupus erythematosus produce IL-17 and infiltrate the kidneys. *J Immunol* 2008;**181**(12):8761–6.

36. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 2008;**117**(25):e510–26.
37. Perez de Lema G, Maier H, Franz TJ, et al. Chemokine receptor CCR2 deficiency reduces renal disease and prolongs survival in MRL/lpr lupus-prone mice. *J Am Soc Nephrol* 2005;**16**:3592–601.
38. Hasegawa H, Kohno M, Sasaki M, et al. Antagonist of monocyte chemoattractant protein 1 ameliorates the initiation and progression of lupus nephritis and renal vasculitis in MRL/lpr mice. *Arthritis Rheum* 2003;**48**(9):2555–66.
39. Kiberd BA. Interleukin-6 receptor blockage ameliorates murine lupus nephritis. *J Am Soc Nephrol* 1993;**4**(1):58–61.
40. Liang B, Gardner DB, Griswold DE, Bugelski PJ, Song XY. Anti-interleukin-6 monoclonal antibody inhibits autoimmune responses in a murine model of systemic lupus erythematosus. *Immunology* 2006;**119**(3):296–305.
41. Ronnblom L, Alm GV, Eloranta ML. The type I interferon system in the development of lupus. *Semin Immunol* 2011;**23**(2):113–21.
42. Diebold SS, Kaisho T, Hemmi H, Akira S, Reis e Sousa C. Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. *Science* 2004;**303**(5663):1529–31.
43. Hemmi H, Takeuchi O, Kawai T, et al. A Toll-like receptor recognizes bacterial DNA. *Nature* 2000;**408**(6813):740–5.
44. Kaser A, Kaser S, Kaneider NC, Enrich B, Wiedermann CJ, Tilg H. Interleukin-18 attracts plasmacytoid dendritic cells (DC2s) and promotes Th1 induction by DC2s through IL-18 receptor expression. *Blood* 2004;**103**(2):648–55.
45. Tucci M, Quatraro C, Lombardi L, Pellegrino C, Dammacco F, Silvestris F. Glomerular accumulation of plasmacytoid dendritic cells in active lupus nephritis: role of interleukin-18. *Arthritis Rheum* 2008;**58**(1):251–62.
46. Chen DY, Hsieh CW, Chen KS, Chen YM, Lin FJ, Lan JL. Association of interleukin-18 promoter polymorphisms with WHO pathological classes and serum IL-18 levels in Chinese patients with lupus nephritis. *Lupus* 2009;**18**(1):29–37.
47. Gao Y, Majchrzak-Kita B, Fish EN, Gommerman JL. Dynamic accumulation of plasmacytoid dendritic cells in lymph nodes is regulated by interferon-beta. *Blood* 2009;**114**(13):2623–31.
48. Jego G, Palucka AK, Blanck JP, Chalouni C, Pascual V, Banchereau J. Plasmacytoid dendritic cells induce plasma cell differentiation through type I interferon and interleukin 6. *Immunity* 2003;**19**(2):225–34.
49. Gallagher KM, Lauder S, Rees IW, Gallimore AM, Godkin AJ. Type I interferon (IFN alpha) acts directly on human memory CD4+ T cells altering their response to antigen. *J Immunol* 2009; **183**(5):2915–20.
50. Ramos HJ, Davis AM, Cole AG, Schatzle JD, Forman J, Farrar JD. Reciprocal responsiveness to interleukin-12 and interferon-alpha specifies human CD8+ effector versus central memory T-cell fates. *Blood* 2009;**113**(22):5516–25.
51. Baechler EC, Batliwalla FM, Karypis G, et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. *Proc Natl Acad Sci USA* 2003;**100**(5):2610–5.
52. Feng X, Wu H, Grossman JM, et al. Association of increased interferon-inducible gene expression with disease activity and lupus nephritis in patients with systemic lupus erythematosus. *Arthritis Rheum* 2006;**54**(9):2951–62.
53. Taylor KE, Remmers EF, Lee AT, et al. Specificity of the STAT4 genetic association for severe disease manifestations of systemic lupus erythematosus. *PLoS Genet* 2008;**4**(5):e1000084.
54. Sigurdsson S, Nordmark G, Garnier S, et al. A risk haplotype of STAT4 for systemic lupus erythematosus is over-expressed, correlates with anti-dsDNA and shows additive effects with two risk alleles of IRF5. *Hum Mol Genet* 2008;**17**(18):2868–76.
55. Anders HJ, Lichtnekert J, Allam R. Interferon-alpha and -beta in kidney inflammation. *Kidney Int* 2010;**77**(10):848–54.
56. Weidenbusch M, Rommaie C, Schrottie A, Anders HJ. Beyond the LUNAR trial: efficacy of rituximab in refractory lupus nephritis. *Nephrol Dial Transplant* 2013;**28**(1):106–11.
57. Sanz I, Lee FEH. B cells as therapeutic targets in SLE. *Nat Rev Rheumatol* 2010;**6**:326–37.
58. Townsend MJ, Monroe JG, Chan AC. B-cell targeted therapies in human autoimmune diseases: an updated perspective. *Immunol Rev* 2010;**237**:264–83.
59. Tucci M, Lombardi L, Richards HB, Dammacco F, Silvestris F. Overexpression of interleukin-12 and T helper 1 predominance in lupus nephritis. *Clin Exp Immunol* 2008;**154**(2):247–54.
60. Ge D, You Z. Expression of interleukin-17RC protein in normal human tissues. *Int Arch Med* 2008;**1**(1):1–19.
61. Weaver CT, Hatton RD, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu Rev Immunol* 2007;**25**:821–52.
62. Qiu Z, Dillen C, Hu J, et al. Interleukin-17 regulates chemokine and gelatinase B expression in fibroblasts to recruit both neutrophils and monocytes. *Immunobiology* 2009;**214**(9–10):835–42.
63. Bettelli E, Carrier Y, Gao W, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature* 2006;**441**(7090):235–8.
64. Baecher-Allan C, Brown JA, Freeman GJ, Hafler DA. CD4+CD25high regulatory cells in human peripheral blood. *J Immunol* 2001;**167**(3):1245–53.
65. Kuhn A, Beissert S, Krammer PH. CD4(+)CD25 (+) regulatory T cells in human lupus erythematosus. *Arch Dermatol Res* 2009; **301**(1):71–81.
66. Lim HW, Hillsamer P, Banham AH, Kim CH. Cutting edge: direct suppression of B cells by CD4+ CD25+ regulatory T cells. *J Immunol* 2005;**175**(7):4180–3.
67. Iikuni N, Lourenco EV, Hahn BH, La Cava A. Cutting edge: regulatory T cells directly suppress B cells in systemic lupus erythematosus. *J Immunol* 2009;**183**(3):1518–22.
68. Scalapino KJ, Tang Q, Bluestone JA, Bonyhadi ML, Daikh DI. Suppression of disease in New Zealand Black/New Zealand White lupus-prone mice by adoptive transfer of ex vivo expanded regulatory T cells. *J Immunol* 2006;**177**(3):1451–9.
69. Scalapino KJ, Daikh DI. Suppression of glomerulonephritis in NZB/NZW lupus prone mice by adoptive transfer of ex vivo expanded regulatory T cells. *PLoS One* 2009;**4**(6):e6031.
70. Gerli R, Nocentini G, Alunno A, et al. Identification of regulatory T cells in systemic lupus erythematosus. *Autoimmun Rev* 2009;**8**(5): 426–30.
71. Group AT. Treatment of lupus nephritis with abatacept: the abatacept and cyclophosphamide combination efficacy and safety study. *Arthritis Rheum* 2014;**66**(11):3096–104.
72. Rovin BH, Zhang X. Biomarkers for lupus nephritis: the quest continues. *Clin J Am Soc Nephrol* 2009;**4**(11):1858–65.
73. Rovin BH, Birmingham DJ, Nagaraja HN, Yu CY, Hebert LA. Biomarker discovery in human SLE nephritis. *Bull Hosp Joint Dis* 2007;**65**(3):187–93.
74. Markowitz GS, D'Agati VD. The ISN/RPS 2003 classification of lupus nephritis: an assessment at 3 years. *Kidney Int* 2007;**71**(6): 491–5.
75. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004;**15**(2):241–50.
76. Dube GK, Markowitz GS, Radhakrishnan J, Appel GB, D'Agati VD. Minimal change disease in systemic lupus erythematosus. *Clin Nephrol* 2002;**57**(2):120–6.
77. Nasr SH, D'Agati VD, Park HR, et al. Necrotizing and crescentic lupus nephritis with antineutrophil cytoplasmic antibody seropositivity. *Clin J Am Soc Nephrol* 2008;**3**(3):682–90.

78. Gourley MF, Austin 3rd HA, Scott D, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. *Ann Intern Med* 1996;**125**(7):549–57.
79. Illei GG, Austin HA, Crane M, et al. Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis. *Ann Intern Med* 2001;**135**(4): 248–57.
80. Houssiau FA, Vasconcelos C, D'Cruz D, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002;**46**(8):2121–31.
81. Chan TM, Li FK, Tang CS, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. *N Engl J Med* 2000;**343**(16): 1156–62.
82. Chan TM, Tse KC, Tang CSO, Mok M-Y, Li FK. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. *J Am Soc Nephrol* 2005;**16**:1076–84.
83. Ginzler EM, Dooley MA, Aranow C, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005;**353**(21):2219–28.
84. Appel GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009;**20**(5):1103–12.
85. Walsh M, Solomons N, Lisk L, Jayne D. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis with poor kidney function: a subgroup analysis of the Aspreva Lupus Management trial. *Am J Kidney Dis* 2013;**61**(5):710–5.
86. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum* 2012;**64**(4):1215–26.
87. Bao H, Liu ZH, Xie HL, Hu WX, Zhang HT, Li LS. Successful treatment of class V+IV lupus nephritis with multitarget therapy. *J Am Soc Nephrol* 2008;**19**(10):2001–10.
88. Liu Z, Zhang H, Liu Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. *Ann Intern Med* 2015;**162**(1):18–26.
89. Flanc RS, Roberts MA, Strippoli GF, Chadban SJ, Kerr PG, Atkins RC. Treatment of diffuse proliferative lupus nephritis: a meta-analysis of randomized controlled trials. *Am J Kidney Dis* 2004;**43**(2):197–208.
90. Jayne D, Passweg J, Marmont A, et al. Autologous stem cell transplantation for systemic lupus erythematosus. *Lupus* 2004;**13**(3): 168–76.
91. Burt RK, Traynor A, Statkute L, et al. Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. *J Am Med Assoc* 2006;**295**(5):527–35.
92. Boumpas DT, Austin HA, Vaughn EM, et al. Controlled trial of pulse methylprenisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 1992;**340**:741–5.
93. Contreras G, Pardo V, Leclercq B, et al. Sequential therapies for proliferative lupus nephritis. *N Engl J Med* 2004;**350**:971–80.
94. Dooley MA, Jayne D, Ginzler EM, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med* 2011;**365**(20):1886–95.
95. Houssiau FA, D'Cruz D, Sangle S, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. *Ann Rheum Dis* 2010;**69**(12):2083–9.
96. Stoenoiu MS, Aydin S, Tektonidou M, et al. Repeat kidney biopsies fail to detect differences between azathioprine and mycophenolate mofetil maintenance therapy for lupus nephritis: data from the MAINTAIN Nephritis Trial. *Nephrol Dial Transplant* 2012;**27**(5):1924–30.
97. Henderson LK, Masson P, Craig JC, et al. Induction and maintenance treatment of proliferative lupus nephritis: a meta-analysis of randomized controlled trials. *Am J Kidney Dis* 2013;**61**(1): 74–87.
98. Moroni G, Doria A, Mosca M, et al. A randomized pilot trial comparing cyclosporine and azathioprine for maintenance in diffuse lupus nephritis over four years. *Clin J Am Soc Nephrol* 2006;**1**:925–32.
99. Chen W, Liu Q, Tang X, et al. Outcomes of maintenance therapy with tacrolimus versus azathioprine for active lupus nephritis: a multicenter randomized clinical trial. *Lupus* 2012; **21**(9):944–52.
100. Zhang H, Liu Z, Zhou M, et al. Multitarget therapy for maintenance treatment of lupus nephritis. *J Am Soc Nephrol* 2017; **28**(12):3671–8.
101. Austin HA, Klippel JH, Balow JE, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986;**314**:614–9.
102. Houssiau FA, Vasconcelos C, D'Cruz D, et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose versus high-dose intravenous cyclophosphamide. *Ann Rheum Dis* 2010;**69**:61–4.
103. Mok CC, Ho CTK, Siu YP, et al. Treatment of diffuse proliferative lupus glomerulonephritis: a comparison of two cyclophosphamide-containing regimens. *Am J Kidney Dis* 2001; **38**:256–64.
104. Hoffman GS, Cid MC, Rendt-Zagar KE, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. *Ann Intern Med* 2007;**146**(9): 621–30.
105. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl* 2012;**2**:221–32.
106. Moroni G, Gallelli B, Quaglini S, et al. Withdrawal of therapy in patients with proliferative lupus nephritis: long-term follow-up. *Nephrol Dial Transplant* 2006;**21**(6):1541–8.
107. Laskari K, Tzioufas AG, Antoniou A, Moutsopoulos HM. Long-term followup after tapering mycophenolate mofetil during maintenance treatment for proliferative lupus nephritis. *J Rheumatol* 2011;**38**(7):1304–8.
108. Roccatello D, Sciascia S, Rossi D, et al. Intensive short-term treatment with rituximab, cyclophosphamide and methylprednisolone pulses induces remission in severe cases of SLE with nephritis and avoids further immunosuppressive maintenance therapy. *Nephrol Dial Transplant* 2011;**26**(12):3987–92.
109. Moroni G, Maccario M, Banfi G, Quaglini S, Ponticelli C. Treatment of membranous lupus nephritis. *Am J Kidney Dis* 1998; **31**(4):681–6.
110. Radhakrishnan J, Kunis CL, D'Agati V, Appel GB. Cyclosporine treatment of lupus membranous nephropathy. *Clin Nephrol* 1994; **42**(3):147–54.
111. Austin 3rd HA, Illei GG, Braun MJ, Balow JE. Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. *J Am Soc Nephrol* 2009;**20**(4):901–11.
112. Mok CC, Ying KY, Lau CS, et al. Treatment of pure membranous lupus nephropathy with prednisone and azathioprine: an open-label trial. *Am J Kidney Dis* 2004;**43**(2):269–76.
113. Radhakrishnan J, Moutzouris DA, Ginzler EM, Solomons N, Siempos II, Appel GB. Mycophenolate mofetil and intravenous cyclophosphamide are similar as induction therapy for class V lupus nephritis. *Kidney Int* 2010;**77**(2):152–60.

QUESTIONS AND ANSWERS

Question 1

Which statement regarding the pathogenesis of LN is NOT true?

A. Glomerular immune complexes may be due to deposition of preformed circulating immune complexes, or may form *in situ*
B. The classical complement pathway is the likely effector arm for complement-mediated kidney injury in LN
C. Genetic factors influence autoantibody formation and immune complex clearance
D. Cytokines and chemokines that contribute to kidney inflammation in LN may be from infiltrating leukocytes or renal tubular epithelial cells

Answer: B

Work with experimental models of LN suggests that amplification of complement activation through the alternative pathway is involved in kidney injury in LN. Blocking complement activation by knocking out C3 may not attenuate LN, possibly because low-level C3 activation through the classical pathway is important in clearing immune complexes and apoptotic debris. Thus B is not true and is the answer to this question. The origin of glomerular immune complexes is not known, but it has been postulated that they could arise from the circulation or be formed *in vivo*, so A is a true statement. Genetic factors influence both the propensity to form autoantibodies and the ability to clear immune complexes, so C is a true statement. Kidney inflammation is amplified by proinflammatory cytokines from both white blood cells entering the kidney and renal parenchymal cells, so D is a true statement.

Question 2

All of the following biopsy findings are highly characteristic of LN EXCEPT:

A. "Full house" IF pattern (IgG, IgA, IgM, C3, and C1q)
B. Osmiophilic and highly dense intramembranous electron dense deposits on electron microscopy
C. Coexistent mesangial, subendothelial, and subepithelial electron dense deposits on electron microscopy
D. Extraglomerular immune type deposits within tubular basement membranes, the interstitium, and blood vessels
E. TRIs in the glomerular endothelial cell cytoplasm on electron microscopy

Answer: B

The pathology of LN can be quite varied and at times cause confusion with other immune complex-mediated glomerulonephritides. Particular biopsy findings are highly characteristic of LN, however. These include: (1) glomerular deposits that stain dominantly for IgG with codeposits of IgA, IgM, C3, and C1q, the so-called "full house" IF pattern; (2) extraglomerular immune type deposits within tubular basement membranes, the interstitium, and blood vessels; (3) the ultrastructural finding of coexistent mesangial, subendothelial, and subepithelial electron dense deposits; and (4) the ultrastructural finding of TRIs, which represent "interferon footprints" in the glomerular endothelial cell cytoplasm. Highly electron dense intramembranous deposits are the hallmark of dense deposit disease and are not expected to be seen in LN.

Question 3

Limitations of the "EuroLupus" induction phase trial of cyclophosphamide include

A. Prolonged use of steroids in the majority of trial participants
B. Use of oral cyclophosphamide in doses not commonly used in clinical practice
C. Homogenous patient population with poor representation among minority patients
D. Both A and C
E. Both B and C

Answer: D

The trial by the EuroLupus Group compared a standard course of six monthly pulses of intravenous cyclophosphamide ($0.5-1\ g/m^2$) followed by every third monthly infusions vs. a shorter treatment course consisting of 500 mg of intravenous cyclophosphamide every two weeks for six doses (total dose 3 g) followed by azathioprine maintenance therapy (2 mg/kg/day). Both regimens were equally effective when various renal and extrarenal outcomes were evaluated, and the shorter ("EuroLupus") regimen had less toxicity. One of the major limitations of this trial was that it was largely performed in white subjects, and thus the "EuroLupus regimen" may not be applicable to nonwhite populations. In addition, while reports from this trial with up to 10 years of follow-up continue to find no differences in outcome between treatment groups, approximately 75% of these patients remained on some dose of steroids throughout this follow-up period. Thus, the "EuroLupus" regimen may not be applicable in patients placed on steroid-free maintenance regimens.

Question 4

Which ONE of the following statements is NOT TRUE regarding maintenance therapy of proliferative LN?

A. MMF was superior to azathioprine in a clinical trial involving a mixed ethnic population who had achieved complete remission
B. Mycophenolate and azathioprine were similar in a clinical trial in a predominately Caucasian population
C. Intravenous cyclophosphamide given every three months is comparable to azathioprine or mycophenolate
D. Calcineurin inhibitors may be used as maintenance therapy

Answer: C

Several options are available for maintenance therapy. Azathioprine has been shown to be comparable to MMF in two clinical trials (Euro-Lupus MAINTAIN trial), and mycophenolate was superior in the ALMS trial. In the Contreras study, three-monthly cyclophosphamide was inferior to azathioprine or mycophenolate. Of note, the ALMS maintenance trial was different from the Euro-Lupus MAINTAIN trial in that the former study was done in a mixed ethnic population and required that the patients were in remission at the time of enrollment. In patients who are unable to receive azathioprine or mycophenolate, calcineurin inhibitors are an option (although there has not been a head-to-head comparison in a clinical trial).

Question 5

A 27-year-old African American woman was treated with intravenous monthly pulse cyclophosphamide and steroids for biopsy-proven class IV LN. After 5 months her S[Cr] fell from 1.0 mg/dL to 0.7 mg/dL (her preillness baseline), and 24-hour urine protein excretion fell from 3 to 1.2 g. She was put on maintenance MMF after completing 6 months of cyclophosphamide. She has been on maintenance MMF for 6 months and discovers she is pregnant. Her S[Cr] is 0.5 mg/dL, and 24-hour urine shows 650 mg of protein. Her complement levels are slightly low.

What is the best option for her immunosuppressive therapy at this time?

A. Switch her to azathioprine to continue maintenance immunosuppression
B. Continue MMF maintenance but decrease the dose by 25%
C. Repeat a kidney biopsy
D. Discontinue all immunosuppression immediately

Answer: A

Of the choices listed the best option is A. The patient has done well and appears to be moving toward a complete clinical renal remission. She has not achieved complete remission yet however, and it would be unwise to stop maintenance immunosuppression, especially in light of the unexpected pregnancy. Thus D can be eliminated. MMF is contraindicated during pregnancy, eliminating B, but azathioprine and/or steroids can be used. Because the patient had fairly recent class IV LN with renal impairment, it is preferable to use azathioprine rather than steroids alone for maintenance. There is no indication for a repeat biopsy in this patient. She does not appear to have a lupus flare, and the ongoing kidney abnormalities are consistent with class IV that is responding to treatment and getting better. Thus C can be eliminated.

Question 6

A 24-year-old African American woman with systemic lupus for 2 years on maintenance hydoxychloroquine is referred with edema, 3+ proteinuria, and 4–5 RBC/HPF on urine exam. Her physical examination is notable for 2+ lower extremity edema and is otherwise normal. Her blood pressure is normal. S[Cr] is 0.7 mg/dL, S[Alb] is 2.8 g/L, and 24-hour urine protein excretion is 7 g. A renal biopsy shows thickened basement membranes on LM and mild mesangial proliferation without endocapillary proliferation. IF microscopy shows granular deposits in the mesangial and subepithelial areas (IgG, IgM, IgA, C3 and C1q), which were confirmed by electron microscopy. She was started on an angiotensin-converting enzyme inhibitor and diuretics. Which ONE of the following is the most appropriate next step in treating this patient?

A. Continue conservative therapy for 3 months and reevaluate
B. Start monthly pulse cyclophosphamide with steroids
C. Start prednisone at 1 mg/kg/day
D. Start MMF 1000 mg twice daily and increase to 1500 mg/day as tolerated, with steroids
E. Start cyclosporine 3 mg/kg/day in divided doses

Answer: D

This patient has pure class V (membranous) LN. She has a relatively high risk for progression, given her race, unremitting proteinuria, and worsening kidney function. Conservative therapy is probably not recommended given these risk factors (especially worsening renal function). Although any of the Choices B to D may be employed, we prefer Answer D—mycophenolate—at this point. Cyclophosphamide and cyclosporine were superior to steroid monotherapy in

a small randomized controlled trial, and mycophenolate was equivalent to cyclophosphamide in a meta-analysis. In this patient of childbearing age, we prefer not to use cyclophosphamide as initial therapy. The choice between mycophenolate and cyclosporine is difficult in the absence of clinical trial data; we favor mycophenolate over cyclosporine, because the latter is associated with nephrotoxicity. In the event of failure with mycophenolate in this high-risk patient, cyclophosphamide may be used. Azathioprine with steroids has also been used and may be a cheaper option compared to mycophenolate. Other therapies such as rituximab and ACTH are under investigation.

CHAPTER

50

Sickle Cell Disease

Phuong-Thu T. Pham[a], *Phuong-Chi T. Pham*[b], *Susie Q. Lew*[c]

[a]Department of Medicine, Nephrology Division, David Geffen School of Medicine at UCLA, Kidney Transplant Program, Los Angeles, CA, United States; [b]Department of Medicine, Nephrology and Hypertension Division, David Geffen School of Medicine at UCLA, UCLA-Olive View Medical Center, Sylmar, CA, United States; [c]Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States

Abstract

Hemolysis, vaso-occlusion, and ischemia reperfusion represent the clinical hallmarks of sickle cell disease (SCD). Renal involvement occurs commonly in SCD. Its manifestations range from the near universal findings of hyposthenuria to various tubular and glomerular functional and anatomical abnormalities—commonly referred to as sickle cell nephropathy. With increasing longevity of SCD patients, overt chronic kidney disease (CKD) and end-stage renal disease have increasingly been observed. Possible risk factors or genetic modifiers are associated with the development and/or progression of CKD. Preventive measures and therapeutic options have been developed.

INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive hemoglobin disorder arising from the substitution of valine for glutamine at the sixth amino acid of the β-globin chain.[1] The mutation results in a poorly soluble hemoglobin tetramer, thereby enhancing its aggregation during cellular or tissue hypoxia, dehydration, or oxidative stress. Such aggregation may reduce the pliability of erythrocytes resulting in the sickling deformity, premature destruction of erythrocytes, and widespread vaso-occlusive episodes, potentially leading to acute or chronic organ damage.[1] Various kidney complications have been suggested to be a consequence of chronic sickling and hemolysis. "Increased urine volume of low specific gravity" or isosthenuria, described more than a century ago, was the first recognized renal abnormality associated with SCD.[2] Sickle cell nephropathy (SCN) encompasses a wide range of both tubular and glomerular functional and anatomical abnormalities. With the increasing longevity of SCD patients, progressive CKD leading to end-stage renal disease (ESRD) has increasingly been observed. Early detection of SCN and appropriate intervention may improve morbidity and mortality.

The various renal syndromes associated with SCD, histopathologic findings, potential pathophysiologic mechanisms, and suggested therapeutic interventions are discussed.

RENAL SYNDROMES ASSOCIATED WITH SICKLE CELL DISEASE

Patients with SCD present with a broad spectrum of renal abnormalities (Table 50.1). Well-described renal manifestations include hematuria, defective urinary concentrating ability, impaired renal acidification and potassium secretion leading to an incomplete form of distal renal tubular acidosis, and supranormal proximal tubular function. An increase in renal blood flow and glomerular filtration rate (GFR) frequently becomes apparent in infancy or early childhood but decreases with age. Progressive decline in GFR associated with increasing proteinuria may lead to glomerular injury and overt CKD or ESRD. Acute kidney injury (AKI) may occur in the presence of precipitating factors. The renal manifestations of SCD are generally less common or less severe in patients with sickle cell trait, with the exception of renal medullary carcinoma, which occurs almost exclusively in patients with sickle cell trait.

Hematuria

First described in 1948, patients with either sickle cell trait or disease commonly present with hematuria.[3]

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00050-4

TABLE 50.1 Renal Manifestations of Sickle Cell Disease

Abnormalities	Comments
Hematuria	10% bilateral, left four times more than right due to increased venous pressure in the left renal vein
Renal Tubular Disorders	
1. Proximal tubular function • Increased sodium reabsorption • Increased phosphate reabsorption • Increased β2-microglobulin reabsorption • Increased uric acid secretion • Increased creatinine secretion • Decreased tubular albumin reabsorption (see text) **2.** Distal tubular function • Decreased concentrating ability (hyposthenuria) • Incomplete form of RTA • Impaired potassium secretion (intact renin-aldosterone system)	• Creatinine-based eGFR may be greatly overestimated • Tubular albuminuria may further contribute to proteinuria and SCN • Urinary diluting capacity remains preserved (see text) • RTA typically not clinically apparent but can be unmasked in the setting of mild decrement in GFR • Defect in potassium secretion typically not clinically apparent but hyperkalemia can manifest in the presence of additional insults (e.g. acute or chronic kidney injury, rhabdomyolysis, volume depletion)
Renal hemodynamics	Pathophysiology of hyperfiltration
Glomerular hyperfiltration leading to microalbuminuria, proteinuria	**1.** Viscocity−vaso-occlusion phenotype **2.** Hemolysis−endothelial dysfunction phenotype **3.** Kinin−Kallikrein system (further studies are needed)
AKI	Risk factors: sepsis, heart failure, volume depletion, acute chest syndrome, pulmonary hypertension, decrease in hemoglobin counts, NSAIDs, tubular obstruction from debris from papillary necrosis
CKD and ESRD	Prevalence increases with age ESRD therapeutic options: hemodialysis, peritoneal dialysis, kidney transplantation
Pathologic findings	See Table 50.2

Abbreviations: *AKI*, acute kidney injury; *CKD*, chronic kidney disease; *eGFR*, estimated glomerular filtration rate; *ESRD*, end-stage renal disease; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *RTA*, renal tubular acidosis; *SCN*, sickle cell nephropathy.

Patients with microscopic or macroscopic hematuria describe it as painless and self-limiting. Hematuria frequently originates from the left kidney, presumably due to the increased venous pressure within the longer left vein when compressed between the aorta and the superior mesenteric artery, the so-called "nutcracker phenomenon." The increased venous pressure leads to increased relative hypoxia in the renal medulla, hence sickling. Bilateral hematuria occurs in approximately 10% of cases. Patients with sickle cell trait have more hematuria than those with homozygous HbSS regardless of age.[4] The presence of flank or abdominal pain, or continued or persistent macroscopic hematuria with or without clots should prompt further evaluation with both cystoscopy and ureteroscopy to exclude renal medullary cancer and other common causes of hematuria, including kidney stones.

Defective Concentrating Ability

SCD patients universally present at an early age with hyposthenuria or impairment in urinary concentrating ability. The higher than usual obligatory urine output associated with hyposthenuria predisposes SCD patients to increased risk of dehydration and/or volume depletion. In children with SCD, the concentrating defect can present as enuresis or nocturia. The prevalence of enuresis in children with SCD ranges from 20% to 69%, while that of nocturia can reach 68%.[5] In young children, maximal urine osmolality can be increased by multiple blood transfusions. However, with repeated sludging of red blood cells (RBCs) causing thrombosis, progressive infarction, and necrosis of the papilla and inner medulla, the capacity to improve renal concentrating ability with blood transfusions progressively declines with age. The defect becomes generally irreversible after the age of 15 years. Adult patients with SCD can achieve maximal urinary osmolality of 400−450 mOsm/Kg under water-deprived conditions. Heterozygotes tend to have more gradual and lesser degrees of impairment. SCD patients dilute urine normally because the diluting segments of the nephron are less affected by sickled RBCs.

Renal Tubular Acidosis

In addition to defects in urinary concentrating ability, other renal functions primarily accomplished in the renal medulla, including renal acidification and potassium secretion, are also impaired in SCD patients. An incomplete form of distal renal tubular acidosis (RTA) results from defective renal acidification. Hydrogen ion excretion depends on the ability of distal nephron cells to maintain an adequate hydrogen ion excretion gradient between their basolateral and luminal membranes, an energy- and oxygen-dependent process. Furthermore, a blunted increase in urinary excretion of titratable acid in SCD patients compared with control subjects was demonstrated.[6–8] Ammonium excretion may be normal or decreased in patients with SCD.[6–8] As a result, SCD patients fail to lower their urine pH below 5.3 following ammonium chloride loading.[6,7] The suboptimal acid handling in SCD patients does not appear clinically under normal conditions but can be unmasked in the setting of mild renal insufficiency as hyperchloremic metabolic acidosis.[9] This defect was not seen in patients with sickle cell trait.[10]

SCD patients do not demonstrate hyperkalemia unless renal functional impairment or stress, such as during volume contraction, occurs during a sickle cell crisis. Like the urinary acidification defect, the defect in potassium secretion does not appear clinically under normal conditions. An intact renin angiotensin aldosterone system axis exists, suggesting the presence of a primary defect in renal potassium secretion, presumably due to ischemic damage to the potassium secreting segment of the distal nephron.[6] Nonetheless, selective aldosterone deficiency and hyporeninemic hypoaldosteronism have been described in patients with SCD.[9,11] Despite impaired potassium secretion, the serum potassium concentration (S[K]) does not increase during potassium loading in patients with SCD, suggesting an increased intracellular shift of potassium, likely *via* β-2 adrenergic stimulation.[12]

Proximal Tubular Function Disorders

SCD patients exhibit increased reabsorptive capacity of the proximal tubule. There is increased reabsorption of solutes such as β_2-microglobulin and phosphate, evidenced by the frequent development of hyperphosphatemia in SCD patients.[12] Since sodium reabsorption in the proximal tubule parallels phosphate reabsorption, an increase in phosphate reabsorption results in increased sodium reabsorption. Increased tubular secretion of uric acid and creatinine by the proximal tubules in SCD patients markedly increases urinary excretion of these substances.[12] Up to 30% of the total urinary creatinine excretion results from tubular secretion in SCD patients.[13] Consequently, serum creatinine concentration (S[Cr]) may be misleadingly low in SCD patients. Assessment of renal function using creatinine-based equations may therefore lead to an overestimation of GFR.[13] Limited studies in SCD patients suggest that GFR estimates using cystatin C (CystC) provide better prediction of renal function than creatinine-based estimated glomerular filtration rate (eGFR).

In contrast to the increased reabsorptive capacity of β_2-microglobulin and phosphate, reduced tubular uptake of albumin has been observed. Recent *in vitro* studies demonstrated that filtered hemoglobin released during hemolytic crisis competes with albumin binding to megalin/cubilin receptors in the proximal tubule and impairs albumin reabsorption. The latter leads to tubular proteinuria independent of glomerular injury, further contributing to albuminuria and SCN.[14]

Glomerular Function Disorders: Hyperfiltration and Microalbuminuria

In patients with SCD, an increase in renal blood flow and GFR frequently becomes apparent 1 year after birth. Renal blood flow and GFR decrease with age. Glomerular changes begin as early as the first decade of life and are characterized by high renal blood flow, glomerular hyperfiltration and hypertrophy, gradual loss of permselectivity leading to microalbuminuria and macroalbuminuria, and a decrease in ultrafiltration coefficient.[15–18] The decrease in ultrafiltration coefficient has been found to be associated with renal insufficiency. In addition, the ultrafiltration coefficient correlates inversely with glomerular permselectivity as assessed by the fractional clearances of albumin and IgG. SCD patients with albuminuria and preserved GFR have reduced glomerular ultrafiltration coefficient compared with normoalbuminuric control SCD subjects. Among those with depressed GFR, a severe reduction in glomerular ultrafiltration coefficient was observed, suggesting that albuminuria represents a sensitive marker of early glomerular damage.[18] The incidence of albuminuria increases over time in patients with SCD and often precedes the elevation of S[Cr].[19,20] In one single-center study of 184 adult patients with HbSS disease, albuminuria occurred in 61% of patients aged 18–30 years. Between the third and fifth decades of life, the percentage of SCD patients with macroalbuminuria doubled. Microalbuminuria was found in up to 79% of patients older than 40 years of age.[20] Albuminuria correlated with age and S[Cr], but not with blood pressure or hemoglobin levels, suggesting that sickle cell glomerulopathy does not solely relate to hemodynamic adaptations associated with chronic anemia. Nonetheless, studies in children with

SCD showed a significant association between markers of hemolysis (low hemoglobin and high lactate dehydrogenase [LDH] levels) and proteinuria.[21]

Acute and Chronic Kidney Injury

AKI associated with vaso-occlusive episodes occurs in 4%–16% of patients. In one retrospective study, 16.2% of admissions for vaso-occlusive painful crisis were associated with AKI (32/197). A larger decrease in hemoglobin from baseline to admission and the total number of days and doses of ketorolac were found to be associated with AKI. For every one-unit decrease in hemoglobin concentration, the risk of AKI increased by 49% (OR = 1.49, 95% CI 1.1–2.0). It was speculated that in the setting of a vaso-occlusive pain crisis, a larger decrease in hemoglobin increases AKI risk *via* an acute, direct toxic effect of plasma-free heme or hemoglobin.[22] In another series of 254 vaso-occlusive episodes in 161 SCD patients, AKI associated with vaso-occlusive episodes occurred in 4.3% of patients.[23] Suggested predisposing risk factors include severe volume depletion, acute chest syndrome, heart failure, sepsis, pulmonary hypertension, decrease in hemoglobin counts, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs). In a population-based study involving SCD patients in California, more than 4% of emergency department visits were due to "dehydration."[24] Whether a single or repeated episodes of AKI predispose SCD patients to the development of CKD and/or CKD progression remains unknown and warrants further studies.

The incidence of CKD in patients with SCD increases with age, similar to albuminuria.[19,20] In a cohort of 98 SCD patients aged 18 years and older, baseline CKD was observed in 28.6% of patients (CKD stages and albuminuria grades were defined according to the 2012 KDIGO guidelines). In patients with eGFR >60 mL/min/1.73 m^2, CKD was diagnosed if grade A2 or A3 albuminuria was present. At a mean follow-up of 5 years, the overall CKD prevalence increased to 41.8% (17 patients developed new CKD). During the study period, CKD progression occurred in eight patients. Multivariate analysis demonstrated that baseline A3 albuminuria (odds ratio, 5.0, $p = 0.048$) and each 1 mm Hg increase in systolic BP (odds ratio, 1.04, $p = 0.039$) predicted CKD development and progression.[25] In a longitudinal cohort study of adult patients with SCD, 44% of individuals between the age of 40 and 60 years had a greater than 50% increase in S[Cr]. CKD was the major cause of death in 43% among those who died over the age of 60 years.[26]

The diagnosis of CKD among SCD patients generally occurs between 30 and 40 years of age, with ESRD developing in approximately 11% of patients. The incidence of CKD among SCD patients varies widely among different parts of the world, with a reported incidence of 2.6% in Senegal, 4.3% in Brazil, 5.9% in Cuba, 11.6% in the US, and 22.5% in Saudi Arabia.[27,28] The discrepancy in incidence rate may be explained by the differences in the definition of CKD, the duration of follow-up, the age of the population studied, hospital vs. clinic settings, and genetic factors or genetic modifiers, among others. Whether CystC-based eGFR may reveal a higher prevalence of CKD compared to creatinine-based GFR estimations among SCD patients remains to be studied. Of interest, SCD patients in the eastern region of Saudi Arabia have less severe disease compared with those in the western region. It is speculated that the presence of Arab Indian beta-globin haplotype among patients in the eastern region results in a much higher HbF level, and hence less severe disease compared with their western counterparts (who commonly have the Benin haplotype). Of 942 patients with SCD who were followed at two large centers in eastern Saudi Arabia between 2003 and 2016, only 11 patients (1.17%) developed ESRD requiring renal replacement therapy.[29]

Suggested factors associated with progression of CKD to ESRD include hypertension, nephrotic range proteinuria, severe anemia, vaso-occlusive crisis, acute chest syndrome, stroke, βS-gene haplotype, pulmonary hypertension, the presence of certain genetic variants (discussed in a later section), and parvovirus B19 infection.[30,31] Studies in older children and adolescents (aged 10–21 years) with SCD demonstrated that nocturnal hypertension and hyperuricemia (uric acid >5.5 mg/dL) were associated with lower eGFR. The mean CystC-based eGFR was 143 mL/min/1.73 m^2 among patients with hyperuricemia vs. 161 mL/min/1.73 m^2 among those with normal uric acid levels ($p = 0.02$). Whether interventions to lower serum uric acid (S[UA]) levels reduce CKD risk or modify disease progression in patients with SCD warrant further studies.[32]

Biomarkers for Early Detection of SCN

CystC elimination occurs exclusively by glomerular filtration and has been suggested to be a more accurate marker of CKD in both children and adults with SCD. In a series of 98 subjects with homozygous SS genotype (55 females; 43 males; mean age 34 ± 2.3 years), a strong association between CystC and GFR and albuminuria was demonstrated. The CystC-based CKD-EPI equation showed the greatest agreement with measured GFR using ^{99m}Tc-DTPA nuclear renal scans compared with other commonly used CystC-based or creatinine-based Modification of Diet in Renal Disease (MDRD) or Chronic

Kidney Disease Epidemiology (CKD-EPI) equations.[33] A smaller study consisting of 14 SCD patients with 33 eGFR measurements similarly demonstrated that the CystC-based CKD-EPI equation best correlated with measured GFR using iohexol renal scans compared with other CystC-based or creatinine-based equations. The latter included the Cockcroft-Gault formula, the MDRD, CKD-EPI Cr, and CKD-EPI Cr-CystC equations. Of note, however, patients with eGFR <60 mL/min/1.73 m^2 were excluded from the study, and all study subjects were on hydroxyurea and losartan therapy for persistent albuminuria. Hence, the study findings may not be generalizable to SCD patients without albuminuria, those not on hydroxyurea and/or angiotensin receptor blocker (ARB) therapy, or those with eGFR <60 mL/min/1.73 m^2.[34] Whether CystC-based equations may enable clinicians to more accurately assess renal function in the SCD population warrants further studies. It should be noted that CystC levels may be increased in high cell turnover states, such as hyperthyroidism, steroid use, malignancy, advanced age, gender and ethnicity, fat mass, and diabetes, among others.

Nephrin, a slit diaphragm protein necessary for the proper function of the glomerular filtration barrier, has long been suggested to be a useful marker of glomerular-specific renal damage in animal studies. In a mouse model of proteinuric renal disease, nephrinuria was observed prior to the development of albuminuria. Recent studies in children with SCD demonstrated an association between urinary nephrin:creatinine ratio (NCR) and albuminuria. In a series of 101 children with SCD, higher urinary NCR was found to be significantly associated with albuminuria. A NCR cut-point of 622 ng/mg (representing the 50th percentile for the population) was associated with a nearly 46 times greater odds of having albuminuria in children with nephrinuria above this value. Such NCR cut-point had a 96% sensitivity, 64% specificity, 47% positive predictive value, and 98% negative predictive value for the presence of albuminuria. The study findings suggest that urinary nephrin could be used as an early marker of glomerular disease in SCD.[35] Other suggested potential useful biomarkers of renal damage in SCD include urinary kidney injury molecule 1 (KIM-1) and N-acetyl-b-glucosaminidase (NAG). In a cross-sectional analysis for nephropathy in 116 patients with SCD, KIM-1 and NAG were found to be strongly associated with albuminuria. In contrast to acute or chronic kidney injury in other renal diseases, liver-type fatty acid binding protein (L-FABP), NAG, neutrophil gelatinase-associated lipocalin, and transforming growth factor-β1 (TGF-β) were not associated with albuminuria in patients with SCD.[36]

RENAL PATHOPHYSIOLOGIC MECHANISMS

Hematuria

Low oxygen tension, low pH, and high osmolality of the renal medullary environment predispose RBCs in the vasa recta to sickle and cause increased blood viscosity, microthrombus formation, and ischemic necrosis.[16] The latter can cause structural changes leading to RBC extravasation and hematuria. In kidneys from SCD patients removed due to protracted hematuria, severe stasis in peritubular capillaries, most marked in the medulla, and extravasation of blood, predominantly in the collecting tubules, are seen.[37] Severe medullary ischemia can cause papillary necrosis and infarction that manifests clinically as painless gross hematuria. Occasionally, sloughed papillae may obstruct urinary outflow leading to AKI and urinary tract infection.

Concentrating Defect

RBC sickling and congestion in the vasa recta leads to ischemia and associated impairment of solute reabsorption by the ascending limb of Henle's loop and the vasa recta with consequent loss of the countercurrent multiplication and exchange system of the inner medulla. The suboptimal maintenance of the high interstitial osmolality in the inner medulla reduces effective water reabsorption across the collecting tubules, resulting in reduced kidney concentrating ability. Since vasopressin synthesis and its release occur normally in SCD, the concentrating defect is not vasopressin-dependent. In contrast to the concentrating defect, the diluting capacity remains relatively preserved in patients with SCD. Urinary dilution is in part dependent on the function of water impermeable thick ascending limb of Henle's loop where active sodium chloride reabsorption occurs *via* the Na-K-2Cl cotransporter. Because the superficial cortical nephrons have short loops and peritubular capillaries of these nephrons have less vaso-occlusion than in the vaso recta found in the inner medullary regions, the diluting capacity of the kidney remains relatively intact.

Glomerular Hyperfiltration and Albuminuria

Two models have been proposed to explain the pathophysiology of glomerular hyperfiltration/albuminuria observed in SCD patients—the viscosity-associated vaso-occlusion, and the hemolysis-associated endothelial dysfunction phenotypes.

Viscosity–Vaso-Occlusion Phenotype

The inner medulla's relatively hypoxic, hypertonic, and acidotic environment predisposes to sickling of RBCs. Repeated sickling of RBCs significantly decreases medullary blood flow through vaso-occlusion. Increased GFR and renal plasma flow (RPF) have been attributed to compensatory hypersecretion of vasodilator prostaglandins and an increase in nitric oxide synthase (NOS) in response to sickling-related medullary hypoxia and ischemia. The administration of indomethacin produces significant decreases in GFR and RPF in SCD patients, but not in control subjects.[38,39] In experimental models of SCN, inducible NO synthase II (iNOS II) increases in the glomeruli and distal nephron of transgenic sickle cell mice, but not in control mice. Furthermore, urinary excretion of the products of NO (NO_2S+NO_3) and GFR increase significantly in a transgenic sickle cell murine model compared with controls.[40] NOS II may increase the synthesis of NO leading to vasodilation, which, in turn, contributes to renal hyperperfusion. The exposure of transgenic sickle cell mice to chronic hypoxia results in the activation of iNOS II, and formation of superoxide radical and peroxynitrite ($ONOO^-$).[41] These reactions may lead to nitration of tyrosine residues of some renal proteins and enhanced apoptosis, ultimately causing structural damage.

Hemolysis–Endothelial Dysfunction Phenotype

In a cross-sectional study of 280 adult homozygous SS patients, markers of intravascular hemolysis (including lower hemoglobin levels, lower hemoglobin F levels, and higher reticulocyte count) were found to be independent risk factors for glomerular hyperfiltration among nonalbuminuric patients. Albuminuric patients were excluded from the study to minimize introduction of another variable. In contrast, the prevalence of typical vaso-occlusive complications such as retinopathy, osteonecrosis, priapism, pulmonary hypertension, and leg ulcerations were not significantly different between the groups with and without hyperfiltration.[42] In another study designed to search for novel markers of hemolysis among patients with SCD and to look for the relationship of such markers with complications linked to the hemolytic process, hemolysis was found to correlate with albuminuria. The ratio between mature RBCs and reticulocyte (RET) hemoglobin (RBC-Hb/RET-Hb) was associated with RBC survival. The log (RBC-Hb/RET-Hb) describes hemolysis better than LDH and total bilirubin. Furthermore, the log (RBC-Hb/RET-Hb) in combination with LDH correlated highly with albuminuria.[43]

Although hemolysis-induced hyperfiltration seems paradoxical because hemolysis commonly induces a vasoconstrictive state secondary to decreased NO bioavailability due to NO scavenging by HbSS, hemolysis can also induce regional or systemic vasodilation due to the unstable nature of HbSS.[44] Such instability leads to the release of heme and the induction of heme oxygenase-1 (HO-1). HO-1 degrades heme to carbon monoxide (CO), which has vasodilatory and antioxidant properties, promoting hyperfiltration:

$$\text{Heme} + O_2 + \text{HO-1} \rightarrow \text{Biliverdin} + Fe^{2+} + \text{CO}$$

Although the cytotoxic properties of heme may cause glomerular injury and proteinuria, its adverse effect can be mitigated by HO-1.

Soluble fms-like tyrosine kinase-1 (sFLT-1), a member of the vascular endothelial growth factor family, was found to be elevated in SCD patients with albuminuria. In a cohort of 73 patients with SCD and 21 healthy, race-matched control subjects, sFLT-1 levels were significantly higher in patients with macroalbuminuria, compared to those with microalbuminuria and normoalbuminuria (120.1 pg/mL vs. 99.7 pg/mL vs. 85.4 pg/mL, respectively; $p = 0.016$). Such association suggests that sFLT-1 may contribute to the development of albuminuria in SCD by inducing endothelial activation and endothelial dysfunction.[45] Another marker of endothelial dysfunction, endothelin-1 (ET-1), was also found to be elevated in SCD subjects with albuminuria.[46] In a mouse model of SCD (HbSS), ET-1 was shown to mediate glomerular injury *via* increased reactive oxygen species (ROS) production. ET-1 and ET_A receptor mRNA were elevated in renal tissue from mice with sickle cell compared with mice heterozygous for sickle cell and Hb A (HbAS controls). Furthermore, sickle mice exhibited enhanced ET_A receptor binding in the renal vasculature. Because oxidative stress is well established in SCD, it is speculated that ET-1 contributes to oxidative stress and glomerular injury in this model. *In vivo* and *in vitro* treatment with ET_A receptor antagonist decreased glomerular ROS production, proteinuria, and nephrinuria.[47]

Whether the viscosity-associated vaso-occlusion or hemolysis-associated endothelial dysfunction phenotype plays a contributory or predominant role in hyperfiltration in SCD in humans remains to be studied. However, it seems plausible that SCN is characterized by both hemolysis and vaso-occlusive processes to variable degrees (Figure 50.1).

The Kinin–Kallikrein System and Hyperfiltration

The kinin–kallikrein system has been suggested to play a contributory role in the hyperfiltration seen in SCD patients, similar to diabetic subjects.[48] High serum

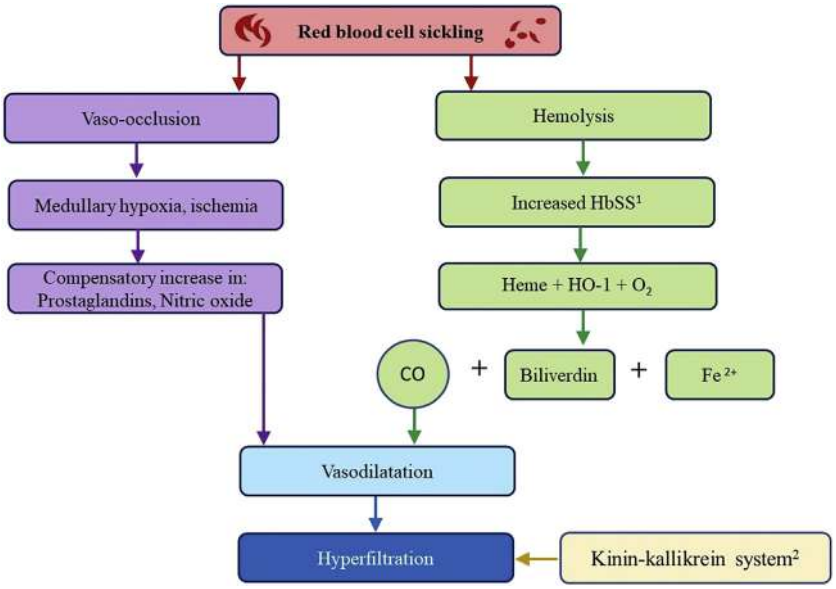


FIGURE 50.1 Suggested pathophysiological scheme for the development of hyperfiltration. [1]HbSS is an unstable structure that leads to increased release of heme and induction of heme oxygenase-1 (HO-1). HO-1 degrades heme to CO + biliverdin + Fe^{2+}. [2]Further studies are needed. *CO*, carbon monoxide; *HbSS*, hemoglobin SS; *HO-1*, Heme oxygenase-1; O_2, Oxygen.

kallikrein concentration appears in diabetic patients and streptozocin-induced diabetic rats with hyperfiltration. Chronic inhibition of renal kallikrein reduces GFR and RPF in streptozocin-induced diabetic rats.[48] In a cross-sectional study conducted to evaluate the role of renal kallikrein as a risk marker for SCN in 73 pediatric patients with SCD, urinary active kallikrein excretion correlated positively and significantly with log urinary albumin excretion rate. In this case, kallikrein, such as albumin, may be a marker of nephropathy.[49] The study had several shortcomings, including the absence of renal function measurements (eGFR or creatinine clearance) and patients with confounding factors (frequent blood transfusions reducing sickled hemoglobin load affecting renal functional impairment expected for age).[50] In children with SCD, early blood transfusion protects against microalbuminuria.[51] Whether the kinin–kallikrein system plays a contributory role in the hyperfiltration process in SCN remains to be studied.

Albuminuria and Progressive CKD

Similar to diabetic and other kidney diseases, glomerular hyperfiltration in patients with SCD can lead to microalbuminuria, proteinuria, glomerulosclerosis, and progressive CKD. Furthermore, the increased filtered sodium load and tubular reabsorption of sodium associated with hyperfiltration can augment renal oxygen consumption. Such hypermetabolic states can promote tubulointerstitial injury, in part through oxidative stress. Renovascular pathology related to chronic NO depletion from ongoing intravascular hemolysis has also been suggested to play a role in the progression of SCN. Chronic NOS inhibition caused systemic and glomerular hypertension, glomerular ischemia, glomerulosclerosis, tubulointerstitial injury, and proteinuria in experimental animal models.[52] Studies in the general population without SCD similarly suggest that CKD-induced NO deficiency contributes to the progression of chronic kidney injury.[53]

Ischemic Model of Chronic SCN

In a murine model of bilateral total renal artery occlusion-induced ischemia, transgenic sickle cell mice but not wild-type mice exhibited glomerulopathic changes including endothelialitis and mesangiolysis. The latter changes, along with the accompanying reparative responses may lead to a chronic glomerulopathy, particularly if repetitively incurred through recurrent cycles of renal ischemia.[54] Vascular congestion in wild-type mice after ischemia was mild and confined to the peritubular capillaries. In contrast, sickle cell mice exhibited massive congestion in the microcirculation involving the medullary and cortical capillaries as well as the glomerular microcirculation. Notably, the marked glomerular congestion and cortical infarction recapitulate the appearance of the glomerulus and cortical infarction observed in SCD patients with AKI. Compared with wild-type mice, sickle cell mice also demonstrated markedly increased amyloid-P component (the murine homologue of C-reactive protein).

TABLE 50.2 Pathologic Findings in Sickle Cell Anemia

Abnormalities	Comments
Papillary necrosis	Usually asymptomatic
Renal cortical infarct	Infarcted area usually small and kidney function generally not affected
Hemosiderin deposits	No correlation between the amount of these deposits and the presence of kidney disease
Glomerular enlargement and congestion	Most marked in juxtamedullary glomeruli
Glomerular lesions	
❖ FSGS: most common glomerular lesion in SCD, closely associated with glomerular hypertrophy ❖ MPGN: commonly occurs without immune-complex deposits ❖ MPGN type 1: uncertain whether cases were attributable to SCD ❖ SCD glomerulopathy: Defined as glomerular hypertrophy with or without mesangial hypercellularity ❖ TMA: associated with history of retinitis	
Tubular atrophy, interstitial fibrosis	
Medullary carcinoma (seen almost exclusively in patients with the sickle cell trait)	

Abbreviations: *FSGS*, focal segmental glomerulosclerosis; *MPGN*, membranoproliferative glomerulonephritis; *SCD*, sickle cell disease; *TMA*, thrombotic microangiopathy.

In the peritubular microcirculation, repeated episodes of marked congestion can lead to peritubular capillary loss, chronic hypoxia, and events that culminate in chronic SCN. Tubulointerstitial scarring may develop as a result of ischemia-induced upregulation of matrix-related genes (such as TGF-β and monocyte chemoattractant protein-1 [MCP-1], and extracellular matrix proteins). It is conceivable that the heightened vascular, glomerular, and tubulointerstitial injuries in sickle cell mice subjected to ischemia act to accentuate the development of SCN.[54]

RENAL MEDULLARY CELL CARCINOMA

Chronic ischemic injuries triggering recurrent degeneration and regeneration of the epithelium of the distal collecting ducts may incite formation of renal medullary cancer, an aggressive tumor specific to patients with sickle hemoglobinopathies.[5,55] Renal medullary cancer, seen almost exclusively in patients with sickle cell trait, occurs at a relatively young age, averaging 21 years.[5,55] Patients may present with gross hematuria, flank pain, and infrequently with an abdominal mass or weight loss. Therefore renal medullary cancer must be differentiated from a renal tubular abnormality associated with abnormal hemoglobinemia. Metastatic disease present at diagnosis portends a poor prognosis.

RENAL ANATOMIC AND PATHOLOGIC FINDINGS ASSOCIATED WITH SICKLE CELL DISEASE

Several major anatomic and pathologic (morphologic) changes of the kidneys occur in SCD patients (Table 50.2). The distinctive abnormalities of the renal medulla and papillae in patients with SCN result from occlusion of blood flow in the vasa recta, which may lead to medullary and papillary necrosis and fibrosis. Renal papillary necrosis (RPN) appears as a common complication of SCD with a reported incidence of 15% −50% in patients with SCD or sickle cell trait.[5] RPN generally presents as a clinically silent and slowly progressive process because of recurrent, subacute sickling in the renal medulla. Renal radiography detects RPN as an incidental finding in asymptomatic patients or during the evaluation of hematuria. Renal cortical infarctions with subsequent renal cortical scarring may develop. The infarction usually affects a small area, and renal function generally remains intact.

Prominent glomeruli distended with blood, as well as necrosis and pigmentation of tubular cells, were first described in SCD in 1923.[56] Subsequently, other pathologic lesions involving both tubular and glomerular lesions were reported. These include glomerular enlargement and congestion (most marked in the juxtamedullary glomeruli), focal scarring in the renal medulla, interstitial fibrosis, tubular atrophy, infiltration with lymphoid cells, and various glomerular

histopathologies. Tubular hemosiderin deposits appear as a universal finding in patients with SCD.[13]

Structural glomerular abnormalities exist in patients with SCD but usually not in heterozygotes. Over the years, a wide spectrum of glomerular lesions has been described in SCD patients. The most frequently identified morphologic lesion associated with SCD is focal segmental glomerulosclerosis (FSGS), which is closely associated with glomerular hypertrophy.[19] Both collapsing and expansive patterns of FSGS have been described in SCD patients.[57,58] Glomerular hypertrophy was found to be greater in HbSS patients than in idiopathic FSGS. Glomerular size did not differ between patients with and without clinical evidence of SCN. Medullary fibrosis was prominent, suggesting that SCD-associated FSGS affects mainly the juxtamedullary nephrons supplied by the vasa rectae.[57,58] FSGS in patients with SCD is thought to be a form of adaptive FSGS. Whether APOL1 high-risk alleles predispose such patients to FSGS remains uncertain.[59] Systematic study of renal histopathology in APOL1-associated SCN remains to be determined.

In one biopsy series performed to investigate progressive renal insufficiency or increasing proteinuria (>0.3 g/day) or both in 18 SCD patients, the glomerular lesions found in order of decreasing frequency included FSGS (39%), membranoproliferative glomerulonephritis (MPGN) (28%), thrombotic microangiopathy glomerulopathy (17%), and specific SCD glomerulopathy (17%). The latter represents glomerular hypertrophy with or without mesangial hypercellularity.[60] All patients exhibited albuminuria, but only 30% displayed renal functional impairment at the time of the kidney biopsy. At a mean follow-up of 28 months after the kidney biopsy, 50% of patients developed CKD and 21% developed ESRD requiring dialysis. A history of acute chest syndrome and chronic organ damage was associated with the occurrence of SCD glomerulopathy, whereas a history of retinitis was associated with thrombotic microangiopathy.

The potential associations between certain clinical characteristics and specific glomerular lesions in SCD patients remain to be explored. While MPGN was initially attributed to immune-complex injury, subsequent studies demonstrated that MPGN commonly occurred without immune-complex deposits.[19] Although definitive immune-complex deposits or MPGN type I have been described in SCD patients, it remains uncertain whether these were attributable to SCD.[19] Irrespective of the type of glomerulopathy present, renal biopsies from SCD patients show hypertrophied glomeruli with distended capillaries due to sickle blood cells. Hence, the term glomerulopathy specific to SCD describes these lesions. Such glomerular pathology can also be found in patients with SCD without clinical evidence of CKD.[4]

Ultrastructural features of the kidneys of SCD patients with nephrosis and the nephrotic syndrome and in the kidneys of rabbits following prolonged intravenous injection of saccharated iron oxide complexes led independent investigators to speculate that iron overload and possibly circulating iron–protein complexes lead to the glomerular lesions observed in patients with SCN.[61] However, glomerular lesions similar to those occurring in SCN have not been seen in β-thalassemia patients despite similar levels of iron overload, nor have they been seen in other conditions of iron overload, such as in idiopathic hemosiderosis or in patients who receive a large number of RBC transfusions. Therefore, iron overload alone fails to explain the pathophysiologic mechanisms associated with nephrotic syndrome in SCD patients.

GENETIC MODIFIERS

Renal dysfunction in SCD appears to be affected by a number of genetic modifiers of SCD. Suggested risk factors associated with progression of CKD to ESRD include APOL1 and HMOX1 rs743811 gene variants. In contrast, higher fetal hemoglobin (HbF) levels and α-globin genotype have been suggested to be protective.

HbF modulates the hematologic and clinical manifestations of SCD. Its level and distribution among sickle erythrocytes varies highly in SCD patients. Patients with the lowest HbF levels are more likely to develop renal failure and vaso-occlusive complications such as acute painful episodes, leg ulcers, osteonecrosis, and acute chest syndromes. In a cohort study of 725 HbSS patients, all patients with "sickle renal failure" had HbF levels of ≤10%.[17] Furthermore, the frequency of the Central African Republic (CAR) β^s CRA haplotype was found to be significantly increased in SCD patients who developed renal failure compared with those who did not, presumably secondary to the lower HbF levels associated with the β^s CRA haplotype.[17]

Coinheritance of α-thalassemia appears to protect against proteinuria and SCN in SCD patients. The coincidence of SCD and α-thalassemia reduces intraerythrocytic concentration of hemoglobin S and RBC volume, and reduces hemolysis. In a cohort of 424 adult African–British patients with SCD, a significant association between hemolytic markers and both the degree and prevalence of albuminuria were found. Further analysis demonstrated a negative association between the number of deleted α genes and the degree of albuminuria and prevalence of microalbuminuria, suggesting that coinheritance of α-thalassemia has a protective effect against albuminuria.[62]

Two APOL1 risk variants alleles (G1 and G2), found in 13% of African Americans, are associated with both an increased risk of nondiabetic glomerulosclerosis and FSGS and more rapid chronic kidney disease progression compared with their non-Black counterparts. In a large study consisting of more than 12,000 adult Hispanic/Latino adults, the presence of two APOL1 high-risk alleles and sickle cell rs334 variant was also found to be associated with albuminuria and/or CKD defined as eGFR $<60\ mL/min/1.73\ m^2$. When patients were grouped into Caribbean vs. Mainland backgrounds, the frequency of albuminuria was similar between the two groups, but the frequency of eGFR $<60\ mL/min/1.73\ m^2$ was approximately twofold higher among the Caribbean compared with Mainland counterparts (4.1% vs. 2.1%, respectively; $p = 5.2 \times 10^{-9}$). Notably, compared with Mainland Hispanics/Latinos, Caribbean Hispanics/Latinos had a tenfold higher frequency of two APOL1 risk alleles vs. zero/one copy (1% vs. 0.1%) and nearly threefold higher frequency of the imputed SCT rs334 risk allele versus zero copies (2% vs. 0.7%).[63] Limited studies in SCD patients similarly demonstrated that APOL1 high-risk variants are associated with albuminuria and CKD progression defined as 50% decline in eGFR or development of ESRD.[64] In a study of 152 SCD patients (age range 24–36 years) who were genotyped for APOL1 G1 G2, GSTM1, GSTT1, GSTP1, and HMOX1 gene variants, homozygous or double-heterozygous APOL G1 and G2 genotypes were found to be strongly associated with ESRD ($p = 0.003$) and higher CKD stages ($p = 0.001$). Furthermore, these genotypes were associated in an age-dependent manner with lower eGFR ($p = 0.008$), proteinuria ($p = 0.009$), and albuminuria ($p < 0.001$) but not with other SCD complications.[65] No association was found between GSTM1, GSTT1, GSTP1, or HMOX1 gene variants and SCN.

Single nucleotide polymorphism in the heme oxygenase-1 gene (HMOX1 rs743811) has been shown to be associated with SCN in some studies but not others. In a study of 221 SCD patients from the University of Illinois in Chicago and 487 patients from the Walk-Treatment of Pulmonary Hypertension and SCD with Sildenafil Therapy (Walk-PHaSST) cohort, *HMOX1 rs743811* variant was found to be associated with lower eGFR, albuminuria, and CKD stage. Of interest, in the Walk-PHaSST cohort, this variant was also associated with ESRD. Such association is independent of APOL1 variants and is thought to be due to reduced protection of the kidney from hemoglobin-mediated toxicity.[64] Nonetheless, a smaller European study ($n = 152$) consisting mainly of SCD patients of Sub-Saharan ancestry failed to show a link between the *HMOX1* variant and SCN.[65] An association between an HOXM1 variant and kidney disease warrants further exploration because of its direct effect on heme catabolism.

TREATMENT

The various clinical manifestations of SCN including hyposthenuria, hematuria, glomerular hyperfiltration, albuminuria, nephrotic syndrome, and progressive CKD leading to the development of ESRD have been well described. However, the pathogenic mechanisms of SCN and their therapeutic implications have yet to be elucidated. Maneuvers to reduce sickling crises are of unclear benefit because neither the frequency of sickling crises nor the severity of anemia has consistently been shown to predict albuminuria or CKD.[19] Nonetheless, management should be directed at specific complications. Adequate fluid intake prevents dehydration due to hyposthenuria. The theoretical benefit of NSAIDs in any patient with glomerular hyperfiltration has not consistently been shown. NSAID use in patients with SCD should be avoided due to the potential for adverse hemodynamic-related renal functional deterioration, precipitation of papillary necrosis, and the development of NSAID-associated interstitial nephritis and glomerulonephropathies.

Blood transfusions may restore urinary concentrating ability in children with SCD, but their potential to cause iron overload should not be overlooked. In patients awaiting kidney transplantation, blood transfusions can lead to allosensitization. Although preoperative blood transfusion to decrease hemoglobin S level has been suggested to decrease the incidence of posttransplant complications, aggressive RBC transfusion should be avoided because increasing RBC mass increases blood viscosity, thereby potentially precipitating RBC sickling. Whether immunosuppression use in the posttransplant period may reduce transfusion-related sensitization risk remains speculative.

There has been compelling evidence that angiotensin converting enzyme inhibitors (ACEIs) and/or ARBs effectively reduce proteinuria and slow the decline in renal function in both diabetic and nondiabetic nephropathy. Data on the effects of ACEIs or ARBs on proteinuria and the progression of CKD among patients with SCN remain limited. One small single-center study demonstrated that treatment with enalapril for 2 weeks resulted in reduction in proteinuria in adult SCD patients with mild renal insufficiency and biopsy documented evidence of glomerular enlargement and perihilar FSGS. Discontinuation of ACEI, however, led to rebound proteinuria.[66] Studies in children with SCD

similarly demonstrated that urinary albumin excretion normalized in 56% of patients treated with an ACEI.[67] The updated 2015 Cochrane database review revealed only one randomized trial comparing ACEI with placebo in SCD patients with microalbuminuria or proteinuria. Twenty-two study subjects were treated with captopril for 6 months. At 6 months, urinary albumin excretion in the captopril group decreased from baseline by a mean of 45 ± 23 mg/day, while it increased by 18 ± 45 mg/day in the placebo group.[68] There has been limited data on ARB use in SCD. In a study of 12 hydroxyurea-treated SCD patients with persistent albuminuria, treatment with losartan was associated with a significant decrease in albumin excretion rate at 1–2 month follow-up (median decrease −134 mcg/min, $p = 0.0063$). No significant differences in GFR or permselectivity were observed at short-term (1–2 months, $n = 12$) or long-term (>12 months; $n = 8$) follow-up.[69]

While evidence-based recommendations remain lacking, a trial of an ACEI and an ARB seems justifiable due to the well-established renoprotective effect of these drugs. Improving nocturia has been reported to be an additional beneficial effect of ACEIs, presumably as a result of reduction in GFR. Hypotension and hyperkalemia, particularly in the presence of impaired kidney function, may limit the use of ACEI and ARB therapy.

Some but not all studies suggest that hydroxyurea (HU) may reduce proteinuria and/or hyperfiltration. One prospective study consisting of 26 patients with SCD demonstrated that HU has a renoprotective effect by decreasing proteinuria but not albuminuria. Twenty-four hour proteinuria in HU ($n = 12$) vs. non-HU ($n = 14$) groups were 226 ± 16 vs. 414 ± 76 mg/dL, respectively, $p = 0.0001$. Urine albumin concentration in HU vs. non-HU groups was 79 ± 15 vs. 55 ± 86 mg/dL, respectively, $p = 0.35$.[70] In contrast, a cross-sectional study of 149 adult patients followed in a comprehensive sickle cell clinic showed that those using HU were less than one-third (odds ratio 0.28, $p = 0.01$) as likely to exhibit albuminuria (defined as either urinary albumin:creatinine ratios [UACRs] ≥30 mg/g or ≥1+ proteinuria on two separate dipstick evaluations).[71] A retrospective study consisting of 63 patients (7–18 years of age) with HbSS or HbSβ^0 thalassemia genotypes similarly demonstrated that HU therapy was associated with significant decrease in urine ACR in children with SCD and albuminuria. Among those with baseline microalbuminuria, the median ACR prior to HU therapy at 1 year and 2 years after treatment were 96 mg/g and 39 mg/g ($p = 0.02$), and 25 mg/g ($p = 0.03$), respectively. Albuminuria normalized in 37.5% after 1 year and in 61% after 2 years of HU therapy. Among those without albuminuria prior to HU therapy, 13% developed albuminuria during HU therapy. The study findings suggest that although HU may ameliorate urine ACR among those with baseline albuminuria, it is not protective against the development of albuminuria.[72]

A multicenter placebo-controlled trial in infants of ages 9–18 months (BABY HUG trial) demonstrated that treatment with HU for 24 months did not influence the GFR. However, treatment was associated with better urine concentrating ability and less renal enlargement, suggesting a possible renoprotective effect.[73] In contrast, in a small study of 23 children of ages 2.5–14 years (the HUSTLE study), HU at the maximum tolerated dose was found to be associated with a decrease in hyperfiltration. After 3 years of treatment, GFR measured by (99m)Tc-DTPA decreased significantly from 167 ± 46 mL/min/1.73 m^2 to 145 ± 27 mL/min/1.73 m^2 ($p = 0.016$). There was no significant change in microalbuminuria. However, only 4 of 23 patients had baseline albuminuria.[74]

Supplemental vitamin E has been suggested to be of therapeutic benefit because of its antioxidant properties. Further studies are needed. Dietary protein restriction is not recommended because of the underlying growth failure and decreased energy state in most patients with SCD.

Therapeutic options for patients with ESRD due to SCN include hemodialysis, peritoneal dialysis, and kidney transplantation.[75] Both hemodialysis and peritoneal dialysis may confer their own theoretical advantages. Hemodialysis may be used for urgent or emergent need for standard and exchange blood transfusions. In contrast, peritoneal dialysis and its inherent slow rate of ultrafiltration may minimize any acute rise in hematocrit and thus lower the risk of vaso-occlusive crisis. Kidney transplantation may offer survival advantage over those remaining on dialysis for appropriately selected patients with ESRD due to SCN. Although survival of transplant recipients with SCD appears to be inferior to that of matched African American recipients without the disease, survival of SCD patients is comparable to that of matched diabetic patients.[76] As in the general population, living donor graft survival among patients with ESRD due to SCN exceeds that of deceased donor transplants. In the current era of transplantation, desensitization protocols may allow transfusion-related highly sensitized patients to undergo a successful kidney transplant.

SUMMARY

Chronic sickling and hemolysis of RBCs in patients with SCD may result in various kidney complications. Figure 50.2 summarizes the pathogenic mechanisms underlying the development of hematuria, concentrating defects, and CKD associated with FSGS

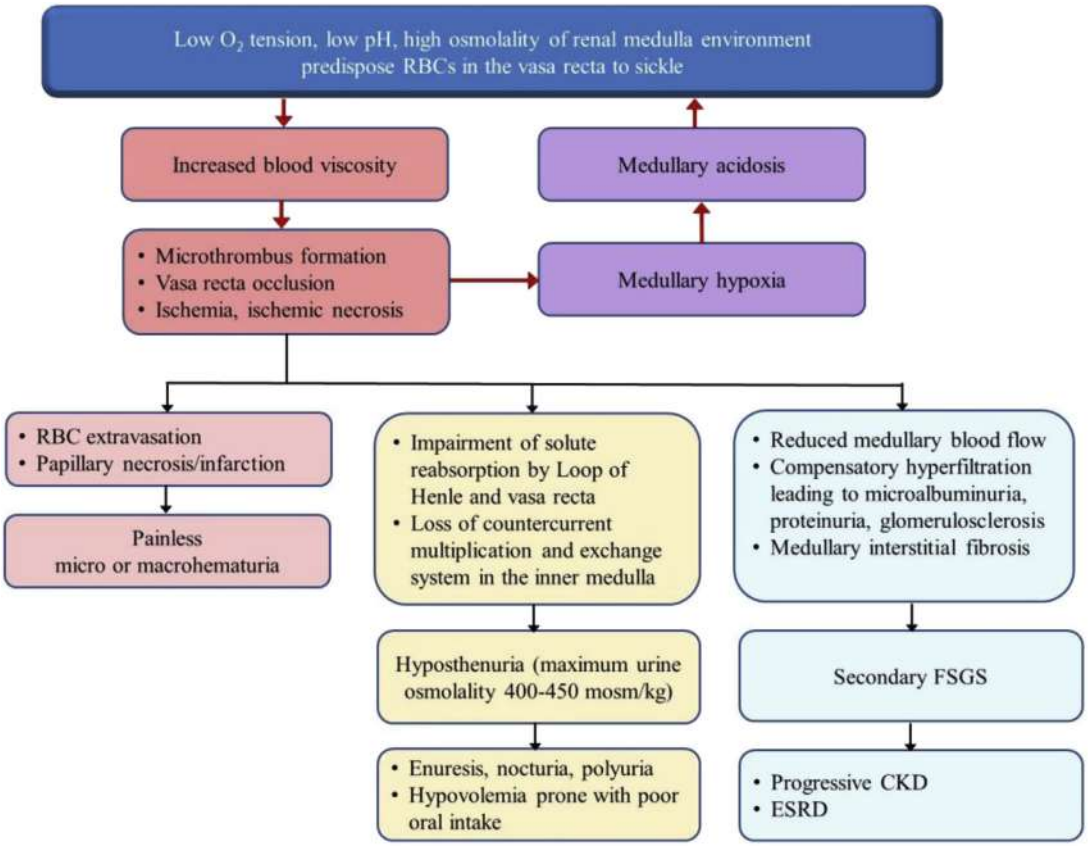


FIGURE 50.2 Pathogenic mechanisms of hematuria, concentrating defect, and CKD associated with FSGS in patients with SCD. The common inciting event is sickling in the vasa recta. *CKD*, chronic kidney disease; *ESRD*, end-stage renal disease; *FSGS*, focal segmental glomerulosclerosis; O_2, Oxygen; *RBC*, red blood cell.

in patients with SCD.[77] All segments of the nephron suffer damage, from the vascular bed, glomerular, and tubulointerstitial structures, to the collecting ducts. Functionally, this translates into signs and symptoms of kidney disease such as hyposthenuria, isosthenuria, hematuria, hyperfiltration, proteinuria, and decrements in GFR. Clinically, patients may develop acute and chronic kidney injury, glomerulonephritis, hyperkalemia, papillary necrosis, and finally ESRD. The underlying mechanisms of kidney injury primarily relate to hypoxia and ischemia. A growing body of literature suggests that intravascular hemolysis with subsequent hemoglobinuria causes kidney injury and CKD progression. Treatments to reduce RBC sickling and better diagnostic tools to detect kidney injury, such as biomarkers, may help forestall chronic kidney damage in SCD patients. Whether the more widespread use of serum CystC may allow early detection and intervention to slow CKD progression remains to be studied. Treatment targeting HbS polymerization to prevent acute and/or chronic multiorgan failure associated with erythrocyte sickling is an area for further research.[78]

References

1. Bunn HF. Pathogenesis and treatment of sickle cell disease. *N Engl J Med* 1997;**337**(11):762–9.
2. Herrick JB. Peculiar elongated and sickle-shaped red blood corpuscules in a case of severe anemia. *Arch Intern Med* 1910;**6**:517–21.
3. Abel MS, Brown CR. Sickle cell disease with severe hematuria simulating renal neoplasms. *J Am Med Assoc* 1948;**136**(9):624.
4. Lopez Revuelta K, Ricard Andres MP. Kidney abnormalities in sickle cell disease. *Nefrologia* 2011;**31**(5):591–601.
5. De Gracia-Nieto AE, Samper AO, Rojas-Cruz C, Gascon LG, Sanjuan JB, Mavrich HV. Genitourinary manifestations of sickle cell disease. *Arch Esp Urol* 2011;**64**(7):597–604.
6. DeFronzo RA, Taufield PA, Black H, McPhedran P, Cooke CR. Impaired renal tubular potassium secretion in sickle cell disease. *Ann Intern Med* 1979;**90**(3):310–6.
7. Goosens JP, Statius van Eps LW, Schouten H, Giterson AL. Incomplete renal tubular acidosis in sickle cell disease. *Clin Chim Acta* 1972;**41**:149–56.
8. Kong HH, Alleyne GA. Studies on acid excretion in adults with sickle cell anemia. *Clin Sci* 1971;**41**(6):505–18.
9. Batlle D, Itsarayoungyuen K, Arruda JA, Kurtzman NA. Hyperkalemic hyperchloremic metabolic acidosis in sickle cell hemoglobinopathies. *Am J Med* 1982;**72**(2):188–92.
10. Oster JR, Lee SM, Lespier LE, Pellegrini EL, Vaamonde CA. Renal acidification in sickle cell trait. *Arch Intern Med* 1976;**136**:30–5.
11. Yoshino M, Amerian R, Brautbar N. Hyporeninemic hypoaldosteronism in sickle cell disease. *Nephron* 1982;**31**(3):242–4.

12. Allon M. Renal abnormalities in sickle cell disease. *Arch Intern Med* 1990;**150**(3):501–4.
13. Sharpe CC, Thein SL. Sickle cell nephropathy – a practical approach. *Br J Haematol* 2011;**155**(3):287–97.
14. Eshbach ML, Kaur A, Rbaibi Y, Tejero J, Weisz OA. Hemoglobin inhibits albumin uptake by proximal tubule cells: implications for sickle cell disease. *Am J Physiol Cell Physiol* 2017;**312**(6): C733–40.
15. Tejani A, Phadke K, Adamson O, Nicastri A, Chen CK, Sen D. Renal lesions in sickle cell nephropathy in children. *Nephron* 1985;**39**:352–5.
16. de Jong PE, Statius van Eps LW. Sickle cell nephropathy: new insights into its pathophysiology. *Kidney Int* 1985;**27**:711–7.
17. Powars DR, Elliot-Mills DD, Chan L, Niland J, Hiti AL, Opas LM. Chronic renal failure in sickle cell disease: risk factors, clinical course, and mortality. *Ann Intern Med* 1991;**115**:614–20.
18. Guasch A, Cua M, Mitch WE. Early detection and the course of glomerular injury in patients with sickle cell anemia. *Kidney Int* 1996;**49**:786–91.
19. Scheinman JI. Sickle cell disease and the kidney. *Nat Clin Pract Nephrol* 2009;**5**(2):78–88.
20. Guasch A, Navarrete J, Nass K, Zayas CF. Glomerular involvement in adults with sickle cell hemoglobinopathies: prevalence and clinical correlates of progressive renal failure. *J Am Soc Nephrol* 2006;**17**: 2228–35.
21. Becton LJ, Kalpatthi RV, Rackoff E, Disco D, Orak JK, Jackson SM. Prevalence and clinical correlates of microalbuminuria in children with sickle cell disease. *Pediatr Nephrol* 2010;**25**(8): 1505–11.
22. Baddam S, Aban I, Hilliard L, Howard T, Askenazi D, Lebensburger JD. Acute kidney injury during a pediatric sickle cell vaso-occlusive pain crisis. *Pediatr Nephrol* 2017;**32**(8): 1451–6.
23. Audard V, Homs S, Habibi A, Galacteros F, Bartolucci P, Godeau B, Renaud B, Levy Y, Grimbert P, Lang P, Brun-Buisson C, Brochard L, Schortgen F, Maitre B, Mekontso Dessap A. Acute kidney injury in sickle patients with painful crisis or acute chest syndrome and its relation to pulmonary hypertension. *Nephrol Dial Transplant* 2010; **25**(8):2524–9.
24. Wolfson JA, Schrager SM, Coates TD, Kipke MD. Sickle-cell disease in California: a population-based description of emergency department utilization. *Pediatr Blood Canc* 2011;**56**(3): 413–9.
25. Gosmanova EO, Zaidi S, Wan JY, Adams-Graves PE. Prevalence and progression of chronic kidney disease in adult patients with sickle cell disease. *J Investig Med* 2014;**62**(5):804–7.
26. Searjeant GR, Searjeant BE, Mason KP, Hambleton IR, Fisher C, Higgs DR. The changing face of homozygous sickle cell disease: 102 patients over 60 years. *Int J Lab Hematol* 2009;**31**:585–96.
27. Da Silva GB, Liborio AB, Daher Ede F. New insights on pathophysiology, clinical manifestations, diagnosis, and treatment of sickle cell nephropathy. *Ann Hematol* 2011;**90**(12):1371–9.
28. Diop S, Diop D, Seck M, Gueye Y, Faye A, Dieye TN. Predictive factors of chronic complications in adult sickle cell anemia patients in Dakar, Senegal. *Med Trop* 2010;**70**:471–4.
29. Alkhunaizi AM, Al-Khatti AA, Alkhunaizi MA. Prevalence of microalbuminuria in adult patients with sickle cell disease in eastern Saudi Arabia. *Int J Nephrol* 2018;**28**:5015764. https://doi.org/10.1155/2018/5015764. eCollection 2018.
30. Nath KA, Hebbel RP. Sickle cell disease: renal manifestations and mechanisms. *Nat Rev Nephrol* 2015;**11**(3):161–71.
31. Wierenga KJ, Pattison JR, Brink N, Griffiths M, Miller M, Shah DJ, Williams W, Serjeant BE, Serjeant GR. Glomerulonephritis after human parvovirus infection in homozygous sickle-cell disease. *Lancet* 1995;**346**(8973):475–6.
32. Lebensburger JD, Cutter GR, Howard TH, Muntner P, Feig DI. Evaluating risk factors for chronic kidney disease in pediatric patients with sickle cell anemia. *Pediatr Nephrol* 2017;**32**(9): 1565–73.
33. Asnani M, Reid M, Cystatin C. A useful marker of glomerulopathy in sickle cell disease? *Blood Cells Mol Dis* 2015;**54**(1):65–70.
34. Yee MEM, Lane PA, Archer DR, Joiner CH, Eckman JR, Guasch A. Estimation of glomerular filtration rate using serum cystatin C and creatinine in adults with sickle cell anemia. *Am J Hematol* 2017; **92**(10):E598–9.
35. Heimlich JB, Chipoka G, Elsherif L, David E, Ellis G, Kamthunzi P, Krysiak R, Mafunga P, Zhou Q, Cai J, Gopal S, Key NS, Ataga KI. Nephrin as a biomarker of sickle cell glomerulopathy in Malawi. *Pediatr Blood Canc* 2018;**65**(6):e26993. https://doi.org/10.1002/pbc.26993.
36. Sundaram N, Bennett M, Wilhelm J, Kim MO, Atweh G, Devarajan P, Malik P. Biomarkers for early detection of sickle nephropathy. *Am J Hematol* 2011;**86**(7):559–66.
37. Mostofi FK, Vorder Bruegge CF, Diggs LW. Lesions in kidneys removed for unilateral hematuria in sickle-cell disease. *Arch Pathol* 1957;**63**(4):336–51.
38. Allon M, Lawson L, Eckman JR, Delaney V, Bourke E. Effects of nonsteroidal anti-inflammatory drugs on renal function in sickle cell anemia. *Kidney Int* 1988;**34**(4):500–6.
39. De Jong PE, De Jong-van Den Berg TW, Sewrajsingh GS, Schouten H, Donker AJ, Statius van Eps LW. The influence of indomethacin on renal hemodynamics in sickle cell anemia. *Clin Sci* 1980;**59**(4):245–50.
40. Bank N, Aynedjian HS, Qiu JH, Osei SY, Ahima RS, Fabry ME. Renal nitric oxide synthases in transgenic sickle cell mice. *Kidney Int* 1996;**50**(1):184–9.
41. Bank N, Kiroycheva M, Ahmed F, Anthony GM, Fabry ME, Nagel RM. Peroxynitrite formation and apoptosis in transgenic sickle cell mouse kidneys. *Kidney Int* 1998;**54**(5):1520–8.
42. Haymann JP, Stankovic K, Levy P, Avellino V, Tharaux PL, Letavernier E. Glomerular hyperfiltration in adult sickle cell anemia: a frequent hemolysis associated feature. *Clin J Am Soc Nephrol* 2010;**5**(5):756–61.
43. Maier-Redelsperger M, Levy P, Lionnet F, Stankovic K, Hayman JP, Lefevre G. Strong association between a new marker of hemolysis and glomerulopathy in sickle cell anemia. *Blood Cells Mol Dis* 2010; **45**(4):289–92.
44. Nath KA, Katusic ZS. Vasculature and kidney complications in sickle cell disease. *J Am Soc Nephrol* 2012;**23**(5):781–4.
45. Ataga KI, Brittain JE, Moore D, Jones SK, Hulkower B, Strayhorn D, Adam S, Redding-Lallinger R, Nachman P, Orringer EP. Urinary albumin excretion is associated with pulmonary hypertension in sickle cell disease: potential role of soluble fms-like tyrosine kinase-1. *Eur J Haematol* 2010;**85**(3): 257–63.
46. Ataga KI, Derebail VK, Caughey M, Elsherif L, Shen JH, Jones SK, Maitra P, Pollock DM, Cai J, Archer DR, Hinderliter AL. Albuminuria is associated with endothelial dysfunction and elevated plasma endothelin-1 in sickle cell anemia. *PLoS One* 2016;**11**(9):e0162652. https://doi.org/10.1371/journal.pone.0162652. eCollection 2016.
47. Heimlich JB1, Speed JS, O'Connor PM, Pollock JS, Townes TM, Meiler SE, Kutlar A, Pollock DM. Endothelin-1 contributes to the progression of renal injury in sickle cell disease via reactive oxygen species. *Br J Pharmacol* 2016;**173**(2):386–95. https://doi.org/10.1111/bph.13380.

48. Jaffa AA, Rust PF, Mayfield RK. Kinin, a mediator of diabetes-induced glomerular hyperfiltration. *Diabetes* 1995;**44**(2):156–60.
49. Bergmann S, Zheng D, Barredo J, Abboud MR, Jaffa AA. Renal kallikrein: a risk marker of nephropathy in children with sickle cell disease. *J Pediatr Hematol Oncol* 2006;**28**(3):147–53.
50. Schwartz GJ, Lerner NB. The kallikrein-kinin system in sickle cell nephropathy: does it play a role? *J Pediatr Hematol Oncol* 2006;**28**(3):111–4.
51. Alvarez O, Montane B, Lopez G, Wilkinson J, Miller T. Early blood transfusions protect against microalbuminuria in children with sickle cell disease. *Pediatr Blood Canc* 2006;**47**(1):71–6.
52. Zatz R, Baylis C. Chronic nitric oxide inhibition model six years on. *Hypertension* 1998;**32**(6):958–64.
53. Baylis C. Nitric oxide deficiency in chronic kidney disease. *Am J Physiol Renal Physiol* 2008;**294**(1):F1–9.
54. Nath KA, Grande JP, Croatt AJ, Frank E, Caplice NM, Hebbel RP. Transgenic sickle mice are markedly sensitive to renal ischemia-reperfusion injury. *Am J Pathol* 2005;**166**(4):963–72.
55. Kiryluk K, Jadoon A, Gupta M, Radhakrishnan J. Sickle cell trait and hematuria. *Kidney Int* 2007;**71**:706–10.
56. Sydenstricker VP, Mulherin WA, Houseal RW. Report of two cases in children with necropsy in one case. *Am J Dis Child* 1923;**26**:132–54.
57. Nasr SH, Markowitz GS, Sentman RL, D'Agati VD. Sickle cell disease, nephrotic syndrome, and renal failure. *Kidney Int* 2006;**69**(7):1276–80.
58. Bhathena DB, Sondheimer JH. The glomerulopathy of homozygous sickle hemoglobin (SS) disease: morphology and pathogenesis. *J Am Soc Nephrol* 1991;**1**(11):1241–52.
59. Rosenberg AZ, Kopp JB. Focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol* 2017;**12**(3):502–17.
60. Maigne G, Ferlicot S, Galacteros F, Belenfant X, Ulinski T, Niaudet P. Glomerular lesions in patients with sickle cell disease. *Medicine* 2010;**89**(1):18–27.
61. McCoy RC. Ultrastructural alterations in the kidney of patients with sickle cell disease and the nephrotic syndrome. *Lab Invest* 1969;**21**(2):85–95.
62. Day TG, Drasar ER, Fulford T, Sharpe CC, Thein SL. Association between hemolysis and albuminuria in adults with sickle cell anemia. *Haematologica* 2012;**97**(2):201–5.
63. Kramer HJ, Stilp AM, Laurie CC, et al. African ancestry-specific alleles and kidney disease risk in Hispanics/Latinos. *J Am Soc Nephrol* 2017;**28**(3):915–22.
64. Saraf SL, Zhang X, Shah B, Kanias T, Gudehithlu KP, Kittles R, Machado RF, Arruda JA, Gladwin MT, Singh AK, Gordeuk VR. Genetic variants and cell-free hemoglobin processing in sickle cell nephropathy. *Haematologica* 2015;**100**(10):1275–84.
65. Kormann R, Jannot AS, Narjoz C, Ribeil JA, Manceau S, Delville M, Joste V, Prié D, Pouchot J, Thervet E, Courbebaisse M, Arlet JB. Roles of APOL1 G1 and G2 variants in sickle cell disease patients: kidney is the main target. *Br J Haematol* 2017;**179**(2):323–35.
66. Falk RJ, Scheinman J, Phillips G, Orringer E, Johnson A, Jennette JC. Prevalence and pathologic features of sickle cell nephropathy and response to inhibition of angiotensin-converting enzyme. *N Engl J Med* 1992;**326**(14):910–5.
67. McKie KT, Hanevold CD, Hernandez C, Waller JL, Ortiz L, McKie KM. Prevalence, prevention, and treatment of microalbuminuria and proteinuria in children with sickle cell disease. *J Pediatr Hema Oncol* 2007;**29**(3):140–4.
68. Sasongko TH, Nagalla S, Ballas SK. Angiotensin-converting enzyme (ACE) inhibitors for proteinuria and microalbuminuria in people with sickle cell disease. *Cochrane Database Syst Rev* 2015;(6):CD009191. https://doi.org/10.1002/14651858.CD009191.pub3.
69. Yee ME, Lane PA, Archer DR, Joiner CH, Eckman JR, Guasch A. Losartan therapy decreases albuminuria with stable glomerular filtration and permselectivity in sickle cell anemia. *Blood Cells Mol Dis* 2018;**69**:65–70.
70. Silva Junior GB, Vieira AP, Couto Bem AX, Alves MP, Meneses GC, Martins AM, Araújo SM, Libório AV, Daher EF. Proteinuria in adults with sickle-cell disease: the role of hydroxycarbamide(hydroxyurea) as a protective agent. *Int J Clin Pharm* 2014;**36**(4):766–70.
71. Laurin LP, Nachman PH, Desai PC, Ataga KI, Derebail VK. Hydroxyurea is associated with lower prevalence of albuminuria in adults with sickle cell disease. *Nephrol Dial Transplant* 2014;**29**(6):1211–8.
72. Tehseen S, Joiner CH, Lane PA, Yee ME. Changes in urine albumin to creatinine ratio with the initiation of hydroxyurea therapy among children and adolescents with sickle cell disease. *Pediatr Blood Canc* 2017;**64**(12). https://doi.org/10.1002/pbc.26665.
73. Alvarez O, Miller ST, Wang WC, Luo Z, McCarville MB, Schwartz GJ, Thompson B, Howard T, Iyer RV, Rana SR, Rogers ZR, Sarnaik SA, Thornburg CD, Ware RE. Effect of hydroxyurea treatment on renal function parameters: results from the multi-center placebo-controlled BABY HUG clinical trial for infants with sickle cell anemia. *Pediatr Blood Canc* 2012;**59**(4):668–74.
74. Aygun Mortier NA, Smeltzer MP, Shulkin BL, Hankins JS, Ware RE. Hydroxyurea treatment decreases glomerular hyperfiltration in children with sickle cell anemia. *Am J Hematol* 2013;**88**(2):116–9.
75. Pham PT. Renal manifestations of sickle cell disease. https://emedicine.medscape.com/article/1957952-overview. [Accessed May 3, 2019].
76. Huang Parke C, Mehrnia A, Kamgar M, Pham PT, Danovitch G, Bunnapradist S. Improved survival among sickle cell kidney transplant recipients in the recent era. *Nephrol Dial Transplant* 2013;**28**(4):1039–46.
77. Pham PM, Qaqish S, Pham PT. Sickle cell nephropathy. In: Lerma EV, Pezarella M, Rosner M, editors. *Current diagnosis and treatment in nephrology and hypertension*. 2nd ed. Lange Medical Books/McGraw-Hill; 2018. p. 584–92.
78. Eaton WA, Bunn HF. Treating sickle cell disease by targeting HbS polymerization. *Blood* 2017;**129**(20):2719–26.
79. Statius van Eps LW, De Jong PE. Sickle cell disease. In: Schrier RW, Gottschalk C, editors. *Diseases of the kidney*. 6th ed. Boston: Little Brown; 1997. p. 2201–19.
80. Alleyne GA. The kidney in sickle cell anemia. *Kidney Int* 1975;**7**(6):371–9.
81. McPherson Yee M, Jabbar SF, Osunkwo I, Clement L, Lane PA, Eckman JR, et al. Chronic kidney disease and albuminuria in children with sickle cell disease. *Clin J Am Nephrol* 2011;**6**(11):2628–33.
82. Friedman AN, Marrero D, Ma Y, Ackermann R, Narayan KM, Barett-Connor E, et al. Value of urinary albumin-to-creatinine ratio as a predictor of type 2 diabetes in pre-diabetic individuals. *Diabetes Care* 2008;**31**(12):2344–8.
83. Pham PT, Pham PC, Wilkinson AH, Lew SQ. Renal abnormalities in sickle cell disease. *Kidney Int* 2000;**57**:1–8.

QUESTIONS AND ANSWERS

Question 1

A 14-year-old African American male in good health sees his pediatrician for a preathletic physical. He attends high school and looks forward to participating in sports. He has no complaints. His vital signs include blood pressure 110/70 mm Hg, pulse 70 beats per minute, temperature 98.7°F, and respiratory rate 12 per minute. He has an unremarkable physical examination. However, on urinalysis he has 1+ heme on dipstick, and 15 RBCs per high power field on microscopic evaluation. The pediatrician reviews his records and notes that the patient has sickle cell trait.

Which **one** of the following is a plausible explanation for hematuria?

A. Urinary tract infection
B. Renal cell carcinoma of the kidney
C. Papillary necrosis
D. Kidney stone
E. Strenuous exercise or activity (march hematuria)

Answer: C

The hypoxic, acidotic, and hyperosmolar environment of the inner medulla promotes sickling of erythrocytes. Sickling of erythrocytes in the vas recta results in increased blood viscosity, impairment in renal medullary blood flow, microthrombus formation, and ischemic necrosis. Ischemic thrombi cause structural changes leading to RBC extravasation and hematuria. Papillary necrosis in patients with sickle cell trait presents with more hematuria than those with homozygous HbSS regardless of age.[79] Microscopic or macroscopic hematuria associated with papillary necrosis presents as painless hematuria and is self-limiting.

Urinary tract infection and kidney stones usually present with dysuria and flank pain, respectively. Urinary tract infection generally presents with frequency, urgency, and dysuria. Urinalysis reveals WBCs and may be accompanied by RBCs. Urine culture identifies the pathogen(s) responsible for the urinary tract infection.

Early stage cancer of the kidney does not present with pain. In the general population, renal cell carcinoma appears in older individuals. An imaging study such as an ultrasound or CT scan would be able to eliminate this diagnosis. However, renal medullary cancer occurs in patients with sickle cell trait at a relatively young age (average of 21 years).

March hematuria or march hemoglobinuria results from repetitive impact injury, such as running on a hard road, or drumming with the palm. The condition was first described in 1881 when soldiers presented with hematuria after marching for long periods of time. The repetitive nature of these types of activities cause mechanical trauma to the RBCs causing hemolysis. Urinalysis would show 1−2+ heme but no RBCs on microscopic examination. Other tests such as a depressed haptoglobin and an elevated lactate dehydrogenase and unconjugated bilirubin confirm hemolysis. Sickled RBCs result in hemolysis and could present with a similar picture.[4,5,37,55,79,80]

Question 2

A 10-year-old African American male with SCD presents for his annual checkup to update his immunization record. The patient has no new complaints or symptoms. He attends school and participates in sport activities.

He looks well-nourished and in no acute distress. His vital signs include blood pressure 100/60 mm Hg, pulse 72 beats per minute, temperature 98.6°F, and respiratory rate 12 per minute. He has pale conjunctiva. Evaluation of the lung reveals clear sounds to auscultation and percussion. He has a grade 1/6 systolic ejection murmur. He has normal bowel sounds and he does not have organomegaly. The legs have no edema. He has pale nail beds.

Laboratory tests show S[Na] 140 mEq/L, S[K] 4.0 mEq/L, S[Cl] 105 mEq/L, S[bicarbonate] 24 mEq/L, BUN 10 mg/dL, S[Cr] 0.2 mg/dL, S[Ca] 9.0 mg/dL, glucose 85 mg/dL. He has WBC count 4.8 cells/μL, hemoglobin 6 g/dL, hematocrit 18%, and platelet count 250,000/mmol. Urinalysis shows specific gravity 1.012, pH 5.0, negative for blood and protein.

Which **one** of the following is a plausible explanation for the low S[Cr] in this case?

A. Poor nutritional intake
B. Glomerular hyperfiltration
C. Liver disease
D. Rhabdomyolysis
E. Increase in fluid intake

Answer: B

Glomerular changes in patients with SCD begin as early as the first decade of life and are characterized by high renal blood flow, glomerular hyperfiltration and hypertrophy, gradual loss of permselectivity, and a decrease in ultrafiltration coefficient. Glomerular hyperfiltration results in low to normal BUN and S[Cr] levels.

Individuals with poor nutritional intake, especially low protein intake, could present with a low BUN. The patient would look malnourished. S[Cr] level would be normal if muscle mass has not been affected.

Patients with severe liver disease cannot convert nitrogenous waste such as ammonia to urea. This patient lacks evidence of severe liver disease such as

ascites, jaundice, or neurological changes associated with hyperammonemia.

Patients with rhabdomyolysis have muscle tenderness and have high serum creatine phosphokinase (CK) levels. A high CK level may result in an elevated S[Cr] but not a low one.

Patients with SCD are encouraged to remain well hydrated to prevent vaso-occlusive disease. Hydration may decrease BUN. S[Cr] rarely changes just from hydration alone. The changes in S[Cr] in this case are most likely a result of changes in GFR associated with hyperfiltration.[13,81]

Question 3

An 18-year-old African American male with SCD presents for his annual checkup as well as for his precollege immunization. The patient has no new complaints or symptoms.

His vital signs include blood pressure 110/70 mm Hg, pulse 72 beats per minutes, temperature 98.6°F, and respiratory rate 12 per minute. He has pale conjunctiva. Evaluation of the lungs reveals clear sounds to auscultation and percussion. He has a grade 1/6 systolic ejection murmur. He has normal bowel sounds and does not have organomegaly. The legs have no edema. He has pale nail beds.

Laboratory tests show S[Na] 140 mEq/L, S[K] 4.0 mEq/L, S[Cl] 105 mEq/L, S[bicarbonate] 24 mEq/L, BUN 8 mg/dL, S[Cr] 0.4 mg/dL, S[Ca] 9.0 mg/dL, glucose 85 mg/dL. He has WBC count 5.6 cells/μL, hemoglobin 7.2 g/dL, hematocrit 18%, platelet count 225,000/mmol. Urinalysis shows specific gravity 1.012, pH 5.5, trace blood, and trace protein. His UACR is 100 μg/mg.

Which **one** of the following is a plausible explanation for microalbuminuria?

A. Loss of glomerular permselectivity
B. High protein diet
C. A marker of pre−diabetes mellitus
D. Tubulointerstitial disease
E. Acute prostatitis

Answer A

Sickle cell patients have high renal blood flow, glomerular hyperfiltration and hypertrophy, gradual loss of permselectivity leading to micro- and macroalbuminuria, and a decrease in ultrafiltration coefficient. Albuminuria increases over time in patients with SCD. Microalbuminuria and macroalbuminuria are harbingers of clinically significant renal disease.[21,81]

Protein intake does not generally affect or cause proteinuria.

Clinicians use albuminuria in diabetic patients to monitor pending diabetic nephropathy. Investigators for the Diabetes Prevention Program Research Group did not find a consistent trend in incident diabetes by quartile of albumin:creatinine ratio.[82]

Patients with tubulointerstitial disease generally have a bland urine (e.g. negative for blood and protein on dipstick). Moreover, tubules secrete Tamms Horsfall proteins that are not measured with a urine dipstick.

Acute prostatitis presents with dysuria and hematuria. Proteinuria is rarely found on urinalysis.

Question 4

A 25-year-old African American male with SCD presents with leg swelling. His physician sees him frequently, especially when he has an episode of sickle crisis. The patient has 1 to 4 sickle crises per year.

He appears pale, with pale conjunctiva and nail beds. His vital signs include blood pressure 130/80 mm Hg, pulse 70 beats per minutes, temperature 98.7°F, and respiratory rate 12 per minute. Evaluation of the lungs reveals clear sounds to auscultation and percussion. He has a grade 2/6 systolic ejection murmur. He has normal bowel sounds and no organomegaly. The legs have 1+ pitting edema.

Laboratory tests show S[Na] 140 mEq/L, S[K] 4.0 mEq/L, S[Cl] 105 mEq/L, S[bicarbonate] 22 mEq/L, BUN 20 mg/dL, S[Cr] 1.0 mg/dL, S[Ca] 9.0 mg/dL, glucose 85 mg/dL. He has WBC count 6.1 cells/μL, hemoglobin 6.4 g/dL, hematocrit 19%, platelet count 245,000/mmol. Urinalysis shows specific gravity 1.010, pH 5.5, 1+ heme, and 2+ protein. Microscopic evaluation shows eight RBCs per high power field, but no casts. Urine protein:creatinine ratio (UPCR) is 3.8 g/g creatinine.

Which **one** of the following is a plausible explanation for proteinuria?

A. Glomerular hyperfiltration
B. AKI
C. Papillary necrosis
D. ESRD
E. Glomerulonephritis

Answer: E

Glomerulonephritis presents with proteinuria, hematuria, hypertension, abnormal renal function, and edema. The patient has several signs and symptoms associated with the syndrome of glomerulonephritis, and the UPCR suggests nephrotic range proteinuria.

An increase in renal blood flow leads to glomerular hyperfiltration and glomerular hypertrophy during the first decade of life in patients with SCD. Glomerular hyperfiltration presents with low BUN and S[Cr] values.

Leg swelling would be unusual with supernormal kidney function unless the patient has decompensated heart failure from chronic severe anemia. This clinical history was not given.

Both AKI and ESRD can present with leg swelling. More importantly, both disorders present with elevated BUN and S[Cr].

Papillary necrosis generally presents with hematuria and rarely with nephrotic range proteinuria.[57,58,60,61]

Question 5

A 25-year-old African American male with SCD presents with proteinuria. His physician sees him regularly. The patient has 1 to 4 sickle crises per year. The patient has some leg swelling.

His vital signs include blood pressure 140/90 mm Hg, pulse 70 beats per minutes, temperature 98.7°F, and respiratory rate 12 per minute. He has pale conjunctiva. Evaluation of the lungs reveals clear sounds to auscultation and percussion. He has a grade 2/6 systolic ejection murmur. He has normal bowel sounds and does not have organomegaly. The legs have 1+ pitting edema. He has pale nail beds. He has hyperpigmented skin lesions near both ankles.

Laboratory tests show S[Na] 140 mEq/L, S[K] 4.0 mEq/L, S[Cl] 105 mEq/L, S[bicarbonate] 22 mEq/L, BUN 20 mg/dL, S[Cr] 1.0 mg/dL, S[Ca] 9.0 mg/dL, glucose 85 mg/dL. He has WBC count 4.2 cells/μL, hemoglobin 5.9 g/dL, hematocrit 20%, platelet count 255,000/mmol. Urinalysis shows specific gravity of 1.009, pH 5.5, 1+ heme, and 2+ protein. Microscopic evaluation shows eight RBCs per high power field, but no casts. The UPCR is 3.8. The patient undergoes a kidney biopsy.

Which **one** of the following is a plausible finding on kidney biopsy?

A. Minimal change disease
B. FSGS
C. Papillary necrosis
D. Membranous glomerulopathy
E. Tubulointerstitial nephritis

Answer: B

A wide spectrum of glomerular lesions has been described in patients with SCD. The most frequently identified morphologic lesion in patients with nephrotic range proteinuria associated with SCD is FSGS. Other glomerular lesions include membranoproliferative glomerulonephritis and SCD glomerulopathy.

Minimal change disease occurs in the very young and very old. Effacement of the basement membrane appears on electron microscopic evaluation. Renal function tends to be normal. The presence of urinary RBCs makes minimal change disease unlikely. A kidney biopsy helps differentiate minimal change disease from other glomerular disorders in this age group.

Papillary necrosis results in concentrating defects. Urinalysis generally reveals hematuria, but rarely nephrotic range proteinuria. Imaging studies identify the lesion.

Membranous glomerulopathy presents mostly in middle-aged Caucasians and is not associated with SCD.

Patients with tubulointerstitial nephritis usually do not have blood or protein on urinalysis. This patient has nephrotic range proteinuria, suggesting a glomerular lesion.[58,60,61]

Question 6

A 30-year-old African American male with SCD presents with nausea, vomiting, and dysgeusia. He was diagnosed with FSGS approximately 5 years ago. He also has pruritis and insomnia.

He has high blood pressure and takes five different antihypertensive medications. He has 1 to 4 sickle crises per year.

His vital signs include blood pressure 160/100 mm Hg, pulse 70 beats per minutes, temperature 98.5°F, and respiratory rate 20 per minute. He has pale conjunctiva. Evaluation of the lungs reveals clear sounds to auscultation and percussion. He has a grade 2/6 systolic ejection murmur. He has normal bowel sounds and does not have organomegaly. The legs have 2+ pitting edema. He has pale nail beds.

Laboratory tests show S[Na] 139 mEq/L, S[K] 5.0 mEq/L, S[Cl] 104 mEq/L, S[bicarbonate] 19 mEq/L, BUN 80 mg/dL, S[Cr] 8.0 mg/dL, S[Ca] 8.0 mg/dL, glucose 88 mg/dL. He has WBC count 5.8 cells/μL, hemoglobin 5 g/dL, hematocrit 15 percent, platelet count 230,000/mmol. Urinalysis shows specific gravity 1.010, pH 5.5, 1+ heme, and 2+ protein. Microscopic evaluation shows 10 RBCs per high power field, but no casts. The UPCR is 1.3. Renal ultrasound does not show hydronephrosis. The right kidney measures 9 cm and the left kidney measures 9.3 cm, both with increased echogenicity.

He starts dialysis for ESRD.

Which **one** of the following is NOT a plausible explanation for renal failure?

A. Diabetic nephropathy
B. Hypertensive nephrosclerosis
C. Papillary necrosis
D. Analgesic nephropathy
E. FSGS

Answer: A

He does not have a history of diabetes mellitus or hyperglycemia.

All the other entities may be present given his history of SCD. He has poorly controlled hypertension despite taking five medications. Compliance with medications may be involved. In addition, he has volume overload as demonstrated by 2+ pedal edema.

Hematuria may be related to papillary necrosis or FSGS.

Patients with SCD take large quantities of analgesic for pain management during crises. Cumulative dose of analgesic ingested, especially combinations, may lead to analgesic nephropathy. Generally, patients with analgesic nephropathy have a bland urine, consistent with tubulointerstitial damage.

ESRD is a common outcome if SCD patients develop FSGS. Nonspecific medical management for FSGS might include an ACEI or ARB. Various treatment regimens for primary FSGS include steroids immunosuppressive and cytotoxic agents. These agents would not be recommended for FSGS from SCD.[19,83]

CHAPTER

51

Approach to Chronic Kidney Disease in the Diabetic Patient

Farsad Afshinnia[a], *Frank C. Brosius, 3rd*[a,b]

[a]Division of Nephrology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, United States;
[b]Division of Nephrology, University of Arizona College of Medicine, Tucson, AZ, United States

Abstract

The diagnosis of diabetic kidney disease (DKD) is generally made clinically, either by increased urinary albumin excretion (>30 mg/day) or declining glomerular filtration rate, usually in the presence of diabetic retinopathy. All diabetic patients should undergo annual measurements of serum creatinine concentration (S[Cr]) and urinary albumin concentration and have their estimated glomerular filtration rate (eGFR) calculated. Control of blood glucose to achieve an HbA1c of 7%, and blood pressure aimed at a level less than 130/80 mm Hg, as tolerated, can delay or prevent onset of DKD. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are first-line treatments in hypertensive and nonhypertensive DKD patients, especially those with increased urinary albumin excretion. The use of sodium-glucose cotransporter 2 inhibitors also prevents DKD progression in patients with both preserved and decreased eGFR. Lipid-lowering therapy is beneficial in the primary prevention of cardiovascular events in DKD patients. Dietary protein restriction should also be considered for DKD patients. All patients with stage 4 or 5 CKD should be evaluated for potential renal replacement therapy (RRT) by a nephrologist. Proper candidates should be prepared for end-stage renal disease therapy by discussing modalities of RRT, including renal transplantation, providing necessary education, creating dialysis access when appropriate, and making necessary referrals.

INTRODUCTION

Over 44% of the new cases of end-stage renal disease (ESRD) in the US are attributed to diabetes mellitus (DM), making it the leading cause of ESRD in the US[1] and in many parts of the world. According to the 2017 US Renal Data System report, in spite of stabilization of adjusted incidence rates, the total number of patients with ESRD from diabetes has continued to increase.[1] The reasons for continued growth in ESRD from diabetic kidney disease (DKD) include the inability to identify patients at high risk of progression of chronic kidney disease (CKD) at relatively early stages, as well as the lack of substantial advances in the treatment of DKD during the past 25 years. It is likely that the incidence of DKD will increase again as the recent major increase in type 2 diabetes, especially in children and young adults, leads to more nephropathy over the next two decades.[2] The diagnostic and prognostic biomarkers of DKD in current clinical practice (S[Cr], cystatin C, estimated glomerular filtration rate [eGFR], and urinary albumin excretion) lack desired sensitivity and specificity, but new useful biomarkers will likely be available soon. Moreover, our general understanding of pathogenic signaling pathways leading to progressive DKD continues to expand.[3] There is new evidence of the substantial therapeutic effect of sodium-glucose cotransporter 2 (SGLT2) inhibitors and other new interventions in slowing the progression of DKD.[4] Continued elucidation of the various molecular signaling pathways and networks that lead to DKD will allow us to test and develop even better diagnostic biomarkers and more effective preventive and therapeutic strategies in the not-too-distant future.[3]

NATURAL HISTORY OF DKD

Glomerular hyperfiltration, i.e. a higher-than-normal glomerular filtration rate (GFR), occurs shortly after diagnosis in most patients with type 1 DM. Hyperfiltration is due to the relative vasodilation of renal glomerular afferent arterioles, leading to increased glomerular

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00051-6

pressure and a resultant increase in GFR. Hyperfiltration is improved or eliminated with good glycemic control.[5] Hyperfiltration also occurs in early type 2 diabetes,[6] but its presence is less consistent. Although hyperfiltration predicts albuminuria and a generally worse prognosis in diabetic patients, there are no convincing long-term prospective studies that establish whether hyperfiltration, *per se*, causes enhanced glomerular or tubular pathology and progression of DKD. The most common initial indicator of DKD is albuminuria, defined as urinary albumin excretion over 30 mg/day. Abnormal urinary albumin excretion usually develops between 5 and 15 years after the diagnosis of diabetes in many type 1 patients who develop nephropathy, and is not present at the onset of diabetes,[7] unless some other kidney disease is present. In contrast, up to 20% of patients with type 2 diabetes may have increased albumin excretion at the time of diagnosis, suggesting the presence of another cause of CKD, such as obesity-related glomerulopathy, or early DKD. Historical data suggest that, without treatment, up to 80% of albuminuric patients with type 1 diabetes develop more significant levels of albuminuria (>300 mg/24 h, historically called macroalbuminuria). Of such patients, 50–75% reach ESRD within 10–20 years. In type 2 diabetes, in contrast, approximately 40% of patients with albuminuria show further increases in albuminuria levels and 20% reach ESRD within the same time frame.[8]

Over the past decade or more, it has become evident that the natural history presented above is not always followed by patients with progressive DKD. In the Diabetes Control and Complications Trial and the follow-up Epidemiology of Diabetes Interventions and Complications study of participants with type 1 diabetes, 28% of the patients with an estimated GFR <60 mL/min/1.73 m^2 did not have abnormal albuminuria.[9–11] It appears that somewhere between 5% and 30% of type 1 DKD patients develop only transient albuminuria or never develop albuminuria, yet still develop progressive nephropathy that is similar pathologically to that in patients with albuminuria and progressive DKD.[12,13] Similarly, a progressive decline in GFR to ESRD in the absence of albuminuria progression occurs in up to 50% of type 2 diabetic patients.[14,15] These changes in DKD patterns may be the result of widespread use of agents such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) that reduce proteinuria but fail to retard progression of disease in some patients. Moreover, enhanced hypertension control in diabetic patients can reduce albuminuria and may have contributed to the generalized reduction in albuminuria seen in DKD patients. Finally, a number of type 2 diabetic patients develop albuminuria before the onset of their diabetes. In some of these individuals, this reflects the presence of generalized endothelial dysfunction rather than glomerular pathology.[16] In addition, kidney disease can result directly from obesity, insulin resistance, and the metabolic syndrome,[17,18] all of which routinely precede the onset of type 2 diabetes. The type of kidney pathology seen in such individuals diverges in several aspects from that of DKD.[19,20] Little is known about the prognosis for kidney disease in such patients in the absence of diabetes. Finally, there is evidence that a number of patients, especially those with type 2 diabetes, develop either nondiabetic kidney diseases or a modified form of DKD, and therefore follow a different clinical course than "typical" DKD patients.

DIAGNOSIS OF DKD

The diagnosis of DKD is made provisionally by detection of persistently elevated albuminuria and/or decline in eGFR in patients with type 1 DM 5 or more years after the onset of DM, or in patients with type 2 DM at or after the time of diagnosis. The American Diabetes Association (ADA) recommends that urinary albumin excretion and eGFR be assessed at least once a year in patients with type 1 diabetes with duration of ≥5 years, in all patients with type 2 diabetes, and in all diabetic patients with comorbid hypertension.[21] Urinary albumin excretion has a wide intraindividual variability, due to a number of reasons, including exercise within 24 h, fever, urinary tract infection, uncontrolled hypertension, marked hyperglycemia, menstruation, and congestive heart failure, all of which can elevate albuminuria independently of kidney damage. Because of this variability, the diagnosis of albuminuria requires its detection in at least 2 out of 3 tests performed over a period of 3–6 months. To detect albuminuria, measurement of a random spot urinary albumin:creatinine ratio (UACR) is preferred for convenience. According to the ADA, timed or 24-hour collections are more burdensome and add little to prediction or accuracy.[21] Once the diagnosis of persistent albuminuria is established, yearly or more frequent measurement of albumin:creatinine ratio (ACR) or urinary protein:creatinine ratio (UPCR) should be performed for monitoring of clinical response or assessment of progression of CKD.[21]

S[Cr] values and estimation of GFR should be obtained at baseline and at least annually. Most eGFR formulae are based on S[Cr] and the patient's age, gender, and ethnicity. Both the Modification of Diet in Renal Disease (MDRD)[22] and Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI)[23] formulae provide reasonable estimates of true GFR in patients with GFRs significantly below normal. However, such creatinine-based formulae are increasingly inaccurate

when the GFR is above 60 mL/min[22,23] and appear to systematically underestimate measured GFR.[24] They also are inaccurate in patients with cachexia where S [Cr] is substantially influenced by muscle mass. In these circumstances, use of a cystatin C-based eGFR formula may be helpful[25] and may better predict cardiovascular events in diabetic populations[26] although its superiority over the creatinine-based CKD-EPI formula for estimation of true GFR has not been uniformly confirmed.[27] Longitudinal data also suggest that the degree of decline in GFR in diabetic patients may be underestimated using eGFR formulae.[28]

The diagnostic evaluation of DKD requires a baseline history, a thorough physical examination, including accurate measurement of resting seated blood pressure, assessment of retinopathy, and laboratory evaluation that includes measurement of urinary albumin, and estimation of GFR. Genitourinary complications such as neurogenic bladder, papillary necrosis, and hydronephrosis are common in diabetic patients, so obtaining a baseline kidney ultrasound may be informative. In patients with type 1 diabetes, the diagnosis of DKD is made largely on clinical grounds, as a patient with a history of diabetes for over 10 years and albuminuria, and some degree of diabetic retinopathy has greater than a 90% likelihood of manifesting DKD,[29] and other types of kidney disease are unusual in this group.

In contrast, diabetic retinopathy coexists less frequently with early DKD in type 2 diabetic individuals. In some reports, over 50% of type 2 diabetic patients were found to have evidence of other types of kidney disease, often in addition to DKD.[30,31] However, these reports have been based on kidney biopsies performed for clinical reasons and have been limited by their lack of racial diversity. Therefore, it is not clear that they are representative of typical type 2 diabetic patients. There is a general impression that the prevalence of nondiabetic forms of CKD in North American patients with type 2 diabetes is lower than the figures suggested by these reports. More precise data will be obtained as more trials that include kidney biopsies of diabetic patients are performed, such as are planned by the Kidney Precision Medicine Project (https://kpmp.org). At present, there needs to be an individualized and nuanced approach to the diagnosis of nephropathy in type 2 diabetic patients, including the performance of kidney biopsies, particularly in those patients who manifest nephropathy very early in the course of their diabetes, develop early and progressive nephrotic range proteinuria, demonstrate substantial glomerular hematuria (as demonstrated by dysmorphic red blood cells or red blood cell casts), or who have a rapid decline in GFR.

MANAGEMENT OF DKD

Glycemic Control

The ADA recommends a target HbA1c of <7% to prevent or retard nephropathy and other microvascular complications of diabetes.[32] As red blood cell survival is reduced in progressive CKD, reliance on HbA1c should be limited, and the clinician should depend more on random or continuous home blood glucose monitoring in patients with advanced CKD and ESRD.[33] The role of intensive control of blood sugar in prevention of DKD was tested in two landmark trials.[34,35] The DCCT/EDIC studies showed a 39% decrease in development of albuminuria of <300 mg/day and a 54% reduction in rate of albuminuria of >300 mg/day in type 1 diabetic patients.[34] The United Kingdom Prospective Diabetes Study (UKPDS) revealed a 25% risk reduction in the composite microvascular complication endpoint in the groups that underwent intensive control of blood sugar compared to patients receiving what was standard control in the 1980s and early 1990s in type 2 diabetes.[35] A smaller trial in Japanese type 2 patients, the Kumamoto trial, revealed a 60% reduction of albuminuria >300 mg/day with intensive glycemic control in type 2 diabetes.[36] Both DCCT and UKPDS cohorts showed that intensive therapy early in the course of diabetes led to a substantial and significant reduction in the incidence of microvascular complications for decades after the difference in glycemic control between the two groups had been eliminated. This phenomenon, known as "metabolic memory," may be responsible for the reduction in the annual incidence of DKD development over the last two decades.[37,38] However, some prominent investigators have argued that intensive control has merely delayed the onset of DKD and not altered the percentage of patients who ultimately develop this complication, or the rate by which it progresses.[39]

It appears that the most beneficial impact of tight glycemic control is achieved if applied early in the course of diabetes. In elderly patients (aged over 65 years) and in those with longstanding diabetes and cardiovascular disorders, evidence does not support intensive lowering of blood sugar.[40,41] In fact, there is some evidence for harm associated with intensive lowering of blood sugar in patients with type 2 diabetes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed no significant reduction in cardiovascular events but revealed a higher mortality by targeting HbA1c below 6% compared to its conventional target of 7–7.9%.[41] There is no identified cut-point for HbA1c below which the beneficial effect of blood glucose–lowering strategies levels off, but increased risk of

hypoglycemia and mortality at lower levels of HbA1c can be counterproductive. Therefore, the appropriate target HbA1c should be individualized according to features such as age, stage of CKD, and comorbid conditions, reserving control of blood sugar with HbA1c <7% for younger patients without other comorbidities and levels >7% for older patients with advanced stages of CKD and cardiovascular comorbidities.

As recommended by the ADA, metformin is the first-line pharmacologic agent for treatment of hyperglycemia in patients with type 2 diabetes,[4] including those with DKD. Metformin is effective, safe, and inexpensive, and may reduce the risk of cardiovascular events and death.[42,43] Compared to sulfonylureas, metformin has beneficial effects on A1C, weight, and cardiovascular mortality.[42] In the past, metformin was felt to be contraindicated in CKD patients with S[Cr] >1.5 mg/dL, because of its structural similarity to phenformin, which caused lactic acidosis in diabetic patients. However, there is substantial evidence that this prohibition was overly restrictive. Importantly, significant lactic acidosis appears to be no more common in patients prescribed metformin than in those who received other glucose-lowering agents.[44] In response to these observations in 2016, the Food and Drug Administration (FDA) changed the guidelines for metformin use with the following points: (1) metformin use in CKD patients should be based on eGFR and not S[Cr]; eGFR screening should be performed before and at least annually during metformin treatment; (2) metformin can be used when the eGFR is <60 mL/min/1.73 m^2, should be monitored closely when eGFR is <45 mL/min/1.73 m^2, should be stopped when the eGFR reaches 30 mL/min/1.73 m^2, and should not be started between eGFRs of 30 and 45 mL/min/1.73 m^2; (3) metformin should be held before iodinated contrast procedures if the eGFR is 30–60 mL/min/1.73 m^2 or if there is any liver disease, alcoholism, or heart failure, or if intraarterial contrast is used. If held, recheck the eGFR 48 h after the procedure and restart metformin when renal function is stable (https://www.fda.gov/Drugs/DrugSafety/ucm493244.htm). In addition, periodic measurement of vitamin B12 should be considered with long-term use of metformin, especially in the presence of anemia and peripheral neuropathy, as it may be associated with vitamin B12 deficiency.[4]

In addition to lifestyle modification, antihyperglycemic therapy, and metformin, addition of agents with proven effect on reduction of cardiovascular events, such as SGLT2 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, should be considered for glycemic control in patients with type-2 diabetes and established atherosclerotic cardiovascular disease.[4] SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) lower glucose levels by blocking glucose reabsorption by the proximal renal tubules. In addition to glucose-lowering properties, and cardiovascular protection, they also promote weight loss and reduce blood pressure. In the EMPA-REG OUTCOME trial, the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke was significantly lower in the empagliflozin arm.[45] In the CANVAS trial, canagliflozin showed a similar cardiovascular protection by lowering major cardiac events compared to standard care.[46]

There is also a strong indication from these trials that SGLT2 inhibitors prevent eGFR decline and development of albuminuria. More convincing renal protection has recently been reported by the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial which studied the effects of canagliflozin treatment in macroalbuminuric patients with DKD and eGFR between 30 and 90 mL/min/1.73m^2 already receiving maximum tolerated standard treatment (including ACEIs or ARBs). In this trial, canagliflozin reduced the development of ESRD, doubling of S[Cr] and cardiovascular or renal death by 30%.[47] While currently SGLT2 inhibitors are approved only for patients with eGFRs >45 mL/min/1.73 m^2 this restriction may well be altered in the near future based on the demonstrated efficacy of canagliflozin on renal outcomes in participants with eGFRs down to 30 mL/min/1.73 m^2. It should be noted that SGLT2 inhibitors are contraindicated all type 1 diabetic patients, due in part to the higher incidence of diabetic ketoacidosis in patients using these drugs.[48,49]

GLP-1 receptor agonists, such as lixisenatide, liraglutide, semaglutide, exenatide, lower glucose by stimulating glucose-dependent insulin secretion, suppressing glucagon secretion, slowing gastric emptying, and reducing appetite.[50] Liraglutide, in the LEADER trial,[51] and semaglutide, in the SUSTAIN-6 trial,[52] were shown to decrease the rate of major cardiac events, and both are approved by the FDA as adjunct agents for lowering blood glucose in patients with type 2 diabetes.[53,54] It is yet unclear whether GLP-1 receptor agonists prevent progression of CKD to ESRD. Like the SGLT2 inhibitors, GLP-1 agonists are contraindicated in patients with eGFR <30 mL/min/1.73 m^2 and cannot be prescribed for type 1 diabetic patients.

Blood Pressure Control and ACEI and ARB Therapy in DKD

In patients with type 1 diabetes, hypertension usually develops around or after the time of the appearance of DKD, but in type 2 diabetes patients it frequently precedes the onset of DKD, often as a manifestation of the metabolic syndrome or due to obesity.[8] Home blood

pressure measurement in hypertensive patients has been endorsed by a number of international societies and often provides a better picture of blood pressure control by providing more numerous readings and elimination of the "white coat" effect.[55,56] Reliance on home BP measurements requires adequate education regarding proper timing and technique, but many studies have demonstrated the reliability of such data and its superiority over routine clinic BP measurement.[57,58] Such monitoring appears to result in improved BP control when coupled with cointerventions, systematic medication titration, education, and lifestyle counseling.[59] As autonomic dysfunction is a common finding in patients with diabetes, orthostatic BP measurements should be obtained.

Reduction of BP in hypertensive patients with DKD has been uniformly found to reduce the incidence of major cardiovascular events and to delay the progression of DKD.[60–64] The optimal range of BP control in hypertensive patients with diabetes has been an area of controversy, and the subject of several clinical trials in the past decade. The ADA currently recommends that most patients with diabetes should have an average seated BP of <140/90 mm Hg, although lower BP targets may be appropriate for individuals at high risk of cardiovascular disease.[65] This necessitates initiation of at least one antihypertensive medication besides lifestyle modification, if the confirmed measure of office BP is ≥140/90 mm Hg, and two antihypertensive medications if the level is ≥160/100 mm Hg.[65] The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for BP control, which were last updated in 2012, also recommend reduction of BP to ≤140/90 mm Hg, using blood pressure–lowering agents if the daily urinary albumin excretion is <30 mg, but recommend further reduction to ≤130/80 mm Hg if daily albumin excretion is >30 mg.[66] Conversely, the newer American Heart Association/American College of Cardiology guidelines issued in 2017 argue for more aggressive control of BP and redefine hypertension as an average seated BP of 130/80 mm Hg or above.[67] Other than the KDIGO guidelines, none of these are specific for CKD patients, and none of the current guidelines have specific guidelines for DKD. The ACCORD trial showed no consistent benefit of lowering systolic BP to <120 mm Hg vs. to <140 mm Hg for diabetic patients including those with early DKD.[68] Specifically, this study found no significant difference in the composite outcome of fatal and nonfatal major cardiovascular events in patients randomized to a systolic blood pressure of <120 mm Hg compared to a less-intensive target of range of <140 mm Hg. Although intensive lowering of blood pressure was associated with a significantly lower incidence of stroke, it was also associated with a significantly higher number of severe adverse outcomes including deaths, life-threatening events, persistent or significant disabilities, hospitalizations, and prolongations of hospital stay, which were numerically greater than the reduction in the number of strokes.[68] Conversely, the SPRINT study, which studied participants at high cardiovascular risk (including CKD patients) but not diabetic patients, found a significant improvement in cardiovascular outcomes with lowering of systolic BP to ≤120 mm Hg.[69] Our conclusion from these conflicting data is that BP control in DKD patients needs to be individualized. The lower the systolic BP, the lower will be the likely cardiovascular risk, but the higher will be the risk of adverse events, including acute kidney injury. Therefore, a more aggressive target than BP of ≤140/90 mm Hg should be individually applied, with the active participation of the patient until more definitive data from future randomized controlled trials (RCTs) are obtained (Table 51.1).

Uncontrolled hypertension is a major contributing factor to progression of DKD.[70] In established DKD patients with hypertension and albuminuria >300 mg/day, well-designed RCTs have shown a beneficial effect of ACEIs or ARBs compared to other antihypertensives on the progression of DKD.[60,63,64] The Collaborative Study Group trial of patients with type 1 DKD randomized to either captopril 25 mg three times a day or placebo showed a reduction in the primary endpoint of doubling of S[Cr] by 56%, and the combined endpoints of death, dialysis, and transplantation by 50%.[63] ARBs were tested in most clinical trials of type 2 DKD, because these studies came after ACEI therapy was already standard of care for treatment of DKD. In general, these studies showed a less-dramatic effect on the progression of DKD in type 2 patients than did the ACEI studies in type 1 patients. For example, the Irbesartan Diabetic Nephropathy Trial (IDNT) randomization of DKD subjects with hypertension to three subgroups (irbesartan 300 mg/day, amlodipine 10 mg/day, or placebo), revealed a 20% reduction with ARB treatment in the primary composite outcome (doubling of S[Cr], development of ESRD, or death) compared to placebo, and 23% reduction compared to amlodipine, over a mean follow-up period of 2.6 years.[64] In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study (RENAAL), type 2 DKD subjects were randomized to losartan vs. placebo. The risk of doubling of S[Cr] was reduced by 25% and incident ESRD by 28% in the losartan group.[60] This difference in effect size in type 1 and type 2 DKD was assumed to be due to differences in the patient populations tested. Although there has never been a head-to-head comparison of ACEIs and ARBs, there is no evidence that one class works better than the other for DKD associated

TABLE 51.1 Recommendations for Management of Diabetic Kidney Disease (DKD).

Management Item	Recommendation
Prevention	The target for adequate glycemic control is an HbA1c of ≤7%.
	An average seated blood pressure of <140/90 mm Hg should be maintained.
	Metformin is the first-line agent for glycemic control in type 2 diabetic patients with eGFR >45 mL/min/1.73 m^2. Given recent findings regarding their cardiovascular and renal protective effects, SGLT2 inhibitors should be considered as second line agents for this subset of type 2 diabetic patients.
	ACEI or ARB therapy is not recommended for primary prevention of DKD. However, ACEIs and ARBs are among the recommended agents for treatment of hypertension in type 1 and type 2 diabetic patients without nephropathy.
Screening and Diagnosis	Measurement of S[Cr] and monitoring for albuminuria (UACR >30 mcg/mg) should be performed annually starting 5 years after diagnosis of type 1 diabetes and at the time of diagnosis of type 2 diabetes.
	Confirm persistent albuminuria by two of three positive tests within a 3–6-month period after eliminating spurious causes of albuminuria.
	Type 1 diabetes: Persistent albuminuria and/or elevated S[Cr] (reduced eGFR) along with diabetic retinopathy is consistent with the diagnosis of DKD.
	Type 2 diabetes: Persistent albuminuria and/or elevated S[Cr] (reduced eGFR) with diabetic retinopathy is consistent with the diagnosis of DKD. Kidney biopsy should be considered when diagnoses other than DKD are suspected.
Treatment	Control of BP to a seated average BP of <140/90 mm Hg will prevent progression of DKD and the incidence of major cardiovascular events. Targeting a BP level of <130/80 mm Hg is encouraged when safe for individual patients.
	ACEIs or ARBs are the first-line antihypertensive therapy for nonpregnant hypertensive patients with DKD to reduce the incidence of major cardiovascular events and progression of DKD. Combined ACEI and ARB therapy is not recommended.
	Normotensive nonpregnant patients with DKD should also be treated with an ACEI or ARB, as tolerated, to reduce progression of DKD.
	Diuretics, mineralocorticoid receptor antagonists, calcium channel blockers, and beta blockers can be used in combination with ACEIs or ARBs to control blood pressure.
	A daily protein intake of 0.8 g/kg body weight is recommended for all nondialysis-dependent DKD patients.
	Lifestyle modification including exercise, weight loss, smoking cessation, and dietary consultation. Reduction of daily protein intake to 0.8–1.0 g/kg body weight should be considered in DKD patients with eGFR >30 mL/min/1.73 m^2 and further reduction to 0.8 g/kg/body weight is recommended in patients with stage 4 or 5 DKD.
	Preparation for renal replacement therapy, including referral to a nephrologist at stage 4 CKD to allow adequate time for required education, and choice of therapy including transplantation, and creation of dialysis access, if indicated is recommended. Lifestyle modification including exercise, weight loss, smoking cessation, and dietary consultation should be recommended.

ACEI, angiotensin-converting enzyme inhibitor; *UACR*, urine albumin:creatinine ratio; *ARB*, angiotensin receptor blocker; *CKD*, Chronic kidney disease; *eGFR*, estimated glomerular filtration rate; *S[Cr]*, Serum creatinine; *SGLT2*, sodium-glucose cotransporter 2.

with either type 1 or type 2 diabetes. ACEIs are often used preferentially due to lower cost and more extensive track record. However, in general the choice of class and specific agent for treatment should depend on tolerability, affordability, and physician and patient preference.

An increase in the level of S[Cr] of approximately 30% above baseline with initiation of renin–angiotensin–aldosterone system blockade is expected and is associated with better preservation of renal function in the long term. However, a more severe decline in renal function, particularly if associated with flash pulmonary edema, may reflect underlying renal artery stenosis. In these rare circumstances ACEI or ARB therapy should be immediately halted. Sometimes, at advanced stages of CKD, ACEIs or ARBs may be withdrawn to help extend the time off dialysis, to mitigate severe hyperkalemia or for other reasons. However, the relative benefits of this approach vs. maintaining ACEI or ARB therapy is not known. To date there have been no published studies assessing the benefits of ACEI/ARB therapy in cardiovascular risk reduction or CKD progression in advanced nondialysis CKD. An

ongoing clinical trial, the STOP ACEI study, should help elucidate the relative benefits and risks of ACEIs/ARBs on renal function and cardiovascular outcomes use in advanced CKD.[71]

Because dual therapy with an ACEI and an ARB results in more complete inhibition of angiotensin II signaling, better control of blood pressure, and a greater reduction in proteinuria, it was hoped that dual ACEI and ARB therapy would lead to even better outcomes in DKD than seen with use of either class of agents alone. However, several randomized controlled trials in the last decade have shown this not to be the case. Both the ONTARGET[72] and NEPHRON-D[73] studies of dual ACEI and ARB therapy showed no significant improvement in cardiac or renal outcomes with combined therapy. Although the ONTARGET trial included few patients with DKD, the NEPHRON-D study focused on this population. In both studies combination therapy was significantly associated with adverse events, including hyperkalemia, hypotension, and acute kidney injury. Thus, dual therapy with an ACEI and ARB is not generally indicated for patients with DKD.

Control of blood pressure in patients with diabetes usually requires prescription of two or more antihypertensive medications. Thiazide diuretics in combination with an ACEI or ARB have been shown to provide additional benefit by providing better reduction of blood pressure, lowering the risk of hyperkalemia, and better augmentation of the antiproteinuric effects of RAAS blockade.[74] Although increased insulin resistance and hyperuricemia often accompany thiazide treatment, the favorable cardiovascular outcomes in diabetic subjects who received the thiazide-like diuretic, chlorthalidone, compared to those who received amlodipine or lisinopril in the ALLHAT study suggest that such metabolic side effects are outweighed by the protective effects of the diuretic.[75] The combination of thiazides with loop diuretics may provide better diuresis and blood pressure control, particularly in patients with salt-sensitive and volume-sensitive hypertension and in more advanced stages of CKD.

Mineralocorticoid receptor antagonists (MRAs), including spironolactone, eplerenone, and finerenone, appear to be underutilized in patients with DKD who are already on ACEI/ARB therapy. Aldosterone has a direct detrimental effect on renal function in diabetes independent of its effects on BP, possibly by enhancing MAP kinase activity and increasing TGF-β expression. Both processes have been implicated in the development of tubulointerstitial fibrosis.[76,77] Patients may develop a rebound increase of aldosterone levels within weeks to months of initiation of ACEI or ARB treatment, a process referred to as aldosterone escape.[78,79] Patients with aldosterone escape appear to have a faster decline of renal function.[80]

The addition of MRAs to ACEIs or ARBs in the treatment DKD patients has been tested in a few small RCTs. Collectively, these studies suggest significant sustained decline in proteinuria, better control of hypertension, and better preservation of renal function.[81–84] Although a significant decline in eGFR occurred immediately after initiation of MRAs in this setting, eGFR then stabilized as opposed to the continuous decline of kidney function found in patients receiving placebo.[84,85] It appears possible to minimize side effects such as hyperkalemia and gynecomastia while maintaining beneficial effects.[81] Two ongoing clinical trials, FIGARO-DKD and FIDELIO-DKD, will determine whether the MRA, finerenone, in addition to standard ACEI or ARB therapy will improve cardiovascular or renal outcomes in participants with progressive DKD (https://clinicaltrials.gov/ct2/show/NCT02545049).

Calcium channel blockers (CCBs) are often used, either with or without ACEIs or ARBs, for BP control in patients with DKD. The safety, efficacy, and similar impact of both dyhidropyridine and nondihydropyridine CCBs on cardiovascular mortality, cardiovascular events, and stroke compared to diuretics, betablockers, or their combinations have been demonstrated in several RCTs.[75,86,87] However, in type 2 diabetic hypertensive participants with or without DKD, there was a higher incidence of fatal and nonfatal myocardial infarction, in those treated with nisoldipine compared to those receiving ACEI or ARB therapy.[88] Similarly, there was a higher rate of the composite outcomes of doubling of S[Cr], ESRD, or death with amlodipine than with irbesartan in the IDNT study of patients with moderate DKD, though this rate was not higher than those treated with placebo.[64] However, a trial of over 11,000 patients with hypertension (approximately 1100 with CKD, and approximately 60% with diabetes) who were at high risk for cardiovascular events showed that the addition of amlodipine compared with the addition of hydrochlorothiazide to maximal ACEI therapy resulted in a major improvement in both cardiovascular and prespecified kidney endpoints.[89,90] Thus, it appears that therapy with CCBs may be beneficial in DKD patients already treated with an ACEI or ARB.

A recent large comparative effectiveness study from four integrated health care systems reinforced this approach. The study showed that CCBs have the best add-on effect to ACEI or ARB therapy in diabetic patients who have better cardiovascular and renal outcomes.[91] In this study, CCBs were associated with a lower risk of significant kidney events, a similar risk of cardiovascular events, and a suggestion of a lower risk of death, over 5 years of follow-up, compared with thiazide diuretics. Although beta blockers were also associated with a lower risk of significant kidney events, they

were associated with a higher risk of cardiovascular events compared with thiazide diuretics. These more recent studies are in accord with the now common practice of adding a CCB as the second antihypertensive agent after maximizing ACEI or ARB therapy in patients with DKD.

Beta blockers appear to be a less-favorable class of antihypertensive medications, due to their reduced effectiveness in preventing cardiovascular events, as well as their adverse metabolic side effects, such as an unfavorable lipid profile, hypoglycemic unawareness, and erectile dysfunction. However, they may help reduce sympathetic overactivity in CKD and therefore may be an effective adjunct therapy in DKD patients who require an additional antihypertensive medication after achieving maximal RAAS blockade[92] or when secondary prevention of cardiac outcomes is warranted.

Direct renin inhibitors also appear to be a less-favorable class of antihypertensives as they have no advantage over ACEI or ARB therapy and can cause significant adverse effects in combination with ACEIs or ARBs.[93,94] Thus, current FDA guidelines recommend avoidance of aliskiren in conjunction with ACEIs and ARBs in patients with DKD (https://www.fda.gov/Drugs/DrugSafety/ucm300889.htm).

Several trials have demonstrated that preemptive treatment with ACEIs or ARBs in normotensive diabetic patients without albuminuria does not reduce the incidence or severity of DKD. Therefore, ACEIs and ARBs are not recommended for primary prevention.[95,96] However, in normotensive diabetic patients with albuminuria, ACEIs or ARBs may be beneficial for patients at high risk of progression of DKD. Such high risk conditions include increasing albuminuria, decreasing GFR, increasing blood pressure, presence of retinopathy, worsening lipid profile, increasing uric acid, family history of hypertension, macrovascular disease, or DKD.[96] Moreover, the ADA recommends ACEIs, ARBs, thiazide diuretics, or dihydropyridine CCBs as first-line pharmacologic therapy for hypertension in diabetic patients without nephropathy.[65]

Lipid Control

The ADA recommends the use of lifestyle modification in all patients with diabetes, consisting of application of weight loss (when indicated), the reduction of saturated fat, trans fat, and cholesterol intake, increase of dietary n-3 fatty acids, viscous fiber, and plant stanols/sterols intake, and increased physical activity aimed at improving lipid profile.[65] For patients with atherosclerotic cardiovascular disease at all ages, high-intensity statins (atorvastatin 40–80 mg/day or rosuvastatin 20–40 mg/day) should be added to lifestyle modification regardless of lipoprotein levels. For patients with diabetes aged <40 years with atherosclerotic cardiovascular disease risk factors, any patients between 40 and 75 years, and those >75 years without atherosclerotic cardiovascular disease, use of moderate intensity statins can be considered (atorvastatin 10–20 mg/day, rosuvastatin 5–10 mg/day, simvastatin 20–40 mg/day, or pravastatin 40–80 mg/day).[65] In patients with atherosclerotic cardiovascular disease, if LDL is ≥70 mg/dL on maximally tolerated dose of statins, addition of another LDL lowering agent such as ezetimibe or PCSK9 inhibitor to the therapeutic regimen should be considered.[65] Despite demonstrated effectiveness of lipid-lowering medications in preventing cardiovascular events in patients with diabetes, similar efficacy in diabetic CKD patients has been demonstrated only in the last decade.[97–102] The Study of Heart and Renal Protection (SHARP) examined the effects of dual treatment with simvastatin and ezetimibe in CKD and dialysis patients, including those with diabetes.[97] This study clearly showed that the combination of simvastatin and ezetimibe led to a significant reduction in major atherosclerotic cardiovascular events but did not appear to reduce the progression of CKD. Despite the observed beneficial effect in nondialysis CKD patients, a subgroup analysis in dialysis patients revealed no cardiovascular benefit with use of statins.[97] This is consistent with results from the 4D, AROURA, and ALERT trials in which no cardiovascular survival benefit was noted in ESRD patients with use of statins.[103–105] The reasons for the lack of beneficial effects from statins on cardiovascular outcomes in dialysis patients are poorly understood and could be due, in part, to impaired reverse cholesterol transport system in ESRD[106] or may be due to differences in the type of cardiovascular events that affect dialysis patients.

Gemfibrozil and fenofibrate are also used frequently in DKD patients. The Diabetes Atherosclerosis Intervention Study and the Fenofibrate Intervention and Event Lowering in Diabetes Study reported a decrease in albuminuria and its regression toward normoalbuminuria with the use of fenofibrate.[107,108] In *post hoc* analysis of the Veterans' Affairs High-Density Lipoprotein Intervention Trial, gemfibrozil reduced the primary composite outcome of coronary death and nonfatal myocardial infarction, but not the need for revascularization or all-cause mortality in CKD.[109] Gemfibrozil when combined with statins increases the risk of increased transaminases and rhabdomyolysis. Gemfibrozil therefore should not be given combined with statins. It is not recommended for use in patients with severe reduction in GFR as well.

Dietary Protein Restriction

High intake of nondairy animal protein may accelerate reduction of renal function.[95] A number of studies, mostly conducted in the 1980s or 1990s, showed that moderate protein restriction reduced the progression of established DKD in terms of GFR decline, albuminuria, and occurrence of ESRD in both type 1 and type 2 diabetic patients.[110–112] Generally, dietary protein was restricted to 1 g/kg body weight/24 h or less in these studies. As current management of DKD has emphasized blood pressure control and ACEI or ARB treatment, it is unclear whether dietary protein restriction provides much additional benefit. Indeed, relatively small studies reported after 2001 have not confirmed a significant improvement in outcomes with similar degrees of dietary protein restriction.[113] However, modest dietary protein restriction may be helpful in a number of DKD patients and will likely do no harm. The ADA currently recommends a daily dietary protein intake of approximately 0.8 g/kg in individuals with nondialysis-dependent DKD.[21]

Other Lifestyle Modifications

In addition to calorie and protein intake, dietary evaluation and recommendations should emphasize sodium restriction in hypertensive DKD patients, as well as in potassium and phosphorus intake when CKD progresses. Exercise should be part of lifestyle modification as tolerated. Supplementation with monounsaturated and polyunsaturated fats have improved glycemic control, lowered blood pressure, reduced albuminuria, and altered high-risk inflammatory biomarkers in the general population and may be beneficial in patients with diabetes and CKD.[33] Smoking cessation and weight loss are integral parts of lifestyle modification, as smoking cessation ameliorates progression of early stage DKD.[114] Weight loss has beneficial renal effects by reducing proteinuria and decreasing blood pressure in patients with mild to moderate CKD with or without diabetes.[115,116] Aspirin (dose of 75–162 mg/day) is indicated for primary prevention of cardiovascular morbidities in all patients with cardiovascular risk factors (aged >50 years with family history of premature atherosclerotic cardiovascular disease, hypertension, dyslipidemia, smoking, or albuminuria), as well as for secondary prevention in patients with a history of atherosclerotic cardiovascular disease.[65] Similarly, low-dose daily aspirin is indicated in all pregnant patients with type 1 and type 2 diabetes, starting from the end of the first trimester until the birth of the baby, aimed at reducing the risk of preeclampsia.[117]

DIABETES IN ESRD

Between 2001 and 2015, adjusted mortality rates in the dialysis and kidney transplant populations declined by 28% and 3%, respectively. After accounting for changes in population characteristics, the adjusted mortality rates decreased by 40% for transplant recipients. These decreases in mortality likely reflect improved care along with an increase in the number of prevalent ESRD patients. In spite of this trend, up to 21.7% of diabetic patients die in the first year after initiation of dialysis and have a 5-year survival rate of only 37.9%,[118] giving ESRD patients with diabetes the highest mortality among all ESRD patients. Preparation for ESRD should start at least 6 months before the start of renal replacement therapy (RRT) is contemplated. Preparation should include education of patients and families regarding the process, prognosis, and different modalities of RRT and projected lifestyle changes. Consultation with a nephrologist for patients who reach stage 4 CKD reduces costs, improves quality of care, and delays dialysis.[119] Decision-making about the modality of RRT should be similar to that in other ESRD patients. Survival rates are much better in patients receiving kidney transplants compared to those treated with dialytic modalities.[120,121]

SUMMARY

DKD remains the leading cause of ESRD in the US and most developing countries. Table 51.1 provides a summary of the approach to prevention, screening, diagnosis, and treatment of diabetic nephropathy. Excellent glycemic control with an HbA1c of ≤7% can prevent or delay the development of DKD. Treatment with an SGLT2 inhibitor should be strongly considered for those patients with eGFR >45 ml/min/1.73 m^2. Treatment of elevated blood pressure to <140/90 mm Hg can also reduce the development and progression of nephropathy. Targeting a BP of <130/80 mm Hg should be considered when it is safe and tolerable. ACEI or ARB therapy is not recommended for primary prevention of DKD in normotensive patients with diabetes as it does not forestall nephropathy. However, ACEIs and ARBs are among the recommended agents for treatment of hypertension in type 1 and type 2 diabetic patients without nephropathy.

Diabetic patients should be monitored for the development of DKD. Measurement of S[Cr], calculation of eGFR, and monitoring for albuminuria (UACR >30) should be performed at least annually starting 5 years after diagnosis of type 1 diabetes, and at the time of diagnosis of type 2 diabetes. Persistent albuminuria should

be confirmed by 2 of 3 positive tests within a 3–6-month period, after eliminating spurious causes of albuminuria. The presence of persistent albuminuria and/or reduced eGFR along with diabetic retinopathy is consistent with the diagnosis of DKD in type 1 diabetic patients. The presence of persistent albuminuria and/or reduced eGFR with diabetic retinopathy is also generally consistent with the diagnosis of DKD in type 2 diabetic patients. However, there is a higher incidence of non-DKD in type 2 diabetic patients. Thus, other diagnoses should be considered, especially if there are acute or subacute increases in albuminuria or acute or subacute decreases in eGFR. Additional evaluation, including kidney biopsy, should be considered when a diagnosis other than DKD is suspected.

Control of blood pressure to a seated blood pressure of less than 140/90 mm Hg will prevent progression of DKD and decrease the incidence of major cardiovascular events. Reducing blood pressure to <130/80 mm Hg is encouraged if tolerated and not contraindicated for other medical reasons. Use of an ACEI or ARB as the first-line antihypertensive therapy is recommended for nonpregnant hypertensive patients with DKD to reduce the incidence of major cardiovascular events and progression of DKD. Combined ACEI and ARB therapy is not recommended. Normotensive nonpregnant patients with DKD should also be treated with an ACEI or ARB, as tolerated, to reduce progression of DKD. Diuretics, MRAs, CCBs, and beta blockers can be used in combination with ACEIs or ARBs to control BP.

Reduction of daily protein intake to 0.8 g/kg body weight is recommended in DKD patients who are not treated with dialysis. Lifestyle modification, including exercise, weight loss, smoking cessation, and dietary consultation should be incorporated into a multidisciplinary approach to treatment for DKD patients. Preparation for RRT, including referral to a nephrologist, should begin when patients reach stage 4 CKD to allow adequate time for required education, and choice of RRT including transplantation, and creation of dialysis access, as indicated.

References

1. USRDS. *Chapter 1: incidence, prevalence, patient characteristics, and treatment modalities*. 2017. https://www.usrds.org/2017/download/v2_c01_IncPrev_17.pdf.
2. Brosius FC, Saran R. Do we now have a prognostic biomarker for progressive diabetic nephropathy? *J Am Soc Nephrol* 2012;**23**:376–7.
3. Brosius FC, Khoury CC, Buller CL, Chen S. Abnormalities in signaling pathways in diabetic nephropathy. *Expert Rev Endocrinol Metab* 2010;**5**:51–64.
4. American Diabetes A. 8. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2018. *Diabetes Care* 2018;**41**:S73–85.
5. Tuttle KR, Bruton JL, Perusek MC, Lancaster JL, Kopp DT, DeFronzo RA. Effect of strict glycemic control on renal hemodynamic response to amino acids and renal enlargement in insulin-dependent diabetes mellitus. *N Engl J Med* 1991;**324**:1626–32.
6. Vora JP, Dolben J, Dean JD, et al. Renal hemodynamics in newly presenting non-insulin dependent diabetes mellitus. *Kidney Int* 1992;**41**:829–35.
7. Mogensen CE. How to protect the kidney in diabetic patients: with special reference to IDDM. *Diabetes* 1997;**46**(Suppl. 2):S104–11.
8. Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH. Diabetic nephropathy. *Diabetes Care* 2003;**26**(Suppl. 1):S94–8.
9. Molitch ME, Steffes M, Sun W, et al. Development and progression of renal insufficiency with and without albuminuria in adults with type 1 diabetes in the diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. *Diabetes Care* 2010;**33**:1536–43.
10. Penno G, Russo E, Garofolo M, et al. Evidence for two distinct phenotypes of chronic kidney disease in individuals with type 1 diabetes mellitus. *Diabetologia* 2017;**60**:1102–13.
11. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. *N Engl J Med* 2003;**348**:2285–93.
12. Marshall SM. Natural history and clinical characteristics of CKD in type 1 and type 2 diabetes mellitus. *Adv Chron Kidney Dis* 2014;**21**:267–72.
13. Robles NR, Villa J, Gallego RH. Non-proteinuric diabetic nephropathy. *J Clin Med* 2015;**4**:1761–73.
14. Chen C, Wang C, Hu C, et al. Normoalbuminuric diabetic kidney disease. *Front Med* 2017;**11**:310–8.
15. Robles NR, Villa J, Felix FJ, Fernandez-Berges D, Lozano L. Non-proteinuric diabetic nephropathy is the main cause of chronic kidney disease: results of a general population survey in Spain. *Diabetes Metab Syndr* 2017;**11**(Suppl. 2):S777–81.
16. Lim SC, Caballero AE, Smakowski P, LoGerfo FW, Horton ES, Veves A. Soluble intercellular adhesion molecule, vascular cell adhesion molecule, and impaired microvascular reactivity are early markers of vasculopathy in type 2 diabetic individuals without microalbuminuria. *Diabetes Care* 1999;**22**:1865–70.
17. Cheng HT, Huang JW, Chiang CK, Yen CJ, Hung KY, Wu KD. Metabolic syndrome and insulin resistance as risk factors for development of chronic kidney disease and rapid decline in renal function in elderly. *J Clin Endocrinol Metab* 2012;**97**:1268–76.
18. Decleves AE, Sharma K. Obesity and kidney disease: differential effects of obesity on adipose tissue and kidney inflammation and fibrosis. *Curr Opin Nephrol Hypertens* 2015;**24**:28–36.
19. Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD. Obesity-related glomerulopathy: an emerging epidemic. *Kidney Int* 2001;**59**:1498–509.
20. Praga M, Hernandez E, Morales E, et al. Clinical features and long-term outcome of obesity-associated focal segmental glomerulosclerosis. *Nephrol Dial Transplant* 2001;**16**:1790–8.
21. American Diabetes Association. 10. Microvascular complications and foot care: standards of medical care in diabetes-2018. *Diabetes Care* 2018;**41**:S105–18.
22. Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. *Ann Intern Med* 2004;**141**:929–37.
23. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12.

24. MacIsaac RJ, Ekinci EI, Premaratne E, et al. The Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation does not improve the underestimation of Glomerular Filtration Rate (GFR) in people with diabetes and preserved renal function. *BMC Nephrol* 2015;**16**:198.
25. Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med* 2013;**369**:932–43.
26. Schottker B, Herder C, Muller H, Brenner H, Rothenbacher D. Clinical utility of creatinine- and cystatin C-based definition of renal function for risk prediction of primary cardiovascular events in patients with diabetes. *Diabetes Care* 2012;**35**:879–86.
27. Iliadis F, Didangelos T, Ntemka A, et al. Glomerular filtration rate estimation in patients with type 2 diabetes: creatinine- or cystatin C-based equations? *Diabetologia* 2011;**54**:2987–94.
28. Gaspari F, Ruggenenti P, Porrini E, et al. The GFR and GFR decline cannot be accurately estimated in type 2 diabetics. *Kidney Int* 2013; **84**(1):164–73.
29. Parving HH, Hommel E, Mathiesen E, et al. Prevalence of microalbuminuria, arterial hypertension, retinopathy and neuropathy in patients with insulin dependent diabetes. *Br Med J* 1988;**296**: 156–60.
30. Prakash J. Non-diabetic renal disease (NDRD) in patients with type 2 diabetes mellitus (type 2 DM). *J Assoc Phys India* 2013;**61**: 194–9.
31. Sharma SG, Bomback AS, Radhakrishnan J, et al. The modern spectrum of renal biopsy findings in patients with diabetes. *Clin J Am Soc Nephrol* 2013;**8**:1718–24.
32. American Diabetes A. 6. Glycemic targets: standards of medical care in diabetes-2018. *Diabetes Care* 2018;**41**:S55–64.
33. Perkovic V, Agarwal R, Fioretto P, et al. Management of patients with diabetes and CKD: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) controversies conference. *Kidney Int* 2016;**90**:1175–83.
34. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977–86.
35. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;**352**:837–53.
36. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care* 2000;**23**(Suppl. 2):B21–9.
37. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *J Am Med Assoc* 2003;**290**:2159–67.
38. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;**359**:1577–89.
39. Krolewski AS, Bonventre JV. High risk of ESRD in type 1 diabetes: new strategies are needed to retard progressive renal function decline. *Semin Nephrol* 2012;**32**:407–14.
40. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;**358**:2560–72.
41. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;**358**: 2545–59.
42. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2016;**164**:740–51.
43. Rojas LB, Gomes MB. Metformin: an old but still the best treatment for type 2 diabetes. *Diabetol Metab Syndrome* 2013;**5**:6.
44. Eurich DT, Weir DL, Majumdar SR, et al. Comparative safety and effectiveness of metformin in patients with diabetes and heart failure: systematic review of observational studies involving 34000 patients. *Circ Heart Fail* 2013;**6**(3):395–402.
45. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–28.
46. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; **377**:644–57.
47. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW. CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2019;**380**:2295–306.
48. Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation* 2014;**129**: 587–97.
49. Perkins BA, Cherney DZ, Partridge H, et al. Sodium-glucose cotransporter 2 inhibition and glycemic control in type 1 diabetes: results of an 8-week open-label proof-of-concept trial. *Diabetes Care* 2014;**37**:1480–3.
50. Holst JJ. Incretin hormones and the satiation signal. *Int J Obes* 2013;**37**:1161–8.
51. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; **375**:311–22.
52. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; **375**:1834–44.
53. Satoh S, Ueda Y, Koyanagi M, et al. Chronic inhibition of Rho kinase blunts the process of left ventricular hypertrophy leading to cardiac contractile dysfunction in hypertension-induced heart failure. *J Mol Cell Cardiol* 2003;**35**:59–70.
54. Sgadari C, Barillari G, Toschi E, et al. HIV protease inhibitors are potent anti-angiogenic molecules and promote regression of Kaposi sarcoma. *Nat Med* 2002;**8**:225–32.
55. Parati G, Stergiou GS, Asmar R, et al. European society of hypertension guidelines for blood pressure monitoring at home: a summary report of the second international consensus conference on home blood pressure monitoring. *J Hypertens* 2008;**26**:1505–26.
56. Pickering TG, Miller NH, Ogedegbe G, Krakoff LR, Artinian NT, Goff D. Call to action on use and reimbursement for home blood pressure monitoring: executive summary: a joint scientific statement from the American Heart Association, American Society of Hypertension, and Preventive Cardiovascular Nurses Association. *Hypertension* 2008;**52**:1–9.
57. Imai Y, Hosaka M, Elnagar N, Satoh M. Clinical significance of home blood pressure measurements for the prevention and management of high blood pressure. *Clin Exp Pharmacol Physiol* 2014; **41**:37–45.
58. Imai Y, Obara T, Asamaya K, Ohkubo T. The reason why home blood pressure measurements are preferred over clinic or ambulatory blood pressure in Japan. *Hypertens Res* 2013;**36**:661–72.
59. Tucker KL, Sheppard JP, Stevens R, et al. Self-monitoring of blood pressure in hypertension: a systematic review and individual patient data meta-analysis. *PLoS Med* 2017;**14**:e1002389.
60. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**:861–9.

61. Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000; **23**(Suppl. 2):B54–64.
62. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998;**351**:1755–62.
63. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993;**329**: 1456–62.
64. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**: 851–60.
65. American Diabetes A. 9. Cardiovascular disease and risk management: standards of medical care in diabetes-2018. *Diabetes Care* 2018;**41**:S86–104.
66. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**: 73–90.
67. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;**71**: e127–248.
68. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;**362**:1575–85.
69. Group SR, Wright Jr JT, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103–16.
70. Van Buren PN, Toto R. Hypertension in diabetic nephropathy: epidemiology, mechanisms, and management. *Adv Chron Kidney Dis* 2011;**18**:28–41.
71. Bhandari S, Ives N, Brettell EA, et al. Multicentre randomized controlled trial of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker withdrawal in advanced renal disease: the STOP-ACEi trial. *Nephrol Dial Transplant* 2016;**31**: 255–61.
72. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;**358**: 1547–59.
73. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;**369**:1892–903.
74. Palmer BF. Improving BP control with combined renin-angiotensin system blockade and thiazide diuretics in hypertensive patients with diabetes mellitus or kidney disease. *Am J Cardiovasc Drugs* 2008;**8**:9–14.
75. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *J Am Med Assoc* 2002;**288**:2981–97.
76. Fujisawa G, Okada K, Muto S, et al. Spironolactone prevents early renal injury in streptozotocin-induced diabetic rats. *Kidney Int* 2004;**66**:1493–502.
77. Terada Y, Kobayashi T, Kuwana H, et al. Aldosterone stimulates proliferation of mesangial cells by activating mitogen-activated protein kinase 1/2, cyclin D1, and cyclin A. *J Am Soc Nephrol* 2005;**16**:2296–305.
78. McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. *Circulation* 1999;**100**:1056–64.
79. Rump LC. Secondary rise of albuminuria under AT1-receptor blockade–what is the potential role of aldosterone escape? *Nephrol Dial Transplant* 2007;**22**:5–8.
80. Sato A, Hayashi K, Naruse M, Saruta T. Effectiveness of aldosterone blockade in patients with diabetic nephropathy. *Hypertension* 2003;**41**:64–8.
81. Epstein M, Williams GH, Weinberger M, et al. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clin J Am Soc Nephrol* 2006;**1**:940–51.
82. Mehdi UF, Adams-Huet B, Raskin P, Vega GL, Toto RD. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. *J Am Soc Nephrol* 2009;**20**:2641–50.
83. Saklayen MG, Gyebi LK, Tasosa J, Yap J. Effects of additive therapy with spironolactone on proteinuria in diabetic patients already on ACE inhibitor or ARB therapy: results of a randomized, placebo-controlled, double-blind, crossover trial. *J Investig Med* 2008;**56**:714–9.
84. van den Meiracker AH, Baggen RG, Pauli S, et al. Spironolactone in type 2 diabetic nephropathy: effects on proteinuria, blood pressure and renal function. *J Hypertens* 2006;**24**:2285–92.
85. Morcos M, Borcea V, Isermann B, et al. Effect of alpha-lipoic acid on the progression of endothelial cell damage and albuminuria in patients with diabetes mellitus: an exploratory study. *Diabetes Res Clin Pract* 2001;**52**:175–83.
86. Black HR, Elliott WJ, Grandits G, et al. Principal results of the controlled onset verapamil investigation of cardiovascular end points (CONVINCE) trial. *J Am Med Assoc* 2003;**289**:2073–82.
87. Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000;**356**:366–72.
88. Estacio RO, Schrier RW. Antihypertensive therapy in type 2 diabetes: implications of the appropriate blood pressure control in diabetes (ABCD) trial. *Am J Cardiol* 1998;**82**:9R–14R.
89. Bakris GL, Sarafidis PA, Weir MR, et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. *Lancet* 2010;**375**:1173–81.
90. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008;**359**:2417–28.
91. Schroeder EB, Chonchol M, Shetterly SM, et al. Add-on antihypertensive medications to angiotensin-aldosterone system blockers in diabetes: a comparative effectiveness study. *Clin J Am Soc Nephrol* 2018;**13**:727–34.
92. Ritz E, Rump LC. Do beta-blockers combined with RAS inhibitors make sense after all to protect against renal injury? *Curr Hypertens Rep* 2007;**9**:409–14.
93. Parving HH, Brenner BM, McMurray JJ, et al. Aliskiren trial in type 2 diabetes using cardio-renal endpoints (ALTITUDE): rationale and study design. *Nephrol Dial Transplant* 2009;**24**:1663–71.
94. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK. Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med* 2008;**358**:2433–46.
95. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl* 2012;**2**:363–9.
96. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis* 2012;**60**:850–86.

97. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**:2181–92.
98. Chonchol M, Cook T, Kjekshus J, Pedersen TR, Lindenfeld J. Simvastatin for secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal insufficiency. *Am J Kidney Dis* 2007;**49**:373–82.
99. Colhoun HM, Betteridge DJ, Durrington PN, et al. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). *Am J Kidney Dis* 2009;**54**:810–9.
100. Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;**361**:2005–16.
101. Shepherd J, Kastelein JJ, Bittner V, et al. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. *J Am Coll Cardiol* 2008;**51**:1448–54.
102. Tonelli M, Keech A, Shepherd J, et al. Effect of pravastatin in people with diabetes and chronic kidney disease. *J Am Soc Nephrol* 2005;**16**:3748–54.
103. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;**360**:1395–407.
104. Holdaas H, Fellstrom B, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet* 2003;**361**:2024–31.
105. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;**353**:238–48.
106. Vaziri ND. Lipotoxicity and impaired high density lipoprotein-mediated reverse cholesterol transport in chronic kidney disease. *J Ren Nutr* 2010;**20**:S35–43.
107. Ansquer JC, Foucher C, Rattier S, Taskinen MR, Steiner G. Fenofibrate reduces progression to microalbuminuria over 3 years in a placebo-controlled study in type 2 diabetes: results from the Diabetes Atherosclerosis Intervention Study (DAIS). *Am J Kidney Dis* 2005;**45**:485–93.
108. Davis TM, Ting R, Best JD, et al. Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. *Diabetologia* 2011;**54**:280–90.
109. Tonelli M, Collins D, Robins S, Bloomfield H, Curhan GC. Gemfibrozil for secondary prevention of cardiovascular events in mild to moderate chronic renal insufficiency. *Kidney Int* 2004;**66**:1123–30.
110. Hansen HP, Tauber-Lassen E, Jensen BR, Parving HH. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. *Kidney Int* 2002;**62**:220–8.
111. Pijls LT, de Vries H, Donker AJ, van Eijk JT. The effect of protein restriction on albuminuria in patients with type 2 diabetes mellitus: a randomized trial. *Nephrol Dial Transplant* 1999;**14**:1445–53.
112. Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR. Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 1991;**324**:78–84.
113. Wheeler ML, Dunbar SA, Jaacks LM, et al. Macronutrients, food groups, and eating patterns in the management of diabetes: a systematic review of the literature, 2010. *Diabetes Care* 2012;**35**:434–45.
114. Phisitkul K, Hegazy K, Chuahirun T, et al. Continued smoking exacerbates but cessation ameliorates progression of early type 2 diabetic nephropathy. *Am J Med Sci* 2008;**335**:284–91.
115. Afshinnia F, Wilt TJ, Duval S, Esmaeili A, Ibrahim HN. Weight loss and proteinuria: systematic review of clinical trials and comparative cohorts. *Nephrol Dial Transplant* 2010;**25**:1173–83.
116. Navaneethan SD, Yehnert H, Moustarah F, Schreiber MJ, Schauer PR, Beddhu S. Weight loss interventions in chronic kidney disease: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2009;**4**:1565–74.
117. American Diabetes A. 13. Management of diabetes in pregnancy: standards of medical care in diabetes-2018. *Diabetes Care* 2018;**41**:S137–43.
118. USRDS. *Chapter 6: mortality*. 2015. https://www.usrds.org/2015/download/vol2_06_Mortality_15.pdf.
119. Smart NA, Dieberg G, Ladhani M, Titus T. Early referral to specialist nephrology services for preventing the progression to end-stage kidney disease. *Cochrane Database Syst Rev* 2014:CD007333.
120. Rabbat CG, Thorpe KE, Russell JD, Churchill DN. Comparison of mortality risk for dialysis patients and cadaveric first renal transplant recipients in Ontario, Canada. *J Am Soc Nephrol* 2000;**11**:917–22.
121. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999;**341**:1725–30.
122. Couser WG. Primary membranous nephropathy. *Clin J Am Soc Nephrol* 2017;**12**:983–97.
123. Winkelmayer WC, Owen Jr WF, Levin R, Avorn J. A propensity analysis of late versus early nephrologist referral and mortality on dialysis. *J Am Soc Nephrol* 2003;**14**:486–92.
124. Yang JY, Huang JW, Chen L, et al. Frequency of early predialysis nephrology care and postdialysis cardiovascular events. *Am J Kidney Dis* 2017;**70**:164–72.
125. Mehrotra R, Devuyst O, Davies SJ, Johnson DW. The current state of peritoneal dialysis. *J Am Soc Nephrol* 2016;**27**:3238–52.
126. Shafi T, Mullangi S, Jaar BG, Silber H. Autonomic dysfunction as a mechanism of intradialytic blood pressure instability. *Semin Dial* 2017;**30**:537–44.
127. Tennankore KK, Na Y, Wald R, Chan CT, Perl J. Short daily-, nocturnal- and conventional-home hemodialysis have similar patient and treatment survival. *Kidney Int* 2018;**93**:188–94.
128. Schjoedt KJ, Astrup AS, Persson F, et al. Optimal dose of lisinopril for renoprotection in type 1 diabetic patients with diabetic nephropathy: a randomised crossover trial. *Diabetologia* 2009;**52**:46–9.

QUESTIONS AND ANSWERS

Question 1

A 58-year-old man is referred for evaluation of kidney disease associated with diabetes. He reports having type 2 diabetes for over 25 years. His diabetes has been under good control. He has chronic hypertension and hyperlipidemia. Six months ago S[Cr] was 1.0 mg/dL and UPCR was 0.12. On a routine clinic visit he is asymptomatic. His medications include lisinopril 20 mg a day, furosemide 20 mg a day, insulin glargine 10 units SQ at night, and atorvastatin 40 mg every night. On physical examination, seated blood pressure is 139/88 mm Hg, heart rate 80 beats per minute, weight 108 kg, and BMI 33 kg/m^2. There is no retinopathy or JVD. Heart sounds are normal and lungs are clear. Abdomen is soft and nontender without evidence of organomegaly. There is 3+ lower extremity pitting edema.

The following labs are obtained:

Serum chemistries
S[Na] 136 mEq/L
Serum potassium concentration (S[K]) 4.8 mEq/L
S[Cl] 103 mEq/L
tCO2 22 mEq/L
BUN 38 mg/dL
S[Cr] 1.5 mg/dL
Glucose 183 mg/dL
HbA1C 7.8%
LDL cholesterol 160 mg/dL
HDL cholesterol 34 mg/dL
UPCR 5.3
Urine microscopy: no cells, casts, crystals, or other abnormalities

Which one of the following is correct in this patient?

A. Addition of losartan 25 mg/day further reduces major cardiovascular events in presence of heavy proteinuria
B. Addition of valsartan 40 mg/day preserves kidney function over the long-term by reducing glomerular hyperfiltration
C. Addition of ezetimibe to atorvastatin delays progression of CKD by better control of the lipid profile
D. A multidisciplinary approach incorporating life-style modification with weight loss, optimization of blood pressure, and blood sugar will result in halting progression of proteinuria
E. Work up for nondiabetic glomerulopathies including age-specific cancer screening and, potentially, a kidney biopsy should be performed.

Answer: E

The subacute onset of proteinuria in the absence of diabetic retinopathy and the presence of type 2 diabetes without nephropathy for 25 years suggest causes of kidney disease other than DKD. Membranous nephropathy is the most common primary glomerulopathy in Caucasian men of this age[122] and is frequently observed in association with malignancy. Therefore, age-specific cancer screening is appropriate in this case. After serologic and other blood and urine testing, a kidney biopsy is likely indicated to help diagnose the glomerulopathy, especially because eGFR has decreased.

The ONTARGET study suggests that dual therapy with ACEI and ARB does not improve the composite outcome of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure compared to single agent therapy in high-risk patients.[72] Such therapy may also result in increased frequency of hypotension, hyperkalemia, and renal insufficiency. This makes Answers **A** and **B** incorrect.

The beneficial effect of lipid-lowering agents in diabetes is mainly by primary prevention of major cardiovascular events. The SHARP trial found no evidence that ezetimibe plus a statin delayed progression of CKD,[97] making **C** an incorrect answer.

A multidisciplinary approach is necessary and essential in management of DKD. However, such an approach may not necessarily halt progression of proteinuria, making Answer **D** incorrect.

Question 2

A 45-year-old man with newly diagnosed type 2 diabetes does not have a history of hypertension, coronary artery disease, stroke or peripheral arterial disease. He does not report blurred vision. On physical examination his sitting blood pressure is 116/78 mm Hg, pulse 78 beats per minute, weight 110 kg, and BMI 32 kg/m^2. Examination of retinas, heart, lungs, abdomen, and extremities is unremarkable. Neurologic examination is normal.

Serum chemistries
S[Na] 142 mEq/L
S[K] 4.2 mEq/L
S[Cl] 108 mEq/L
tCO2 24 mEq/L
BUN 20 mg/dL
S[Cr] 1.0 mg/dL
glucose 221 mg/dL
HbA1C 8.5%
Urinalysis: no protein or blood by dipstick. Spot UACR is 0.07. Urine microscopy: no cells, casts, crystals, or other abnormalities.

Which one of the following is correct in this patient?

A. Initiation of lisinopril reduces the risk of the new onset of microalbuminuria
B. In type 2 diabetes losartan is more effective than lisinopril in reducing the risk of DKD
C. Intensive lowering of blood glucose is an effective preventive strategy to delay incident DKD
D. Intensive lowering of blood glucose prolongs longevity by decreased risk of major cardiovascular events
E. Metformin is contraindicated as it increases risk of lactic acidosis in diabetic patients

Answer: C

The role of intensive lowering of blood glucose in primary prevention of DKD has been shown in both type 1 and type 2 diabetes.[34,35]

Several studies have shown that in normotensive diabetic patients without albuminuria, ACEI or ARB treatment does not reduce the incidence of DKD, making Answer **A** and **B** incorrect.

In type 2 diabetes intensive lowering of blood sugar does not reduce cardiovascular events.[40,41]

A number of systematic reviews and meta-analyses revealed safety of metformin along with no evidence for increased risk of lactic acidosis compared to other oral hypoglycemic agents.[42–44] Therefore, metformin is not contraindicated in type 2 diabetic patients with normal or moderately reduced kidney function.

Question 3

A 55-year-old woman with recently diagnosed type 2 diabetes is referred for counseling regarding kidney disease in diabetes. She denies a prior history of hyperlipidemia, or heart or lung disease. She has an older sister with a history of diabetes and advanced CKD. She had a UACR of 88 noted on annual screening 4 months ago. Currently, on physical examination her blood pressure is 130/85 mm Hg, heart rate 86 beats per minute, weight 85 kg, and BMI 31 kg/m^2. Examination of heart, lungs, abdomen, and extremities is unremarkable. S[Cr] is 1.2 mg/dL. UACR is 106. Which one of the following is correct in counseling her regarding clinical course of kidney disease in diabetes?

A. The probability of progression of DKD to ESRD is over 50% in her lifetime
B. Without specific treatment of nephropathy, the likelihood of development of ESRD increases to over 80%
C. Sustained intensive control of blood sugar should now be employed as excellent glycemic control is most effective at delaying progression of DKD rather than preventing its occurrence
D. Initiation of an ACEI or ARB is indicated given the presence of high urinary albumin excretion
E. Decrease of blood pressure to less than 120/80 mm Hg as compared to her current blood pressure delays progression of CKD

Answer: D

Initiation of ACEI or ARB treatment in nonpregnant type 2 diabetic patients with persistently increased urinary albumin excretion is recommended even in normotensive patients.

In type 2 diabetes up to 40% of patients with microalbuminuria develop overt proteinuria, of whom 20% may progress to ESRD over 10–20 years.[8,9] Thus, Answers **A** and **B** are incorrect.

The DCCT/EDIC and UKPDS studies have shown that the sustained tight control of blood sugar early during the course of diabetes in both type 1 and type 2 diabetic patients leads to prolonged preservation of kidney function even if such tight control does not persist.[37,38] This phenomenon is referred to as metabolic memory. Therefore, tight control of blood sugar is most beneficial earlier during the course of diabetes before increased albumin excretion occurs, rather than after development of DKD, making **C** incorrect.

The ACCORD-BP trial found no evidence for improved preservation of renal function or delay in progression of CKD with more intensive treatment of BP to <120/80 mm Hg compared to less-intensive treatment of BP to <140/90 mm Hg,[68] making Answer **E** incorrect.

Question 4

A 61-year-old woman had type 2 diabetes diagnosed 15 years ago. She does not comply with a low-salt diet and often eats in restaurants. She denies chest pain, orthopnea, or dyspnea on exertion. Recently she has had difficulty in control of her blood pressure. Her home medications include 20 mg lisinopril daily, 25 mg hydrochlorothiazide daily, 15 units insulin glargine daily at night, 20 mg simvastatin daily, and 81 mg aspirin daily. On physical examination her seated blood pressure is 164/95 mm Hg, heart rate 88 beats per minute. There is no rub or murmur, but there is mild jugular venous distension. There are bibasilar crackles. Abdomen is soft with normal bowel sounds. Lower extremities have 2+ pitting edema.

Serum chemistry
S[Na] 134 mEq/L
S[K] 4.5 mEq/L
S[Cl] 102 mEq/L
tCO2 23 mEq/L
BUN 42 mg/dL,
S[Cr] 2.1 mg/dL

glucose 193 mg/dL
HbA1C 8.1%
CKD-EPI eGFR: 29 mL/min/1.73 m^2
UPCR 2.5
Urine microscopy: no cells, casts, crystals, or other abnormalities

Which one of the following is NOT correct in management of the patient?

A. Consultation with a nephrologist at this point may reduce cost, improve quality of care, and retard progression to ESRD
B. Initiation of spironolactone at 25 mg/day will further reduce proteinuria
C. Continued decline of GFR with initiation of spironolactone will preclude effective use of this medication
D. Combination of a thiazide with a loop diuretic will be more effective than use of a thiazide alone in control of her blood pressure
E. Addition of direct renin inhibition with aliskiren would be associated with an increased risk of adverse renal outcomes and nonfatal stroke

Answer: C

Short-term randomized clinical trials have shown that treatment with MRA such as spironolactone can acutely reduce the GFR in diabetic subjects, which stabilizes over time, compared to continued decline of GFR in placebo-treated subjects.[81,84] This may potentially translate to better preservation of kidney function and therefore does not preclude its use.

Referral to a nephrologist is indicated by the time patients with CKD progress to stage 4, as studies have shown long-term outcomes and planning for ESRD are better in this setting.[123,124] Therefore, Answer **A** is a true statement.

Initiation of MRA can further reduce proteinuria and provide better control over blood pressure[81–84]; therefore, Answer **B** is a true statement.

In salt-sensitive hypertension a combination of a thiazide and a loop diuretic may provide better diuresis and control of hypertension[74]; hence Answer **D** is true. Dietary counseling to reduce salt intake should accompany treatment with diuresis.

The ALTITUDE trial of aliskerin in DKD was terminated early due to higher incidence of hypotension, hyperkalemia, renal complications, and nonfatal stroke in association with aliskiren; hence Answer **E** is a true statement.

Question 5

A 51-year-old man with a history of type 1 diabetes for over 35 years presents with progressive DKD. He does not report a change in appetite, presence of a sleep disturbance, reduced energy level, metallic taste, shortness of breath at rest, or orthopnea. His S[Cr] has slowly and steadily increased to 3.5 mg/dL from 2.8 mg/dL last year. His UPCR is increased to 9 from 3.5 last year.

Which one of the following is correct in discussion of preparation of the patient for RRT?

A. Preparation for ESRD including choice of RRT, vein mapping, and access creation should start at stage 4 CKD in anticipation of progression to ESRD because starting these processes early will improve morbidity and mortality after onset of ESRD
B. There is no reason to push for early listing for kidney transplantation in the absence of a living kidney donor because deceased donor kidney transplantation is not associated with improved survival compared to maintenance hemodialysis (HD) in patients with ESRD from long-lasting diabetes
C. HD is the preferred modality for this patient because peritoneal dialysis (PD) is associated with increased risk of hyperglycemia, hypertriglyceridemia, and weight gain
D. When dialysis is initiated more aggressive ultrafiltration should be well-tolerated by this patient because diabetic patients are more likely to be volume overloaded than patients with other causes of ESRD
E. In-center HD is preferred because short daily home HD provides inadequate clearance compared to traditional in-center HD.

Answer: A

Preparation for ESRD should start when stage 4 CKD is reached. If the decision is made for HD as the preferred modality of RRT, patients should undergo vein mapping and be referred for access creation in anticipation of progression to ESRD. Ideally, patients should start HD through an established arteriovenous fistula (or a graft when a fistula is not feasible). However, urgent indications for initiation of dialysis, delays in access creation and maturation, or absence of nephrologist involvement in ESRD planning may lead to initiation of HD using a catheter. HD using tunneled catheters is associated with higher risk of infective complications and therefore is less favorable.

Deceased donor kidney transplantation provides significant survival benefit in diabetes compared to other modalities of RRT,[120,121] so Answer **B** is incorrect.

Although increased risk of hyperglycemia, hypertriglyceridemia, and weight gain is associated with PD in diabetic patients, PD outcomes are not clearly worse than HD outcomes and choice of modality of RRT is not different in DKD compared to other etiologies of ESRD,[125] so Answer **C** is incorrect. Patient preference

after consultation with the nephrologist should guide modality choice.

Autonomic dysfunction is a common complication in diabetic patients, which makes effective ultrafiltration with dialysis more difficult and challenging,[126] so Answer **D** is incorrect.

Short daily dialysis has similar patient/treatment survival compared with traditional in-center dialysis[127] and can be preferable when ultrafiltration of large volumes with each dialysis becomes difficult, making Answer **E** incorrect.

Question 6

A 32-year-old woman with type 1 diabetes for 25 years developed albuminuria at age 24 and has been on lisinopril 40 mg daily ever since. Her medication regimen includes humulin insulin *via* an insulin pump, which she has been adjusting over the past 2 months due to large glycemic swings, hydrochlorothiazide 25 mg daily, atorvastatin 10 mg daily. Her urinary albumin excretion is now greater than 800 mg/day. Her home blood pressure readings are between 120 and 130/60−70 mm Hg. On physical examination her seated blood pressure is 125/75 mm Hg, heart rate 96 beats per minute. There is no rub, murmur, or jugular venous distension. Lower extremities have 1+ pitting edema. The following labs are obtained:

Serum chemistries
S[Na] 136 mEq/L
S[K] 4.5 mEq/L
S[Cl] 101 mEq/L
tCO2 25 mEq/L
BUN 42 mg/dL
S[Cr] 1.6 mg/dL
glucose 142 mg/dL
HbA1C 9.4%
UACR 874
Urine microscopy: no cells, casts, crystals, or other abnormalities

Which one of the following is correct regarding the assessment and treatment of her albuminuria?

A. Increasing lisinopril dose to 60 mg daily will further reduce albuminuria and blood pressure
B. Addition of spironolactone to reduce albuminuria will likely increase S[K] to >6.0 mEq/L and is therefore contraindicated
C. The increased albuminuria does not predict further progression of her CKD toward ESRD so does not need to be treated
D. Albuminuria can vary especially with swings in glycemic control. ACR should be rechecked before making a therapeutic change
E. An increase in hydrochlorothiazide dose to 50 mg daily will improve blood pressure and albuminuria

Answer: D

Exercise, infection, fever, congestive heart failure, marked hyperglycemia, and marked hypertension may each cause increases in urinary albumin excretion. Thus, if albuminuria increases rapidly since the last check, these potentially confounding factors should be corrected if present and the urine albumin:creatinine (or protein:creatinine) level should be rechecked before committing a nonhypertensive patient to an additional medication.

Increasing lisinopril above 40 mg daily does not result in improved proteinuria or blood pressure control in type 1 diabetic patients[128]; hence Answer **A** is incorrect.

Addition of spironolactone can cause a further increase in S[K] in diabetic patients with CKD treated with either an ACEI or an ARB, but this increase is usually <0.5 mEq/L. In two RCTs in patients with diabetic nephropathy, S[K] increased no more than 0.8 mEq/L after add-on spironolactone therapy for up to 52 weeks.[84] Hence, Answer **B** is incorrect.

If validated and persistent, the increased albuminuria in this patient would be associated with a greater risk of progression to ESRD, so Answer **C** is incorrect.

Hydrochlorothiazide at doses above 25 mg has little increased efficacy on blood pressure control and does not directly improve albuminuria, so Answer **E** is incorrect.

CHAPTER

52

Human Immunodeficiency Virus Infection and Chronic Kidney Disease

Scott D. Cohen[a], *Jeffrey B. Kopp*[b], *Helen Cathro*[c], *Paul L. Kimmel*[a]

[a]Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States; [b]National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, United States; [c]Department of Pathology and Laboratory Medicine, University of Virginia Medical Center, Charlottesville, VA, United States

Abstract

The prevalence of chronic kidney disease (CKD) in human immunodeficiency virus (HIV)-infected patients has increased over the past two decades. Renal biopsy series show a variety of lesions associated with CKD in this patient population, including HIV-associated nephropathy (HIVAN), HIV-associated immune complex renal disease (HIVICD), thrombotic microangiopathy (TMA), tubulointerstitial renal diseases including some related to combination antiretroviral therapy (cART), diabetic nephropathy, arterionephrosclerosis, and diseases related to coinfection with hepatitis B and C virus. Screening for renal disease is recommended in all patients with newly diagnosed HIV infection. Approximately 10–15% of all HIV-infected patients have microalbuminuria. Estimating equations for glomerular filtration rate (GFR) have not been widely validated in patients with HIV infection. Serum creatinine concentration-based GFR estimating equations including the Chronic Kidney Disease Epidemiology Collaboration and Modification of Diet in Renal Disease may have limited utility in patients with HIV infection who have decreased muscle mass, but equations are being evaluated in this population. Therapy for CKD in the setting of HIV infection focuses on reducing viral replication, and control of traditional risk factors for CKD progression, including hypertension, hyperglycemia, and hyperlipidemia. Use of cART may slow CKD progression, especially in patients with renal disease manifesting as classic HIVAN. Renin-angiotensin-aldosterone system inhibitors should be employed in all patients with proteinuria and CKD unless a contradiction exits, such as hyperkalemia. *APOL1* genetic variants contribute to HIV nephropathy, but at this time do not influence choice of therapy. Future studies should focus on optimal screening tools to facilitate early detection of CKD in this patient population.

INTRODUCTION

Combination antiretroviral therapy (cART) has revolutionized the outcomes of human immunodeficiency virus (HIV)-infected patients over the past two decades.[1–5] As patients with HIV infection life expectancies continue to rise, the prevalence of comorbid conditions including diabetes, hypertension, and chronic kidney disease (CKD) has also increased.[5–9] HIV-associated renal diseases are the third most common cause of end-stage renal disease (ESRD) among black patients between the ages of 20 and 64 years of age.[3,10,11] 10–15% of HIV-infected patients are estimated to have CKD or proteinuria.[12–14] While HIV-associated nephropathy (HIVAN), a form of collapsing focal segmental glomerulosclerosis (FSGS), remains the most common cause of renal failure among HIV-infected African Americans, other forms of HIV-associated renal disease are increasingly recognized and may be more common in whites and individuals of other ethnicities.[4,15,16] In addition to HIVAN, the effects of HIV infection on the kidney are also manifested by a number of renal syndromes (Table 52.1), including acute kidney injury (AKI), immune complex-mediated forms of glomerulonephritis, tubulointerstitial renal injury (especially related to particular forms of cART), TMA, and fluid, electrolyte, and acid-base abnormalities.[15–19] The relationship between HIV infection and the development of CKD and strategies for the screening, diagnosis, and management of CKD in HIV-infected patients are evolving.

https://doi.org/10.1016/B978-0-12-815876-0.00052-8

TABLE 52.1 Renal Syndromes Leading to Chronic Kidney Disease in the Setting of HIV Infection

HIV-Associated Nephropathy
HIV immune complex–mediated kidney disease
Tubulointerstitial renal injury including combination antiretroviral therapy–related nephropathy
Acute kidney injury
Thrombotic microangiopathy

HISTORY

The first cases of HIV infection were reported in 1981 by the Center for Diseases Control. The initial association between HIV infection and kidney injury was made in 1984 based on case reports from Miami, Florida, and New York City.[20,21] These urban medical centers reported HIV-infected patients with proteinuria and rapid progression to ESRD within 2–4 months. Although the report from SUNY Downstate emphasized the presence of a single diagnosis, the study from the University of Miami highlighted a spectrum of renal diseases, including mesangial lesions and glomerulosclerosis, as well as immune complex-associated renal diseases. In both studies, patients were recognized to have a distinct clinical syndrome now termed HIVAN, characterized by collapsing FSGS, or collapsing glomerulopathy, which is one of the most common renal histologic lesions seen in biopsy series of HIV-infected patients, particularly when modern cART is not used. It has subsequently been recognized that other forms of renal disease may exist in association with HIV infection, including HIV-associated immune complex kidney disease (HIVICD).[4,5,15–18] The emergence of cART and its associated metabolic side effects is changing the epidemiology of renal biopsy studies in the setting of HIV infection to include other classic forms of CKD including diabetic nephropathy, arterionephrosclerosis, diseases related to coinfection with hepatitis B and C viruses (HBV and HCV), and other tubulointerstitial renal processes that at times may be related to a unique nephrotoxicity of cART.[22]

RENAL SYNDROMES THAT CAUSE CKD IN HIV-INFECTED PATIENTS

Acute Kidney Injury

HIV-infected patients are at increased risk for the occurrence of AKI,[23] which is a major risk factor for the development of CKD.[19,24,25] HIV-infected patients who are hospitalized with AKI have a significantly higher likelihood of progression to ESRD.[23,25] HIV-infected patients with dialysis-dependent AKI have an approximately 20-fold higher likelihood of developing ESRD.[25] Prompt diagnosis and treatment of AKI in this high-risk patient population is essential.

The causes of AKI in HIV-infected patients are similar to those encountered in the general patient population, with prerenal azotemia and acute tubular necrosis (ATN) being the most frequent etiologies.[19] HIV-infected patients are at risk for volume depletion related to superimposed gastrointestinal illnesses and poor oral intake.[19,23] Obstructive etiologies of AKI related to HIV infection include retroperitoneal lymphadenopathy from lymphomas and crystal nephropathies secondary to use of indinavir, sulfadiazine, and acyclovir causing renal tubular obstruction.[19,26] In addition to ATN, other intrinsic etiologies of AKI in the setting of HIV infection include nephrotoxic acute renal tubular injury and acute interstitial nephritis (AIN), possibly related to cART and the antimicrobials used to treat opportunistic infections. HIV infection, particularly when CD4 counts are very low, has also been associated with TMA requiring plasma exchange.[19,26] HIV is directly myotoxic and has been associated with increased risk for rhabdomyolysis.[19,26] HIVAN, HIVICD, and other forms of tubulointerstitial renal disease, including nephropathies related to cART, may be associated with either AKI or CKD.

HIV-Associated Nephropathy

Clinical Presentation and Therapy

HIVAN remains one of the most prevalent forms of renal disease associated with this viral infection. HIVAN is especially common among individuals of African descent. There is an underlying genetic predisposition leading to this strong association in people of African descent. It has become apparent that this genetic susceptibility is largely explained by genetic variants in the *APOL1* on chromosome 22, encoding apolipoprotein L1. The *APOL1* gene family underwent rapid evolution in primates, probably due to the roles that the encoded proteins play in innate immunity. ApoL1 is present in plasma, where it is a component of HDL, and acts to kill *Trypanosoma brucei brucei* (which causes sleeping sickness in cattle, which lack APOL1). *T. b. rhodesiense* evolved the serum resistance antigen, which binds and inactivates APOL1, preventing trypanosomal killing. Two APOL1 variants, termed G1 and G2, have the ability to kill T. *b. rhodesiense*, and these genetic variants have reached high prevalence, particularly in West Africa. These variants are strongly associated with development of specific forms of CKD, generally acting in a recessive fashion (e.g. genotypes G1/G1, G2/G2, or G1/G2). The odds ratio for those with two *APOL1* risk alleles is 17 for primary FSGS and 29 in US studies

and 89 in a study from South Africa for HIVAN.[5,27–29] Approximately three quarters of both groups carry two *APOL1* risk alleles.[27,28] *APOL1* risk alleles are also associated with hypertension-attributed arterionephrosclerosis.[29]

It appears that with the advent of cART, kidney disease in those with two *APOL1* risk alleles may have shifted from HIVAN to FSGS and hypertensive arterionephrosclerosis. The mechanism by which *APOL1* risk alleles affect glomerular function, and presumably disturb podocyte biology, is the focus of considerable attention. Emerging evidence suggests APOL1 variants may injure podocytes *via* alterations in membrane ion flux, dysregulation of endolysosomal, mitochondrial and autophagic function, and increase in recruitment of cellular inflammatory pathways.[5]

HIVAN is characterized by glomerular collapse and marked hypertrophy of visceral epithelial cells (Figure 52.1). These cells were once considered to be dysregulated podocytes, but it is now apparent that these cells mostly likely derive from parietal epithelial cells.[30] The mechanisms responsible for their excess proliferation and failure to undergo differentiation into podocytes are unknown. Other characteristic features of HIVAN include microcystic tubular changes with proteinaceous casts and occasional tubuloreticular inclusions within the glomerular endothelial cells seen on electron microscopic examination (Figure 52.2).[10,11] Clinical characteristics of patients with this condition include proteinuria, often in the nephrotic range, and reduction in glomerular filtration rate (GFR). Edema may be less common than in other forms of nephrotic syndrome, due to an underlying salt wasting nephropathy, tubular dysfunction, or malnutrition. Enlarged and echogenic kidneys may be detected by renal ultrasound. A renal biopsy is required to make a diagnosis of HIVAN.[31] HIV-infected patients with renal disease who do not undergo a renal biopsy may be inappropriately labeled with this diagnosis. Several renal biopsy series confirm that a variety of renal histologic diagnoses exist in association with HIV infection.[5,16,18]

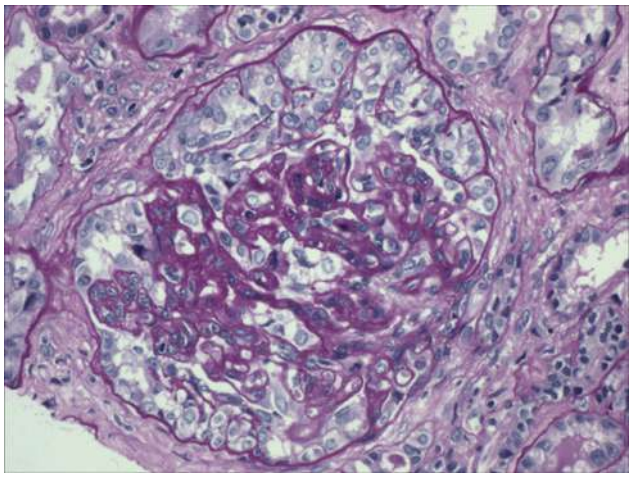


FIGURE 52.1 Light microscopy in HIV-associated nephropathy: a glomerulus from a patient with HIV infection and collapsing focal segmental glomerulosclerosis. The glomerular tufts are collapsed and Bowman's space is filled by proliferating parietal epithelial cells (periodic acid Schiff, magnification ×200).

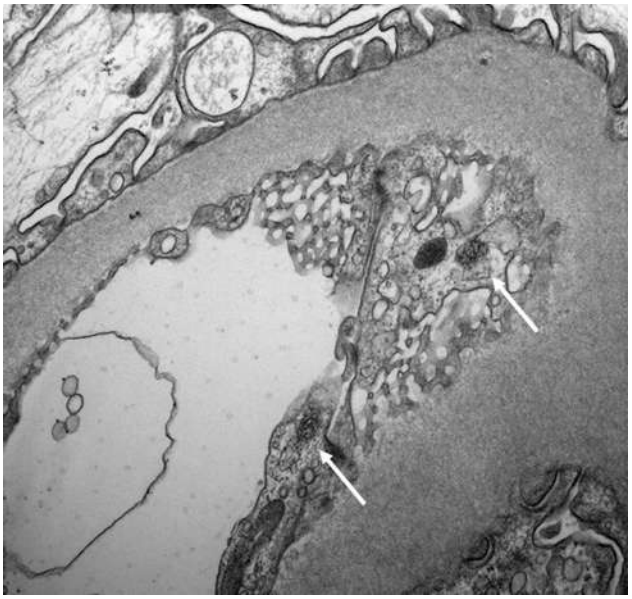


FIGURE 52.2 Electron microscopy in HIV-associated nephropathy: a glomerulus with tubuloreticular inclusion bodies (*arrows*) within the glomerular endothelial cell (magnification ×12,000).

cART remains the cornerstone of treatment for HIVAN, and HIVAN is an indication to start antiretroviral therapy.[2,7,10,11,32] cART may slow the progression of HIVAN to ESRD,[10,11] although this hypothesis has not been tested in randomized controlled trials. There are also data that earlier initiation of cART in HIV-infected patients improves renal outcomes. Case reports have shown improvement in GFR and regression of characteristic HIVAN pathologic features with initiation of cART.[33,34] General therapies to slow progression of CKD also apply in this condition. Blood pressure control with use of renin–angiotensin–aldosterone system (RAAS) inhibitors should be encouraged where clinically appropriate, coupled with dietary sodium restriction and judicious use of diuretics, including thiazides, both of which potentiate antifibrotic effects of RAAS antagonism.[35–37] The target blood pressure in this patient population has not been established, but aiming for BP less than 130/80 mm Hg seems reasonable while awaiting the results of randomized clinical trials. There are also limited data supporting a role for corticosteroids in the treatment of HIVAN.[38] However, caution should be applied particularly in this immunocompromised patient population.

Pathogenesis

HIVAN is characterized by loss of differentiated podocytes and repopulation of that niche by proliferating parietal epithelial cells. It appears that viral factors and host factors are both required for the development of disease. The HIV-1 genes Nef and Vpr[39,40] are each sufficient to induce podocyte injury and glomerulosclerosis when expressed in the podocytes of transgenic mice. The molecular pathways by which these genes act have been only partly unraveled. The *APOL1* genetic variants appear to be required, or at least strongly facilitate HIV infection to damage podocytes and promote aberrant parietal cell repopulation of the glomerular tuft. HIV-1 nucleic acid is present in dysmorphic visceral epithelial cells and tubular epithelial cells, the principal sites of pathologic change in HIVAN. The precise role that *APOL1* plays in the development of HIVAN is an active area of research. The genetic effect is strongly recessive, which is most commonly associated with loss-of-function mutations. On the other hand, several lines of evidence suggest that APOL1 may not play a critical role in podocyte biology, which would argue against a loss-of-function mutation. Therefore, it may be that the mutations confer a gain in function. In support of this hypothesis, in the setting of HIV infection, a single APOL1 risk allele is sufficient to increase risk for HIVAN in some populations.[41]

HIV-Associated Immune Complex Renal Disease

Clinical Presentation and Therapy

Approximately half of HIV-infected patients with CKD who undergo a renal biopsy have a diagnosis other than HIVAN.[18,42] In many of these cases, a form of HIVICD is identified. Patients typically present with active urine sediment, reduced renal function, hypertension, and proteinuria. There may also be serologic evidence of immune complex activity with hypocomplementemia.

There are a variety of renal histologic lesions that may be associated with HIVICD, including IgA nephropathy, lupus-like glomerulonephritis with "full-house immunofluorescence," (Figures 52.3 and 52.4), postinfectious glomerulonephritis with diffuse endocapillary proliferation, mesangioproliferative (Figures 52.5 and 52.6), and membranoproliferative glomerulonephritis, membranous nephropathy, cryoglobulinemic glomerulonephritis, and fibrillary/immunotactoid glomerulopathies.[15–18,43] One study has advocated excluding IgA nephropathy in the setting of HIV from the HIVICD group of diseases based on differing outcomes.[44] A recent KDIGO report suggested dropping the term HIVICD altogether and replacing it with each immune complex-associated disease followed by "in the setting of HIV." The rationale is the heterogeneous nature of these diseases and the uncertainty regarding causal associations with HIV infection in most cases.[18,45]

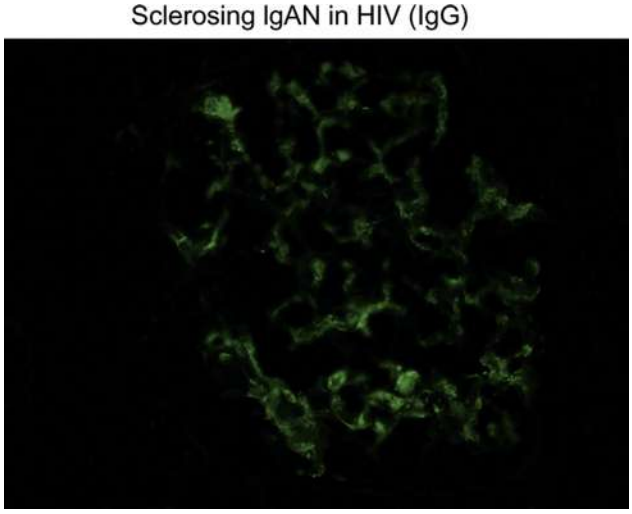


FIGURE 52.3 Immunofluorescence in HIV-associated immune complex renal disease: a glomerulus from a patient with HIV infection and IgA nephropathy showing mesangial deposits of IgG with codominant deposition of IgA (not pictured) (intensity 2+; scale trace through 3+, magnification ×400).

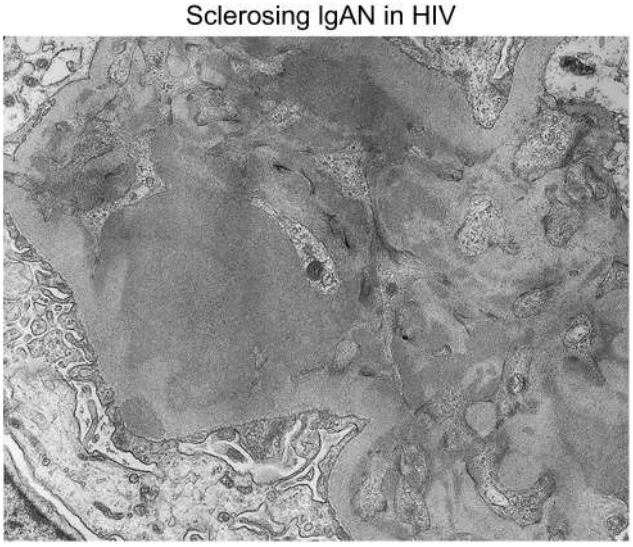


FIGURE 52.4 Electron microscopy in HIV-associated immune complex renal disease: a glomerulus from a patient with HIV infection and IgA nephropathy showing mesangial deposits (magnification ×7000).

Unlike classic HIVAN, it is not clear whether HIVICD progression is slowed with cART. An observational study of patients with HIVAN and other non-HIVAN lesions failed to show an effect of cART to slow the progression of renal disease in HIV-infected patients without HIVAN.[16] A nested case-control study of 751

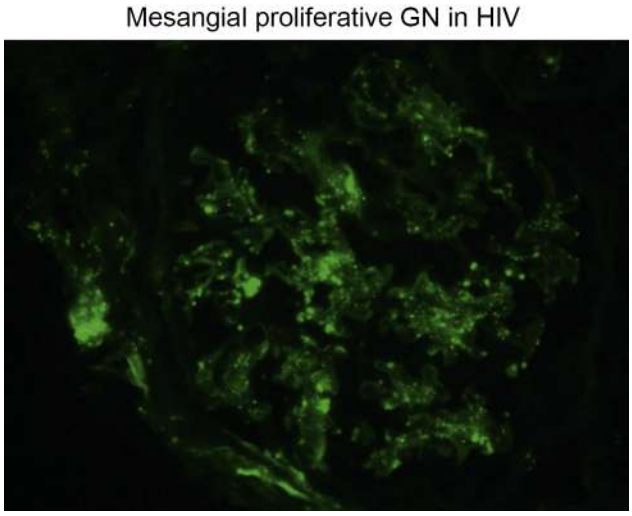


FIGURE 52.5 Immunofluorescence in HIV-associated immune complex renal disease: a glomerulus from a patient with HIV infection and mesangioproliferative glomerulonephritis showing mesangial deposits of IgM (intensity 2+, magnification ×400).

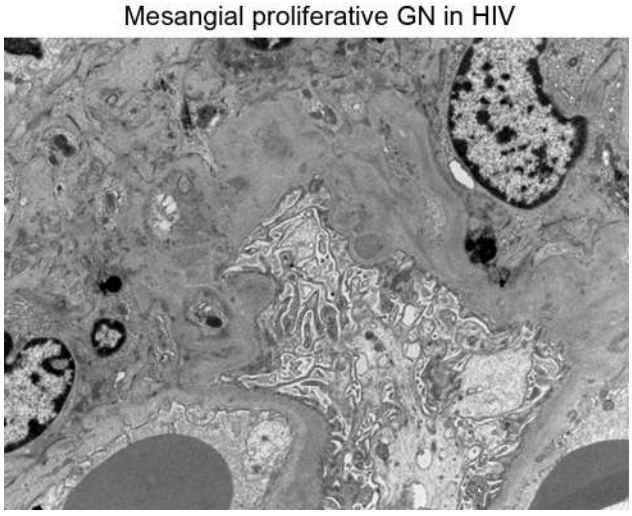


FIGURE 52.6 Electron microscopy in HIV-associated immune complex renal disease: a glomerulus from a patient with HIV infection and mesangioproliferative glomerulonephritis showing mesangial electron dense deposits (magnification ×8000). *Images courtesy of Dr. Helen Cathro, University of Virginia Health Sciences Center.*

HIV-positive patients from Baltimore confirmed the results of the previous study. Foy et al.[46] showed that use of cART did not reduce the incidence of ESRD secondary to HIVICD. Although immunosuppressive therapies are frequently considered in the treatment of immune complex renal disease, extreme caution should be used in HIV-infected patients given their immunocompromised state. The risks and benefits of immunomodulatory therapy should be carefully balanced before initiation of immunosuppression.[5,17,18]

Patients with HIVICD may be coinfected with other pathogens including HBV and HCV. The immune complex renal disease may improve following antiviral therapy for hepatitis.[17,18] Immunotherapy including steroids may also promote increased viral replication. Therefore, patients with HIVICD should be screened for coexistent hepatitis infection before proceeding with additional therapeutic options.[17] As with other forms of CKD, optimization of blood pressure control with antagonists of the RAAS should be instituted when clinically feasible.

Pathogenesis

Polyclonal hypergammaglobulinemia frequently occurs in the setting of HIV infection.[17] This predisposes to the development of circulating immune complexes. Kimmel et al. demonstrated that circulating immune deposits, made up of HIV antigens and antibodies directed against them, can lead to glomerulonephritis,[15,17,18,47] directly linking the infection with the renal disease in a causal pathway in some cases. Research techniques are necessary to directly link HIV infection with a particular glomerular disease in individual cases. The relationship between IgA nephropathy and HIV infection appears to be particularly compelling. There may be "passive trapping" of immune complexes containing HIV antigen in renal tissue.[4,15,17,18,47] There may also be "*in situ*" immune complex deposition with preformed antibodies in the circulation binding to HIV antigens on glomerular cells.[4,15,17,47] It is unclear whether the "passive trapping" or "*in situ*" mechanism of immune complex deposition plays the predominate role in HIVICD.[17,18] As with other forms of glomerulonephritis, cellular mediated immune injury may also lead to progressive disease.[15,17,47]

Thrombotic Microangiopathy and HIV Infection

The prevalence of TMA in the setting of HIV infection has decreased since the introduction of cART.[5,48–50] TMA is a histologic pattern seen in a variety of diseases, including thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), disorders of complement regulatory proteins (atypical HUS), disseminated intravascular coagulation, malignant hypertension, and antiphospholipid antibody syndrome. TMA is clinically characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency. Neurologic deficits and fever may also occur. TMA is more likely to be seen in patients with advanced HIV infection, including those with low CD4 counts and high HIV viral loads.[48]

Risk factors for endothelial injury leading to TMA in HIV-infected patients include the direct cytopathic effects of HIV or associated opportunistic infectious agents, antiretroviral medications, or other comorbid conditions including malignancy.[4] The HIV p24 antigen has been isolated from endothelial cells in patients with TTP and HIV infection.[51] The HIV envelope protein gp120 can increase a procoagulant factor in arterial smooth cells potentially leading to TMA.[52] The von Willebrand factor cleaving protease ADAMTS 13 may be deficient in the TMA associated with HIV infection.[53,54] TMA may present as AKI or a recurrent subacute disease that can ultimately lead to CKD.

On renal biopsy, the microscopic features of TMA are often subtle and sparse. They include fragmented red cells within hilar arterioles, microthrombi within glomerular capillaries, and less often fibrinoid necrosis of arterial walls. The presence of specific microscopic features is not a reliable way to differentiate between the underlying disease processes.[55]

Treatment options for patients with HIV-associated TMA include antiretroviral therapy, plasma exchange, and possibly eculizumab.[4,5] If the disease is refractory, immunosuppression should be considered only after carefully balancing the risks and benefits in this immunocompromised patient population. There have been mixed results regarding the effects of immunomodulatory agents on HIV-associated TMA, which includes corticosteroids, immunoglobulin infusions, rituximab, and splenectomy.[4] Randomized controlled clinical trials have not been performed to determine which therapy leads to the best clinical outcomes in this patient population.

Tubulointerstitial Renal Diseases and HIV Infection

The impact of HIV infection on the kidney is not limited to glomerular diseases. It is increasingly recognized that a distinct subset of patients have AKI and CKD secondary to tubulointerstitial nephritis (TIN).[22] Parkhie et al.[56] showed that 11% of 262 HIV-infected patients who underwent renal biopsy had AKI secondary to AIN. TIN was also found in 26.6% of HIV-infected patients who underwent a renal biopsy from a single center in Paris, France.[22] These results highlight the importance of obtaining a renal histologic diagnosis whenever possible, especially when the clinical history does not match that usually associated with the development of classic HIVAN. As in the general population, TIN in the setting of HIV infection may be secondary to medications, autoimmune diseases, infections, or idiopathic causes.

cART Nephropathy

cART has become a major cause of tubular and interstitial renal injury in HIV-infected patients.[2,5,22] Tenofovir, a nucleotide reverse transcriptase inhibitor (NRTI), a commonly prescribed primary treatment of HIV infection, is associated with nephrotoxicity.[5] Tenofovir has two formulations: the older formulation tenofovir disoproxil fumarate (TDF) and a newer formulation tenofovir alafenamide (TAF). The latter is believed to have less nephrotoxic potential.[5,57] Following metabolism of TDF by gut and serum esterases, tenofovir is taken up by the basolateral membrane of the proximal tubular cell through organic anion transporter proteins-1 and 3 (OAT 1,3) and is secreted into the tubular lumen of the nephron through a multidrug-resistant protein-4 (MRP4).[5,58,59] Tenofovir may accumulate in the proximal tubule, damaging mitochondria or interfering with the function of tubular cell proteins, leading to the development of Fanconi syndrome, followed in some cases by AKI, often due to ATN. Risk factors for tenofovir-associated renal injury include presence of preexisting CKD, polymorphisms in the ABCC2 gene (which encodes for the proximal tubule apical membrane channel MRP2), increased age, and decreased body mass index.[60,61] There may also be an increased risk of nephrotoxicity in patients taking protease inhibitors concomitantly with tenofovir.[62,63] TAF is absorbed intact through the gut and is taken up by peripheral blood mononuclear cells. Plasma tenofovir levels are significantly lower following TAF administration compared with the older formulation TDF.[5] In contrast to tenofovir, TAF is not a substrate for OAT1 and OAT3, which likely contributes to the decreased nephrotoxicity seen with this newer formulation of the drug.[5]

Clinical characteristics of tenofovir nephrotoxicity are initially those of a classic proximal tubulopathy, with hypophosphatemia, normoglycemic glycosuria, hypouricemia, a nongap metabolic acidosis, and proteinuria.[64] Dysfunction may progress to a form of nephrogenic diabetic insipidus and ATN from diffuse renal tubular injury. The characteristic finding on renal biopsy is the presence of enlarged, distorted mitochondria seen ultrastructurally in proximal tubular cells. Over the long-term, there are mixed results regarding the risk of CKD in HIV-infected patients treated with tenofovir.[2] If Fanconi syndrome or ATN is recognized early, the medication can often be discontinued before significant irreversible renal injury occurs. However, AKI is an important risk factor for CKD. Therefore, it is postulated that therapy with tenofovir can lead to the development of CKD.

Two studies evaluated the long-term impact of chronic tenofovir use on the average decline in estimated GFR (eGFR). In two separate cohorts, there was no significant difference in the median eGFR decline in HIV-infected patients who received tenofovir-based cART compared with those on a cART regimen lacking tenofovir.[65,66] However, several more recent studies have contradicted these initial results.[67,68] HIV-infected patients taking tenofovir enrolled in the Johns Hopkins clinical cohort had a significantly greater decrease in renal function over three years of follow-up compared with patients not on tenofovir-based therapy.[67] A study from the San Francisco Veterans Administration Medical Center[68] of 10,841 HIV-infected patients also showed an increased risk for CKD in patients with prolonged exposure to tenofovir. The disparate results are likely related to differences in study designs and characteristics of the patient populations among the various cohorts.[69]

There are other antiretroviral therapies with nephrotoxic potential. Indinavir is associated with intratubular crystalline precipitation leading to acute renal tubular injury, but this drug is no longer commonly used.[2] Atazanavir has also been associated with the development of nephrolithiasis, crystalluria, and granulomatous interstitial nephritis.[2,5] Several forms of cART have also been associated with interstitial nephritis and the presence of CKD.[22,64]

A number of antiretroviral therapies including the protease inhibitors have metabolic effects which increase the likelihood of diabetes, hyperlipidemia, and hypertension in HIV-infected patients.[2] Increasingly, diabetic nephropathy and hypertensive arterionephrosclerosis are recognized as causes of CKD in HIV-infected patients. The causal implications of the concordance of the two diseases are unknown.

Other Causes of Tubulointerstitial Nephritis

While medications are a common cause of TIN in HIV-infected patients and in the general population, other etiologies unique to HIV infection should be considered. Patients with HIV infection may develop immune reconstitution inflammatory syndrome and diffuse infiltrative lymphocytosis syndrome which are both associated with a form of TIN.[5,19] These may require treatment with corticosteroids. Opportunistic infections related to the immunocompromised state, such as CMV infection and other bacterial infections, may lead to a form of TIN.[19]

EPIDEMIOLOGY OF CKD IN PATIENTS WITH HIV INFECTION

In seven studies carried out between 1994 and 2011, a consistent rate of microalbuminuria of 10–15% was found.[5,70] One study, involving three urine samples collected over 6–9 months, found a rate of 14%, using the geometric mean of the samples to diagnose period microalbuminuria.[70] The negative predictive value of a single sample for microalbuminuria was 98%, whereas the positive predictive value was only 74%. Thus, for periodic screening, a single negative test suffices, but positive tests should be repeated. The implications of microalbuminuria in this population are uncertain, but likely causes include glomerulopathy, tubulopathy, and metabolic syndrome, although febrile proteinuria is also a possibility.[71]

Between 2 and 10% of HIV-infected patients also have a reduction in eGFR.[13,14,72,73] The presence of proteinuria and reduced eGFR is associated with increased mortality in HIV-infected patients.[74,75] Therefore, close attention should be paid to HIV-infected patients with manifestations of CKD. Potential risk factors for CKD in this patient population include older age, black race, diabetes mellitus, hypertension, low CD4 cell count, increased HIV viral load, coinfection with HBV and HCV, and previous episodes of AKI.[73]

SCREENING FOR CKD IN HIV-INFECTED PATIENTS

Screening for CKD remains essential in this patient population. Detection of CKD involves assessment for proteinuria and albuminuria, review of the urine microscopy, and estimation of the GFR. Guidelines from the Infectious Diseases Society of America recommend checking renal function and screening for proteinuria in all patients with newly diagnosed HIV infection.[7] There was initial concern that GFR estimating equations were not adequately validated in HIV-positive patients.[76] However, more recent studies have validated the use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in HIV-infected patients with utilization of cystatin C in those individuals with severely reduced muscle mass.[5,77,78]

Proteinuria is one of the main indicators of renal injury and is frequently present in screening tests of HIV-infected patients. Proteinuria may be screened using urine dipsticks, or spot urine protein or albumin: creatinine ratios (UPCRs or UACRs). A study of 166 HIV-infected patients compared the utility of urine dipstick testing vs. spot UPCRs to assess for proteinuria.[79] Approximately 20% of patients with proteinuria ranging from 300 to 999 mg/g creatinine were not detected by urine dipstick testing.[79] Therefore, UACRs or UPCRs may be preferred as screening tools to detect clinically significant proteinuria. KDIGO guidelines advocate use of UACRs in the staging of patients with CKD.[45,80]

Cystatin C is increasingly being used to estimate GFR in patients with CKD, especially in those individuals with borderline low eGFR using the creatinine-based CKD-EPI and Modification of Diet in Renal Disease equations. This cystin-protease inhibitor has the advantage of being constantly produced by all nucleated cells, is not affected by muscle mass, is freely filtered at the glomerulus, and is fully reabsorbed and catabolized in the renal tubules.[73] However, inflammation is known to affect circulating cystatin C levels.[73] This is particularly relevant in patients with chronic infections such as HIV where inflammation may have a significant effect on cystatin C levels. Additional studies are needed to validate the use of cystatin C estimating equations in the setting of HIV infection. In the interim, use of S [Cr]-based estimating equations, such as CKD-EPI, remains the first approach to screening of patients with CKD and HIV infection.[5,73,77,78]

Other potential biomarkers of renal injury in HIV-infected patients are being studied, including neutrophil gelatin-associated lipocalin, kidney injury marker-1, interleukin-18 (IL-18), asymmetric dimethylarginine, and liver-type fatty acid-binding protein.[73,81] Urinary markers of tubular injury may also be useful in the early detection of cART nephrotoxicity, including *N*-acetyl-β-D-glucosaminidase, β2 microglobulin, and α1 microglobulin.[69,73] In light of the lack of clarity regarding the clinical utility of these evaluations, additional studies of these biomarkers are necessary before their potential use in clinical settings can be assessed.

TREATMENT OF CHRONIC KIDNEY DISEASE IN HIV-INFECTED PATIENTS

Early identification of CKD remains essential in all patients including those infected with HIV. Therapy for CKD in this patient population presents unique considerations, especially with respect to the multitude of antiretroviral medications and their potential for nephrotoxicity.[82] Close consultation with infectious disease and nephrology specialists as part of a multidisciplinary team is essential in the treatment of HIV-infected patients. Renal and hepatic function should always be considered in prescribing and dose calculation of cART.

Biopsy-proven HIVAN is an indication for initiation of cART regardless of the absolute CD4 cell count and HIV PCR viral load.[83] Other potential treatment options for HIVAN include use of RAAS inhibitors and corticosteroids.[38,82] As with other forms of CKD, treatment of coexisting comorbid conditions including hypertension and diabetes may be important in slowing progression.

Hypertension is present in approximately 12–20% of HIV-infected patients.[84] Extrapolating from the literature in the general population, target blood pressure in HIV-positive patients with CKD should typically be <130/80 mm Hg, especially in those with significant proteinuria.[7,82] How more recent study results might affect these recommendations in patients with CKD and HIV infection is unclear. Glycemic control should include a target HbA1c less than 7%. Another treatment consideration is controlling hyperlipidemia. Caution is necessary in HIV-infected patients treated concomitantly with statins and protease inhibitors, due to a common metabolism through the cytochrome P450 hepatic enzyme system. Patients coinfected with HBV and HCV should be considered for antiviral therapy.[82,85–87]

KIDNEY TRANSPLANTATION FOR HIV PATIENTS

Kidney transplantation has become an option for HIV-infected patients with CKD. Acute rejection rates are somewhat higher than in other recipients,[88,89] but medium-term patient survival falls between that of the general kidney transplant population and that of recipients greater than 64 years of age.[88] It is important to select appropriate candidates for kidney transplantation. Those with detectable plasma HIV RNA, CD4 count <100 cells/μL, malignancy, and opportunistic infection are excluded. Immunosuppressive strategies have generally involved an IL-2-inhibitor (basiliximab) for induction (avoiding T-cell depleting agents), followed by triple therapy with prednisone, a calcineurin inhibitor (or sirolimus), and mycophenolate mofetil.[90] Multiple drug interactions between these immunosuppressive agents and cART, as well as antihypertensive agents and antibiotics that may be required, pose a challenge and require pharmacologic expertise and therapeutic drug monitoring. The rate of malignancy may be higher in patients with HIV infection and a kidney transplant. Therefore, cancer surveillance is recommended. When HIV-infected patients receive HIV-negative kidneys, the transplanted kidney can be infected with HIV even when plasma HIV RNA remains undetectable.[91] In some cases, HIV RNA was present in podocytes and tubular epithelial cells and those with podocyte infection had faster functional decline after transplant.[91] Organs from deceased HIV-positive individuals can be transplanted into HIV-positive individuals in the US under a research program sponsored by the HIV Organ Policy Equity Act.[5,92] This approach was pioneered in South Africa, where a report of 14 subjects suggested that plasma HIV viral levels remain suppressed following successful kidney transplantation.[93–96]

CONCLUSION

The widespread use of cART has dramatically decreased the mortality and improved the clinical outcomes of HIV-infected patients. The success of cART has led to an increase in the prevalence of chronic medical conditions including CKD in HIV-infected patients. The range of diseases known to cause CKD in the setting of HIV infection includes but is not limited to HIVAN, HIVICD, TMA, TIN (including cART-related nephropathy), as well as renal diseases associated with diabetes, hypertension, and coinfection with HCV and HBV. The metabolic consequences of chronic cART are increasing the rates of diabetes, hypertension, and hyperlipidemia in HIV-positive patients, which will likely further add to the CKD burden in this patient population. Additional clinical studies are needed to determine the optimal approach to diagnose and treat CKD in HIV-infected patients. Early screening for CKD in HIV patients is important to ensure prompt diagnosis and therapy.

Acknowledgments

This work was supported in part by NIDDK Intramural Research Programs.

References

1. Lucas GM, Lau B, Atta MG, et al. Chronic kidney disease incidence, and progression to end-stage renal disease, in HIV-infected individuals: a tale of two races. *J Infect Dis* 2008;**197**:1548–57.
2. Estrella MM, Fine DM, Atta MG. Recent developments in HIV-related kidney disease. *HIV Ther* 2010;**4**:589–603.
3. Naicker S, Han TM. HIV/AIDS-dominant player in chronic kidney disease. *Ethn Dis* 2006;**16**:S2–56.
4. Rachakonda AK, Kimmel PL. CKD in HIV-infected patients other than HIV-associated nephropathy. *Adv Chron Kidney Dis* 2010;**17**: 83–93.
5. Cohen SD, Kopp JB, Kimmel PL. Kidney diseases associated with human immunodeficiency virus infection. *N Engl J Med* 2017;**377**: 2363–74.
6. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the Euro SIDA study: an observational study. *Lancet* 2003;**362**:22–9.
7. Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2005;**40**:1559–85.
8. Schwartz EJ, Szczech LA, Ross MJ, et al. Highly active antiretroviral therapy and the epidemic of HIV+ end-stage renal disease. *J Am Soc Nephrol* 2005;**16**:2412–20.
9. Eggers PW, Kimmel PL. Is there an epidemic of HIV infection in the US ESRD program? *J Am Soc Nephrol* 2004;**15**:2477–85.
10. Wyatt CM, Meliambro K, Klotman PE. Recent progress in HIV-associated nephropathy. *Annu Rev Med* 2012;**63**:147–59.
11. Ross MJ, Klotman PE. Recent progress in HIV-associated nephropathy. *J Am Soc Nephrol* 2002;**13**:2997–3004.
12. Szczech LA, Grunfeld C, Scherzer R, et al. Microalbuminuria in HIV infection. *AIDS* 2007;**21**:1003–9.
13. Fernando SK, Finkelstein FO, Moore BA, Weissman S. Prevalence of chronic kidney disease in an urban HIV infected population. *Am J Med Sci* 2008;**335**:89–94.
14. Jones CY, Jones CA, Wilson IB, et al. Cystatin C and creatinine in an HIV cohort: the nutrition for healthy living study. *Am J Kidney Dis* 2008;**51**:914–24.
15. Kimmel PL, Phillips TM, Ferreira-Centeno A, et al. HIV-associated immune-mediated renal disease. *Kidney Int* 1993;**44**:1327–40.
16. Szczech LA, Gupta SK, Habash R, et al. The clinical epidemiology and course of the spectrum of renal diseases associated with HIV infection. *Kidney Int* 2004;**55**:1145–52.
17. Cohen SD, Kimmel PL. Immune complex renal disease and human immunodeficiency virus infection. *Semin Nephrol* 2008;**28**:535–44.
18. Nobakht E, Cohen SD, Rosenberg AZ, Kimmel PL. HIV-associated immune complex kidney disease. *Nat Rev Nephrol* 2016;**12**:291–300.
19. Cohen SD, Chawla LS, Kimmel PL. Acute kidney injury in patients with human immunodeficiency virus infection. *Curr Opin Crit Care* 2008;**14**:647–53.
20. Rao TK, Fillipone EJ, Nicastri AD, et al. Associated focal and segmental glomerulosclerosis in the acquired immunodeficiency syndrome. *N Engl J Med* 1984;**310**:669–73.
21. Pardo V, Aldana M, Colton RM, et al. Glomerular lesions in the acquired immunodeficiency syndrome. *N Engl J Med* 1984;**310**: 669–73.
22. Zaidan M, Lescure FX, Brocheriou I, et al. Tubulointerstitial nephropathies in HIV-infected patients over the past 15 years: a clinic-pathological study. *Clin J Am Soc Nephrol* 2013;**8**:930–8.
23. Franceschini N, Napravnik S, Eron Jr JJ, et al. Incidence and etiology of acute renal failure among ambulatory HIV-infected patients. *Kidney Int* 2005;**64**:1526–31.
24. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. *Kidney Int* 2012;**82**: 516–24.
25. Choi AI, Li Y, Parikh C, et al. Long-term clinical consequences of acute kidney injury in the HIV-infected. *Kidney Int* 2010;**78**:478–85.
26. Kalim S, Szczech LA, Wyatt CM. Acute kidney injury in HIV-infected patients. *Semin Nephrol* 2008;**28**:556–62.
27. Kopp JB, Nelson GW, Sampath K, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol* 2011;**22**:2129–37.
28. Atta MG, Estrella MM, Kuperman M, et al. HIV-associated nephropathy patients with and without apolipoprotein L1 gene variants have similar clinical and pathological characteristics. *Kidney Int* 2012;**82**:338–43.
29. Fine DM, Wasser WG, Estrella MM, et al. APOL1 risk variants predict histopathology and progression to ESRD in HIV-related kidney disease. *J Am Soc Nephrol* 2012;**23**:343–50.
30. Dijkman HB, Weening JJ, Smeets B, et al. Proliferating cells in HIV and pamidronate-associated collapsing focal segmental glomerulosclerosis are parietal epithelial cells. *Kidney Int* 2006;**70**:338–44.
31. Cohen SD, Kimmel PL. Renal biopsy is necessary for the diagnosis of HIV-associated renal diseases. *Nat Clin Pract Nephrol* 2009;**5**: 22–3.
32. Lucas GM, Eustace JA, Sozio S, et al. Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: a 12-year cohort study. *AIDS* 2004;**18**:541–6.
33. Wali RK, Drachenberg CI, Papdimitriou JC, et al. HIV-1-associated nephropathy and response to highly-active antiretroviral therapy. *Lancet* 1998;**352**:783–4.
34. Winston JA, Bruggeman LA, Ross MD, et al. Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. *N Engl J Med* 2001;**344**:1979–84.
35. Kimmel PL, Mishkin GJ, Umana WO. Captopril and renal survival in patients with human immunodeficiency virus nephropathy. *Am J Kidney Dis* 1996;**28**:202–8.

36. Wei A, Burns GC, Williams BA, et al. Long-term renal survival in HIV-associated nephropathy with angiotensin-converting enzyme inhibition. *Kidney Int* 2003;**64**:1462–71.
37. Bird JE, Durham SK, Giancarli MR, et al. Captopril prevents nephropathy in HIV-transgenic mice. *J Am Soc Nephrol* 1998;**9**:1441–7.
38. Eustace JA, Nuermberger E, Choi M, et al. Cohort study of the treatment of severe HIV-associated nephropathy with corticosteroids. *Kidney Int* 2000;**58**:1253–60.
39. Zuo Y, Matsusaka T, Zhong J, et al. HIV-1 genes vpr and nef synergistically damage podocytes, leading to glomerulosclerosis. *J Am Soc Nephrol* 2006;**17**:2832–43.
40. Ideura H, Hiromura K, Hiramatsu N, et al. Angiotensin II provokes podocyte injury in murine model of HIV-associated nephropathy 2007;**293**:F1214–1221.
41. Kasembeli AN, Duarte R, Ramsay M, et al. APOL1 risk variants are strongly associated with HIV-associated nephropathy in black South Africans 2015;**26**:2882–90.
42. Weiner NJ, Goodman JW, Kimmel PL. The HIV-associated renal diseases: current insight into pathogenesis and treatment. *Kidney Int* 2003;**63**:1618–31.
43. Haas M, Kaul S, Eustace JA. HIV-associated immune complex glomerulonephritis with "lupus-like" features: a clinicopathologic study of 14 cases. *Kidney Int* 2005;**67**:1381–90.
44. Booth J, Hamzah L, Jose S, et al. Clinical characteristics and outcomes of HIV-associated immune complex kidney disease. *Nephrol Dial Transplant* 2016;**31**(12):2099–107.
45. Swanepoel CR, Atta MG, D'Agati VD, et al. Kidney disease in the setting of HIV infection: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. *Kidney Int* 2018;**93**(3):545–59.
46. Foy MC, Estrella MM, Lucas GM, et al. Comparison of risk factors and outcomes in HIV immune complex kidney disease and HIV-associated nephropathy. *Clin J Am Soc Nephrol* 2013;**8**:1524–32.
47. Kimmel PL, Phillips TM, Ferreira-Centeno A, et al. Brief report: idiotypic IgA nephropathy in patients with human immunodeficiency virus infection. *N Engl J Med* 1992;**327**:702–6.
48. Becker S, Fusco G, Fusco J, et al. HIV-associated thrombotic microangiopathy in the era of highly active antiretroviral therapy: an observational study. *Clin Infect Dis* 2004;**39**(Suppl. 5):S267–75.
49. Berliner AR, Fine DM, Lucas GM, et al. Observations on a cohort of HIV-infected patients undergoing native renal biopsy. *Am J Nephrol* 2008;**28**:478–86.
50. Gervasoni C, Ridolfo AL, Vaccarezza M, et al. Thrombotic microangiopathy in patients with acquired immunodeficiency syndrome before and during the era of introduction of highly active antiretroviral therapy. *Clin Infect Dis* 2002;**35**:1534–40.
51. Del Arco A, Martinez MA, Pena JM, et al. Thrombotic thrombocytopenic purpura associated with human immunodeficiency virus infection: demonstration of p24 antigen in endothelial cells. *Clin Infect Dis* 1993;**17**:360–3.
52. Schecter AD, Berman AB, Yi L, et al. HIV envelope gp120 activates human arterial smooth muscle cells. *Proc Natl Acad Sci USA* 2001; **98**:10142–7.
53. Franchini M, Montagnana M, Targher G, et al. Reduced von Willebrand factor-cleaving protease levels in secondary thrombotic microangiopathies and other diseases. *Semin Thromb Hemost* 2007; **33**:787–97.
54. Sahud MA, Claster S, Liu L, et al. von Willebrand factor-cleaving protease inhibitor in a patient with human immunodeficiency syndrome-associated thrombotic thrombocytopenic purpura. *Br J Haematol* 2002;**116**:909–11.
55. Brocklebank V, Wood KM, Kavanagh D. Thrombotic microangiopathy and the kidney. *Clin J Am Soc Nephrol* 2018;**13**:300–17.
56. Parkhie SM, Fine DM, Lucas GM, Atta MG. Characteristics of patients with HIV and biopsy-proven acute interstitial nephritis. *Clin J Am Soc Nephrol* 2010;**5**:798–804.
57. Wyatt CM. Will a new tenofovir prodrug for the treatment of HIV reduce the risk of nephrotoxicity? *Kidney Int* 2016;**89**:5–6.
58. Cihlar T, Ho ES, Lin DC, et al. Human renal organic anion transporter 1 (hOAT1) and its role in the nephrotoxicity of antiviral nucleotide analogs. *Nucleos Nucleot Nucleic Acids* 2001;**20**:641–8.
59. Ray AS, Cihlar T, Robinson KL, et al. Mechanism of active renal tubular efflux of tenofovir. *Antimicrob Agents Chemother* 2006;**50**: 3297–304.
60. Rodriguez-Novoa S, Labarga P, Soriano V, et al. Predictors of kidney tubular dysfunction in HIV-infected patients treated with tenofovir: a pharmacogenetic study. *Clin Infect Dis* 2009;**48**:e108–16.
61. Young B, Buchacz K, Moorman A, et al. Renal function in patients with preexisting renal disease receiving tenofovir-containing highly active antiretroviral therapy in the HIV outpatient study. *AIDS Patient Care* 2009;**23**:589–92.
62. Kiser JJ, Carten ML, Aquilante CL, et al. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. *Clin Pharmacol Ther* 2008;**83**:265–72.
63. Chan L, Asriel B, Eaton EF, Wyatt CM. Potential kidney toxicity from the antiviral drug tenofovir: new indications, new formulations, and a new prodrug. *Curr Opin Nephrol Hypertens* 2018;**27**: 102–12.
64. Kalyesubula R, Perazella MA. Nephrotoxicity of HAART. *AIDS Res* 2011;**2011**.
65. Izzedine H, Hulot JS, Vittecoq D, et al. Long-term renal safety of tenofovir disoproxil fumarate in antiretroviral-naïve HIV-1 infected patients. Data from a double-blind randomized active controlled multicenter study. *Nephrol Dial Transplant* 2005;**20**: 743–6.
66. Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naïve patients: 144 week analysis. *J Acquir Immune Defic Syndr* 2008;**47**:74–8.
67. Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. *Clin Infect Dis* 2005;**40**:1194–8.
68. Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. *AIDS* 2012;**26**:867–75.
69. Ascher SB, Scherzer R, Estrella MM, et al. Association of urinary biomarkers of kidney injury with estimated GFR decline in HIV-infected individuals following tenofovir disoproxil fumarate initiation. *Clin J Am Soc Nephrol* 2018;**13**:1321–9.
70. Hadigan C, Edwards E, Rosenberg A, et al. Microalbuminuria in HIV disease. *Am J Nephrol* 2013;**37**:443–51.
71. Kimmel PL, Umana WO, Bosch JP. Abnormal urinary protein excretion in HIV-infected patients. *Clin Nephrol* 1993;**39**:17–21.
72. Overton ET, Nurutdinova D, Freeman J, et al. Factors associated with renal dysfunction within an urban HIV-infected cohort in the era of highly active antiretroviral therapy. *HIV Med* 2009;**10**: 343–50.
73. Estrella MM, Fine DM. Screening for chronic kidney disease in HIV-infected patients. *Adv Chron Kidney Dis* 2010;**17**:26.
74. Gardner LI, Holmberg SD, Williamson JM, et al. Development of proteinuria or elevated serum creatinine and mortality in HIV-infected women. *J Acquir Immune Defic Syndr* 2003;**32**:203–9.
75. Szczech LA, Hoover DR, Feldman JG, et al. Association between renal disease and outcomes among HIV-infected women receiving or not receiving antiretroviral therapy. *Cin Infect Dis* 2004;**39**: 1199–206.

76. Rule AD, Cohen SD, Kimmel PL. Editorial comment: screening for chronic kidney disease requires creatinine reference ranges not equations. *AIDS Read* 2007;**17**:262–3.
77. Wyatt CM, Schwartz GJ, Ong'or WO, et al. Estimating kidney function in HIV-infected adults in Kenya: comparison to a direct measure of glomerular filtration rate by iohexol clearance. *PLoS One* 2013;**8**(8):e69601.
78. Mocroft A, Ryom L, Reiss P, et al. A comparison of estimated glomerular filtration rates using Cockcroft-Gault and the Chronic Kidney Disease Epidemiology Collaboration estimating equations in HIV infection. *HIV Med* 2014;**15**:144–52.
79. Siedner MJ, Atta MG, Lucas GM, et al. Poor validity of urine dipstick as a screening tool for proteinuria in HIV-positive patients. *J Acquir Immune Defic Syndr* 2008;**47**:261–3.
80. http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pd.
81. Shlipak MG, Scherzer R, Abraham A, et al. Urinary markers of kidney injury and kidney function decline in HIV-infected women. *J Acquir Immune Defic Syndr* 2012;**61**:565–73.
82. Ando M, Tsuchiya K, Nitta K. How to manage HIV-infected patients with chronic kidney disease in the HAART era. *Clin Exp Nephrol* 2012;**16**:363–72.
83. Hammer SM, Eron Jr JJ, Reiss P, et al. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. *J Am Med Assoc* 2008;**300**:555–70.
84. Gazzaruso C, Bruno R, Gazaniti A. Hypertension among HIV patients: prevalence and relationships to insulin resistance and metabolic syndrome. *J Hypertens* 2003;**21**:1377–82.
85. Lacombe K, Rockstroh J. HIV and viral hepatitis co-infections: advances and challenges. *Gut* 2012;**61**:i47–58.
86. Rockstroh JK, Bhagani S. Managing HIV/hepatitis C co-infection in the era of direct acting antivirals. *BMC Med* 2013;**11**:234.
87. AIDSinfo. Guidelines for antiretroviral use in patients with coinfections. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/26/hcv-hiv.
88. Stock PG, Barin B, Murphy B, et al. Outcomes of kidney transplantation in HIV-infected recipients. *N Engl J Med* 2010;**363**:2004–14.
89. Malat GE, Ranganna KM, Sikalas N, et al. High frequency of rejections in HIV-positive recipients of kidney transplantation: a single center prospective trial. *Transplantation* 2012;**94**:1020–4.
90. Harbell J, Terrault NA, Stock P. Solid organ transplants in HIV-infected patients. *Curr HIV AIDS Rep* 2013;**10**:217–25.
91. Canaud G, Dejucq-Rainsford N, Avettand-Fenoel V, et al. The Kidney as a reservoir for HIV-1 after renal transplantation. *J Am Soc Nephrol* 2014;**25**:407–19.
92. Muller E, Barday Z, Mendelson M, Kahn D. HIV-positive-to-HIV positive kidney transplantation-results at 3 to 5 years. *N Engl J Med* 2015;**372**:613–20.
93. Muller E, Barday Z, Mendelson M, et al. Renal transplantation between HIV-positive donors and recipients justified. *S Afr Med J* 2012;**102**:497–8.
94. Muller E, Kahn D, Mendelson M. Renal transplantation between HIV-positive donors and recipients. *N Engl J Med* 2010;**362**:2336–7.
95. Muller E, Barday Z, Kahn D. HIV-positive-to HIV-positive transplantation. *N Engl J Med* 2015;**372**:2070–1.
96. Muller E, Barday Z. HIV-Positive kidney donor selection for HIV-positive transplant recipients. *J Am Soc Nephrol* 2018;**29**:1090–5.

QUESTIONS AND ANSWERS

Question 1

A 44-year-old African-American man with a history of HIV infection, CD4 count 200 cells/μL, and viral load 4,000,000 copies/mL presents for initial evaluation of proteinuria. His primary care physician did a 24-hour urine collection which showed 5 g of proteinuria. His S[Cr] is 1.6 mg/dL and blood urea nitrogen is 20 mg/dL. His S[Cr] was 1.5 mg/dL four months ago. A complete blood count was within normal limits. You ordered a renal ultrasound which showed 14 cm echogenic kidneys bilaterally. Urine sediment was bland with no cellular casts visualized. A renal biopsy was performed. Which of the following lesions is most likely to be found on the biopsy?

A. TMA
B. HIV-associated immune complex kidney disease
C. Collapsing FSGS with microcystic tubular dilatation
D. TIN
E. ATN

Answer: C

This patient's clinical presentation is most consistent with HIVAN with nephrotic-range proteinuria, reduced eGFR, and enlarged echogenic kidneys. HIVAN is also more common in individuals of African descent. The bland urine sediment is not consistent with HIVICD. The normal complete blood count does not support a diagnosis of TMA. The nephrotic-range proteinuria suggests a glomerulopathy rather than a tubular or interstitial renal disease process.[2–5]

Question 2

A 44-year-old Caucasian man with a history of HIV infection, a CD4 count 450 cells/μL, and viral load undetectable on chronic cART, as well as HCV infection (viral load 1,000,000 copies/mL), presents to your office for initial evaluation of subnephrotic proteinuria and microscopic hematuria. His S[Cr] is 1.2 mg/dL and was previously 0.9 mg/dL six months ago. A complete blood count was normal. Urinalysis showed 3+ protein/3+ blood/trace leukocyte esterase, 10–20 RBC/hpf, and 10-20 WBC/hpf, with rare red blood cell casts. Complement C3 and C4 are reduced. You order a renal biopsy. Which of the following is the most likely diagnosis?

A. HIVAN
B. HIVICD
C. TIN
D. ATN
E. TMA

Answer: B

This patient has an active urine sediment and hypocomplementemia, which is consistent with immune complex renal disease. In the classic clinical presentation of HIVAN, patients often have nephrotic-range proteinuria. In addition, HIVAN tends to be more common in individuals of African descent. The patient is also coinfected with HCV which may make immune complex renal disease more likely. The incidence of HIVICD compared with HIVAN in renal biopsy series is increasing perhaps due to the more common treatment of HIV-infected patients earlier in the course of disease, with cART.[5,15–17]

Question 3

A 45-year-old African-American man with a history of HIV infection not on cART, CD4 count 50 cells/μL, and viral load 2,000,000 copies/mL presents to the emergency room with headache and altered mental status. He is found to have a S[Cr] of 4.5 mg/dL and BUN 54 mg/dL. His hemoglobin was 8.4 g/dL and platelet count 75,000. Haptoglobin is undetectable and LDH is 1200. His urinalysis showed 2+ protein, 3+ blood/negative leukocyte esterase. Microscopy revealed 10–20 RBC/hpf, 0–3 WBC/hpf, and no cellular casts visualized. There is no baseline S[Cr]. A renal ultrasound showed 12 cm kidneys bilaterally with normal cortical echogenicity. Which of the following is the most likely etiology of the patient's renal disease?

A. ATN
B. TIN
C. IgA nephropathy secondary to HIV infection
D. Lupus-like glomerulonephritis
E. TMA

Answer: E

This patient exhibits a classic presentation for TMA with thrombocytopenia, microangiopathic hemolytic anemia, renal failure, and altered mental status. The other answer choices do not fit this patient's clinical history.[4,5,48]

Question 4

A 47-year-old man with HIV CD4 count 350/μL and viral load 3000 copies/mL on cART presents to your office for initial evaluation of proteinuria. You perform chemistries which are notable for a S[Cr] of 1.4 mg/dL (previously 0.8 mg/dL nine months ago), BUN 24 mg/dL, glucose 100 mg/dL, HCO_3 18 mEq/L, uric acid 2.1 mg/dL, and phosphate 2.0 mg/dL. His urinalysis shows 2+ protein, 2+ blood, positive glucose, negative leukocytes, and urine pH 6.5. Which of the following would most likely explain the above disorder?

A. cART nephropathy
B. HIVAN
C. HIVICD
D. TMA
E. AKI

Answer: A

This patient has the classic presentation of a proximal tubulopathy from presumed tenofovir nephrotoxicity with normoglycemic glycosuria, hypouricemia, hypophosphatemia, bicarbonaturia (alkaline urine pH), and renal insufficiency. The other answer choices are not consistent with this clinical presentation.[5,59–63]

Question 5

A 49-year-old woman with CKD secondary to biopsy-proven HIVAN diagnosed four years ago, last CD4 count 300 μL, and HIV viral load undetectable presents to your office for management of hypertension. Her blood pressure at today's office visit is 145/95 mm Hg. Urinalysis is notable for 2+ protein and is otherwise negative. Most recent chemistries show S[Cr] 1.5 mg/dL, BUN 24 mg/dL, and potassium 4.3 mEq/L. Which of the following medications is the most appropriate first-line agent to control her hypertension?

A. Clonidine
B. Hydrochlorothiazide
C. Propranolol
D. Hydralazine
E. Ramipril

Answer: E

RAAS antagonists slow the progression of CKD. If there are no contraindications to RAAS inhibitors, these agents are the first-line antihypertensive agents in all patients with CKD and proteinuria. The other answer choices are all second-line agents that should be tried only after the dose of the ramipril has been maximized.[35–37]

Question 6

A 35-year-old African-American man with a history of HIV infection, CD4 count 500 μL, and viral load 5000 copies/mL presents to your office for initial evaluation of nephrotic-range proteinuria with a spot UPCR of 6000 mg/g creatinine. His S[Cr] is 1.6 mg/dL (S[Cr] was 1.5 mg/dL three months prior). Urinalysis revealed 4+ protein, trace blood, negative leukocytes, and negative glucose. A renal ultrasound revealed 13 cm echogenic kidneys symmetric bilaterally. A renal biopsy was performed which revealed collapsing FSGS. Which of the following would be most effective in slowing the progression of his CKD?

A. cART
B. Corticosteroids
C. Cyclosporine
D. Adrenocorticotropic hormone
E. Cyclophosphamide

Answer: A

cART would be most effective in slowing the progression of CKD secondary to HIVAN. Immunosuppression (choices B–E) should be used with extreme caution in immunocompromised patients. There are case reports of improved eGFR and regression of HIVAN lesions following initiation of cART.[5,33,34]

CHAPTER

53

Liver Disease and Chronic Kidney Disease

Joel Neugarten, Ladan Golestaneh

Albert Einstein College of Medicine, Renal Division, Montefiore Medical Center, Bronx, NY, United States

Abstract

Recent investigations have established the existence of robust cross talk between the liver and kidney. These bidirectional interactions mediate deleterious effects of liver disease on the development and progression of kidney disease as well as effects of kidney disease on liver injury and hepatic drug metabolism. Although the full spectrum and consequences of liver/kidney cross talk remains to be elucidated, the clinical relevance of these interactions is clear.

INTRODUCTION

The association of liver disease with immunologically mediated glomerular disease and tubulointerstitial renal injury has long been recognized (Table 53.1). However, more recently, attention has focused on the existence of bidirectional cross talk between the liver and the kidneys. It has been suggested that chronic liver disease may accelerate the progression of CKD and that CKD may accelerate the progression of chronic liver disease, as well as alter hepatic drug metabolism. The existence of cross talk between the liver and the kidney may affect therapeutic interventions directed toward slowing the progression of both liver and kidney disease and may significantly influence drug dosing in patients with combined liver and renal disease.

HEPATORENAL SYNDROME

The most dramatic manifestation of liver/kidney cross talk is the development of hepatorenal syndrome (HRS).[1–5] Our understanding of the pathogenesis of the HRS has undergone a dramatic evolution in the past decade. From its initial conception as a functional disorder mediated by systemic circulatory dysfunction accompanying decompensated liver failure, HRS has been transformed into a more complex systemic disorder characterized by systemic inflammation and multiorgan dysfunction.[1–5] In 2015, the International Club of Ascites redefined HRS to incorporate a modified version of the Kidney Disease: Improving Global Outcomes criteria for the diagnosis of acute kidney injury (AKI).[6,7] HRS-AKI was defined as AKI that developed in a patient with cirrhosis and ascites that did not respond to diuretic withdrawal and plasma expansion in the absence of shock, nephrotoxic drugs, or evidence of structural renal injury.

The classification of HRS into types 1 and 2 was not incorporated into the new definition. In earlier nomenclature, type 1 HRS was characterized by rapidly progressive renal failure, whereas type 2 HRS referred to a more indolent decline in renal function that was more moderate in severity. Type 2 HRS was characterized by refractory ascites and diuretic resistance, with an average survival of 6 months.[1,3] Type 2 HRS is now referred to as HRS-CKD.

Role of Systemic Circulatory Dysfunction in HRS

HRS-AKI has primarily been defined as a renal event; however, new insights into the pathophysiology of decompensated liver disease suggest that HRS is also an indicator of severe systemic inflammation, indolent multiorgan dysfunction, and failure of hemodynamic compensatory mechanisms. Cirrhosis is characterized by deranged liver architecture, leading to increased intrahepatic vascular resistance that in turn leads to increased portal vein pressure.[1–5] Release of systemic vasodilators, classically thought to arise as a response to portal hypertension, leads to peripheral vasodilation and decreased vascular resistance. Numerous vasodilatory agents have been proposed as pathogenetic mediators.[1–5] Decompensated cirrhosis is associated with increased endothelial cell production of nitric

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00053-X

TABLE 53.1 Kidney Lesions Associated with Liver Disease*

Hepatitis C	Membranoproliferative glomerulonephritis with or without cryoglobulinemia
	Membranous nephropathy
	Focal and segmental glomerulosclerosis
	Immunoglobulin A nephropathy
	Fibrillary glomerulopathy
	Immunotactoid glomerulopathy
	Thrombotic microangiopathy
	Amyloidosis
	Interstitial nephritis
	Diabetic nephropathy
Hepatitis B	Membranous nephropathy
	Immunoglobulin A nephropathy
	Membranoproliferative glomerulonephritis
	Minimal change disease
	Focal and segmental glomerulosclerosis
	Crescentic glomerulonephritis
	Polyarteritis nodosa
	Cryoglobulinemia
	Amyloidosis
Alcoholic cirrhosis	Immunoglobulin A nephropathy
	Membranoproliferative glomerulonephritis with immunoglobulin A deposition
Primary sclerosing cholangitis	Membranous nephropathy
	Membranoproliferative glomerulonephritis
	Tubulointerstitial nephritis
	Antineutrophil cytoplasmic antibody-associated vasculitis/glomerulonephritis
Primary biliary cirrhosis	Interstitial nephritis
	Membranous nephropathy
	Antineutrophil cytoplasmic antibody-associated vasculitis/glomerulonephritis
	Antiglomerular basement membrane disease
Alpha-1 antitrypsin deficiency	Membranous nephropathy
	Antiglomerular basement membrane disease

* *Cause and effect relationships have not been established in all cases.*

oxide, carbon monoxide, prostacyclin, calcitonin gene-related peptide, adrenomedullin, endocannabinoids, and plasma substance P which may contribute to arterial vasodilatation.[1–5] An increase in regional blood flow in response to portal hypertension, splanchnic vasodilation, and portosystemic shunting leads to pooling of blood in the splanchnic circulation.[1–5] The recruitment of compensatory mechanisms to maintain renal perfusion in the face of reduced effective arterial volume constitute the hallmark of HRS. These compensatory mechanisms include release of systemic vasoconstrictors, upregulation of the renin–angiotensin system, and activation of the sympathetic nervous system.

Animal models of portal vein hypertension support a direct neural connection between hepatic osmo- and baroreceptors and the kidney.[8,9] Acute induction of experimental portal hypertension activates hepatic baroreceptors, which in turn increase renal sympathetic efferent nerve activity. Activation of the renal sympathetic nervous system is associated with renal vasoconstriction and reduced renal blood flow, increased renin release, and enhanced renal tubular salt and water reabsorption.[1–5] Reduced effective circulating volume also leads to increased nonosmotic release of vasopressin and increased generation of potent vasoconstrictors, including leukotrienes and endothelin-1.[1–5] In contrast, local compensatory renal vasodilators, such as prostaglandins, are reduced.[1–5] Consistent with this scenario, an increased renal resistive index on renal Doppler ultrasonography, an index of reduced diastolic renal blood flow, predicts the subsequent development of HRS.[10–12]

Lack of cardiac compensation in response to severe systemic vasodilation worsens this cycle. In early stages of cirrhosis, increased cardiac output maintains renal perfusion.[1–5] However, in advanced cirrhosis, the ability of the heart to compensate is limited by cirrhotic cardiomyopathy and cardiac output declines. In this setting, beta blockers are deleterious to cardiac function and worsen hemodynamic dysfunction by sensitizing the sympathetic nervous system. In addition, renin–angiotensin blockade may increase renal vasoconstriction and promote AKI. Because cardiac preload may play a crucial role in cardiac function in this setting, nitrates are also contraindicated.

Hepatorenal Syndrome as a Systemic Inflammatory State

It has recently been suggested that the primary factor responsible for the release of vasodilatory mediators in HRS is increased circulating levels of cytokines and chemokines resulting from chronic inflammation associated with decompensated liver disease.[2,13] Cirrhosis is associated with increased gastrointestinal permeability, altered gastrointestinal microbiome, and translocation

of bacteria and bacterial products (pathogen-associated molecular patterns) from the gastrointestinal tract into the circulation.[2] These bacterial products, along with danger-associated molecular patterns released by apoptotic and necrotic hepatocytes, stimulate the production of proinflammatory cytokines and chemokines, reactive oxygen and nitrogen species, and activate immune cells, which in turn magnifies the proinflammatory response.[2]

Decompensated cirrhosis is associated with increased circulating levels of proinflammatory cytokines and chemokines including interleukin-6 (IL-6), IL-8, and tumor necrosis factor-alpha (TNF-α), which may contribute to renal injury.[2,5,13,14] Circulating levels of IL-6, TNF-α, and vascular cell adhesion molecules are higher in patients with cirrhosis and HRS-AKI compared with those without HRS-AKI.[5] Patients with spontaneous bacterial peritonitis and renal dysfunction have higher IL-6 and TNF-α levels than patients with spontaneous bacterial peritonitis without renal dysfunction.[14] Similarly, other investigators have correlated renal dysfunction associated with decompensated liver failure with circulating levels of IL-6, IL-8, and irreversibly oxidized nonmercaptalbumin 2.[13]

The functional nature of HRS has recently been challenged. Renal histologic injury has never been systematically excluded because careful renal biopsy studies in patients who satisfy the clinical criteria used to diagnose HRS have not been performed. Urinary biomarkers suggest tubular injury in HRS-AKI diagnosed by traditional criteria.[5,15] Pathogen-associated molecular patterns and danger-associated molecular patterns may be injurious to proximal tubule epithelial cells and downregulate mitochondrial metabolism. Lastly, it has been suggested that cholestasis, with resultant hyperbilirubinemia, may promote deposition of bilirubin in the renal tubular lumen to induce tubular obstruction and direct toxic tubular injury.[16,17] This disorder has been referred to as bile cast nephropathy.[16,17] Bile acid casts were demonstrated in 11 of 13 renal specimens obtained from patients meeting the clinical criteria for HRS.[17]

HRS-CKD

HRS-CKD is uncommon, accounting for only 5−11% of patients with cirrhosis and renal dysfunction. Treatment with intravenous albumin and terlipressin or noradrenaline can reverse HRS-CKD in more than half the cases.[18,19] However, responders experience a high relapse rate early after withdrawal of therapy. Relapse occurs in two-thirds of initial responders.[18,19] Multiple relapses in the same patient are also frequent.[18,19] It has been postulated that a persistent proinflammatory state or rebound activation of vasoconstrictor pathways are responsible for this high relapse rate.[18]

Treatment of HRS-CKD with albumin volume expansion and vasoconstrictors is controversial and is not recommended by international practice guidelines due to inconsistent outcomes data.[2,18] In a retrospective study of 56 patients with "type 2" HRS awaiting liver transplant and treated with terlipressin and albumin, no difference in pretransplantation or posttransplantation outcomes was observed between responders and nonresponders.[19] There was no difference in the mortality of wait-listed responders and nonresponders. After liver transplantation, there was no difference in estimated glomerular filtration rate (eGFR) or in the development of CKD on follow-up, ranging up to 1 year, based on response to therapy. Length of hospitalization, development of AKI, need for renal replacement therapy (RRT), and survival did not differ between responders and nonresponders. The authors suggest that the failure of therapy to improve outcomes in these patients may reflect unrecognized underlying renal parenchymal injury.

Transjugular intrahepatic portosystemic shunting as a bridge to orthotopic liver transplantation has been associated with improved renal function in patients classified as type 2 HRS.[20] European Association for the Study of the Liver Clinical Practice Guidelines state that transjugular intrahepatic portosystemic shunting "could be suggested in selected patients with HRS-NAKI."[2]

Intra-abdominal hypertension may also contribute to hemodynamic-mediated renal dysfunction in patients with decompensated cirrhosis with ascites. Clinical studies of decompensated liver disease have demonstrated correlations between intra-abdominal pressure and sodium avidity and azotemia. A reduction of intra-abdominal pressure by paracentesis is associated with an improvement in renal blood flow and urine output in patients with decompensated cirrhosis and intra-abdominal hypertension.[4,21] In a murine model of cirrhosis, increased intra-abdominal pressure was associated with renal dysfunction.[22] It is postulated that nephro-congestion leads to an increase in intratubular pressure, a reduced pressure gradient for filtration, and reduced glomerular filtration rate.

Serum creatinine concentration (S[Cr]) is a poor marker of renal disease in liver failure, frequently overestimating renal function and underestimating renal injury. Because the Model for End-Stage Liver Disease score uses S[Cr] as a marker of renal disease, the lack of sensitivity of S[Cr] for the diagnosis of CKD or AKI is highly problematic vis-a-vis allocation of donor liver organs. In patients with cirrhosis, where significant muscle atrophy, reduced hepatic conversion of creatine

into creatinine, and reduced tubular secretion of creatinine are commonplace, significant renal dysfunction may be masked by an ostensibly normal S[Cr] value.

HEPATITIS C VIRUS INFECTION

Hepatitis C virus (HCV) infection affects approximately 3.5 million Americans and over 71 million individuals worldwide.[23] The annual incidence rate in the US is estimated to be 13.9 cases per 100,000 population.[24] HCV infection is among the most common causes of liver transplantation in the US and Europe. HCV infection disproportionately affects patients with CKD and end-stage renal disease (ESRD). Among CKD patients who have never been transfused, the prevalence of HCV antibody is approximately 10-fold higher than in the blood donor population.[25] HCV infection not only represents a major cause of morbidity and mortality in the CKD population but may also independently influence the natural history of the underlying kidney disease.

Numerous investigators have suggested that HCV infection is associated with the development and accelerated progression of CKD leading to an increased risk for ESRD. Although many epidemiologic studies show an association between HCV infection and CKD, as do several meta-analyses, the results have not been entirely consistent. In fact, some studies have found a protective effect of HCV infection on CKD.

Fabrizi et al.[26] performed a meta-analysis of 40 studies, containing over 4 million patients, that used multivariate analysis to examine the association of HCV infection with CKD. An association between HCV infection and an increased incidence of CKD was demonstrated in 15 longitudinal studies containing 2,299,134 patients (295,773 of whom were HCV-infected) (HR 1.54). The diagnosis of HCV infection was based on anti-HCV seropositivity, detection of HCV RNA, or an administrative code indicating a diagnosis of HCV infection. The risk of CKD increased with aging and duration of follow-up. HCV infection was also associated with the prevalence of proteinuria in 10 cross-sectional studies containing 378,769 patients (63,365 of whom were HCV-infected) (HR 1.63). Overall, no association between HCV and an increased prevalence of CKD was observed. However, an association between HCV and an increased prevalence of CKD was demonstrable in Asian populations (HR 1.2).

A recent report by Tartof et al.[27] found that the risk of a 25% reduction in eGFR or progression to ESRD was greater in a cohort of 1603 subjects with CKD and HCV infection compared with 151,974 subjects with CKD alone.

Another meta-analysis examined the association of HCV with CKD in human immunodeficiency virus (HIV)/HCV coinfected patients.[28] An association between HCV infection and increased risk of incident CKD was demonstrated in eight longitudinal studies of 105,462 coinfected patients (HR 1.64). HCV infection was also an independent risk factor for proteinuria in six studies that included 26,835 coinfected patients (HR 1.23). In contrast, in five cross-sectional studies of 13,853 patients, the prevalence of CKD was not increased in HIV/HCV coinfected patients.

Representative of studies that reported no effect or a protective effect of HCV infection on CKD is a cohort of over 13,000 anti-HCV seropositive subjects from an urban area with a high prevalence of HIV studied by Moe at al.[29] In a cross-sectional analysis of these subjects, HCV infection was associated with a reduced prevalence of CKD compared with anti-HCV seronegative subjects. In a longitudinal analysis of a subset of over 7000 subjects without CKD followed for a median of 3.5 years, there was no difference in the incidence of CKD in adjusted analysis. In another adjusted analysis of a demographically diverse cohort of insured individuals followed for a mean of over 2 years, Asrani et al.[30] found no difference in the prevalence, incidence, or rate of progression of CKD among 13,384 HCV-infected subjects compared with 154,185 subjects without HCV infection.

HCV infection was associated with proteinuria and an increased mean eGFR, but not with CKD, among participants in the 1988–1994 and 1999–2012 National Health and Nutritional Examination Survey ($n = 33{,}729$ and 15,029, respectively).[31,32] Rogal et al.[33] followed 71,528 US veterans for a mean of 6 years. Recent HCV seroconversion was documented in 2599 of the cohort. They found that HCV-infected individuals were less likely to develop CKD, but showed no difference in the rate of progression of CKD. However, in a much larger cohort of 920,531 uninfected and 100,518 HCV-infected US Veterans, Molnar et al.[34] found an association between HCV infection and increased incidence of CKD, progressive loss of renal function, and the development of ESRD.

In adjusted analysis of HCV/HIV coinfected women, Tsui et al.[35] reported no association between HCV infection and the prevalence of CKD, but found that in those with established CKD, HCV infection was associated with accelerated progression. In a large cohort of 474,369 US Veterans (52,874 of whom were anti-HCV seropositive), Tsui et al.[36] found that although the prevalence of CKD was lower in infected patients and there was no significant difference in the rate of progression of CKD, HCV-infected patients who did progress did so at a more rapid rate, leading to a higher incidence of ESRD.

Interpretation of available clinical studies is complicated by heterogeneity in subject demographics, including differences in age, sex, ethnicity, socioeconomic status, alcohol use, angiotensin-converting enzyme inhibitor therapy, and coinfection with HIV or hepatitis B virus (HBV), and by differences in the number of treatment-naïve vs. experienced patients. Methods to identify HCV infection differ among the studies, and include detection of anti-HCV antibody, detection of HCV RNA, and use of administrative codes to diagnose HCV infection. Because only 60–70% of HCV-infected patients demonstrate chronic viremia, diagnosis of HCV infection solely by the detection of HCV RNA may miss mild cases, leading to severity bias. Errors in administrative coding may also lead to misclassification. In addition, multiple confounding factors must be considered. Patients infected with HCV are more likely to suffer from diabetes, hypertension, obesity, HIV, cirrhosis, coronary artery disease, and hyperlipidemia and to have a history of intravenous drug use. Unmeasured confounding variables represent a significant issue in analyses of these data. A longer duration of HCV infection has been associated with an increased risk of CKD.[37] In this regard, many of the cohorts that failed to demonstrate an association between HCV infection and incident CKD were followed for only 2–3 years. Patients with HCV may also receive a higher intensity of medical care with more frequent follow-up visits, leading to detection bias due to earlier detection of CKD.

The REVEAL-HCV Study Group[38] found an increased CKD prevalence in those infected with genotype 2. This observation might help explain inconsistent data regarding the association of HCV infection and CKD. Meta-analysis has shown that the pooled risk for CKD among HCV-infected cohorts is higher in Asian populations than in the US or Europe.[26] These geographic variations in CKD risk parallel the relative prevalence of the HCV genotype 2. However, another publication from the REVEAL-HCV Study Group reported that genotype 1, not genotype 2, was a strong predictor of ESRD in their cohort.[39] Numerous other investigators found no association between HCV genotype and the incidence or prevalence of CKD.[37,40] Studies seeking to establish an association between CKD and viremia in HCV-infected patients have also yielded inconsistent results.[37–43] Peters et al.[40] reported an association between HCV viremia and the incidence rate of CKD among over 8000 HIV/HCV coinfected patients. Those who cleared their viremia showed an incidence rate similar to anti-HCV seronegative patients. Similarly, a high plasma HCV RNA level was associated with the prevalence of CKD in separate cohorts of 434 and 552 anti-HCV seropositive patients, as well as with the risk of progressive CKD in a third cohort of 34,441 HIV/HCV coinfected patients.[37,38,42] However, other investigators found no relationship between viremia and the incidence, prevalence, or rate of progression of CKD.[41,44]

Numerous mechanisms have been suggested to explain the purported association of HCV with CKD. Glomerular disease is a well-described, albeit uncommon, extrahepatic manifestation of HCV infection.[45–47] A systemic immune response to HCV infection is thought to contribute to glomerular injury. Glomerular disease may be mediated by HCV-antibody immune complex deposition with or without cryoglobulin formation. Deposition of immune complexes containing viral antigens has been demonstrated in mesangial and subendothelial locations. The most common histologic pattern of glomerular injury is membranoproliferative glomerulonephritis; however, membranous glomerulopathy, focal and segmental glomerulosclerosis, IgA nephropathy, immunotactoid and fibrillary glomerulopathies, amyloidosis and thrombotic microangiopathy have been described in HCV-infected patients (Table 53.1).[45–49] The prevalence of membranoproliferative glomerulonephritis and of cryoglobulinemia in patients chronically infected with HCV, identified by administrative codes reported to the National Inpatient Sample of the Healthcare Cost and Utilization project, has been reported to be 0.38% and 0.33%, respectively.[50] Similarly, the prevalence of membranoproliferative glomerulonephritis and of cryoglobulinemia, identified by administrative codes, among 34,204 HCV-infected hospitalized US veterans was 0.36% and 0.57%, respectively.[51] Postmortem series have identified a higher prevalence of nondiabetic glomerular disease in HCV-infected subjects, ranging from 8.8 to over 50% of cases.[47,52] A series of kidney biopsies obtained from liver transplant recipients showed glomerulonephritis in over 83% of cases.[49] Perhaps the inconsistencies in these data can be reconciled by the observation that many patients with membranoproliferative glomerulonephritis documented by kidney biopsy have clinically silent renal involvement.[49]

HCV may also exert direct cytopathic effects in renal tissue.[45,46,53] HCV viral particles or antigen has been identified in glomeruli, endothelial cells, and tubules in renal biopsy specimens from HCV-infected patients.[45,46] HCV exposure has also been associated with increased expression of toll-like receptors in renal glomeruli.[54] HCV core protein also directly inhibits insulin signaling, leading to a state of insulin resistance associated with compensatory hyperinsulinemia.[45,46,55] HCV activates the mammalian target of

rapamycin/ribosomal S6 kinase signal transduction pathway, which in turn alters the function of glucose transporters, insulin receptors, and the gluconeogenesis enzyme phosphoenolpyruvate carboxykinase 2, leading to insulin resistance.[45,46,55] HCV core protein induces increased oxidative stress and induces endothelial dysfunction by decreasing endothelial nitric oxide synthase activity and nitric oxide synthesis. HCV also exerts immunomodulatory effects.[45,46,55] HCV infects peripheral dendritic cells, monocytes, and macrophages and stimulates B cells, which in turn modulates B- and T-cell function. HCV core protein increases the synthesis of proinflammatory cytokines including IL-6, C-reactive protein, and nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB).[55] Other downstream effects of HCV include increased levels of insulin-like growth factor-1, transforming growth factor-beta (TGF-β), and endothelin-1, and increased angiotensin II type 1 receptor density.

Use of DAA Medications to Eradicate HCV in Patients with CKD

Newer and highly effective therapeutic strategies for treatment of HCV have had a significant impact in the CKD and ESRD populations and may play a role in the prevention of HCV-related kidney injury. In the past, interferon and ribavirin constituted the only treatment option for HCV, and outcomes were suboptimal because of adherence issues related to toxicity.[56] By far, the most serious complication was hemolytic anemia associated with ribavirin, which precluded its use in most CKD patients. Research into the HCV life cycle identified the opportunity to arrest viral replication and infectivity within hepatocytes.[57] The four types of direct acting antivirals (DAAs) that were developed include (1) NS3/4A protease inhibitors, (2) NS5A inhibitors, (3) NS5B nonnucleoside polymerase inhibitors, and (4) NS5B nucleoside polymerase inhibitors.[57] They are given for a finite duration, usually in combination, avoid the difficult adverse effects of interferon-based therapies, and are curative. HCV type 1 is most successfully treated with combination DAA therapy, with cure rates exceeding 90%.[57] Initial DAA regimens used these agents in conjunction with pegylated interferon and ribavirin. Sofosbuvir-containing regimens later supplanted these strategies, and though effective, were contraindicated in patients with a GFR less than 30 mL/min.[58] Sofosbuvir is a nucleotide prodrug inhibitor of NS5B polymerase whose active metabolite is eliminated predominantly through the kidney.[58,59] Phase 3 clinical studies examining sofosbuvir and ledpasvir combinations did not include patients with CKD.[59–61] However, sofosbuvir was subsequently found to be well tolerated and effective in patients with stages 3–5 CKD, including dialysis-dependent CKD.[58,62–66] Notwithstanding these data, FDA approval of sofosbuvir is limited to individuals with an eGFR >30 mL/min/1.73 m^2. Other regimens are now available for advanced CKD[58,62]

The C-SURFER trial was the first to examine an all oral, ribavirin-free treatment for HCV in patients with stages 4 and 5 CKD.[67] The regimen used was grazoprevir (NS 3/4A protease inhibitor) in combination with elbasvir (NS5A inhibitor). The recruited patients were infected with HCV genotype 1; 76% were dialysis-dependent. Less than 1% of the grazoprevir and elbasvir combination is excreted by the kidney and less than 5% of grazoprevir is removed by hemodialysis.[67,68] The regimen was generally well tolerated and after 12 weeks of therapy, 99% achieved a sustained virologic response (SVR).[67] In the RUBY-1 trial of 20 patients with hepatitis C infection and stage 4 CKD (14 of whom required dialysis), the combination of ombitasvir/partparevir/ritonavir and dasabuvir with or without ribavirin was examined.[69] After 12 weeks of therapy, all 20 patients had completed the trial and 18 achieved SVR. A phase 3 multicenter, open-label trial (EXPEDITION 4) evaluated a 12 week course of therapy with combination of glecaprevir (NS3/4A protease inhibitor) and pibrentasvir (NS5A inhibitor) in 104 patients infected with HCV genotypes 1, 2, 3, 4, 5, or 6 and a baseline eGFR <30 mL/min/1.73 m^2.[70] SVR was achieved in 98% of patients. The current DAA regimens approved for use in patients with advanced CKD (stages 4 and 5) include Zepatier (combination of grazoprevir and elbasvir), Viekira (combination of ombitasvir, paritaprevir, dasabuvir, and ritonavir), and Mavyret (combination of glecaprevir and pibrentasvir).

The European Association for the Study of the Liver Recommendations on Treatment of Hepatitis C, 2018 state that "All patients with HCV infection must be considered for therapy, including treatment-naïve and individuals who failed to achieve SVR after prior treatment."[71] Many commentators have suggested that patients with mild to moderate CKD are especially attractive candidates for therapy and strongly recommended universal therapy of such patients. They emphasize the potential benefits of SVR on prevention of diabetes mellitus, improvement in glycemic control and cardiovascular outcomes and amelioration of CKD progression. The purported benefits of SVR on CKD are based on an emerging body of evidence suggesting that SVR is associated with a reduced incidence and prevalence of CKD, an improvement in eGFR, a slower rate of progression of CKD, and a reduced incidence of ESRD. Although the benefit of HCV therapy and SVR on renal outcomes in HCV-associated

glomerulonephritis is well established, the effects of therapy designed to achieve SVR on renal outcomes in the broader CKD population have not been entirely consistent. Moreover, studies are often compromised by small numbers of subjects, the frequent lack of an untreated control group, and heterogeneity in treatment regimens. These studies must also be interpreted in light of the bias inherent in the selection of patients for treatment.

Feng et al.[72] performed a meta-analysis of 11 clinical trials involving 225 patients with HCV-associated glomerulonephritis treated with interferon-based antiviral therapy. They reported a 2.71 g/24 h decrease in urinary protein excretion associated with SVR. Mean S[Cr] fell by 0.23 mg/dL. Others have found that DAA therapy is associated with a full or partial remission of cryoglobulinemic glomerulonephritis in nearly two-thirds of cases.[73]

Among 12,384 Taiwanese HCV-infected patients who were treated with pegylated interferon plus ribavirin and followed for over 8 years, the multivariate-adjusted risk of ESRD, identified by administrative codes, was reduced by 85% compared with propensity score-matched untreated HCV controls.[74] Among 919 HCV-infected patients treated with an interferon-based regimen in the same Taiwanese cohort, the 7-year cumulative incidence of CKD was lower by 58% in adjusted analysis compared with propensity score-matched untreated HCV controls.[75] Similar results have been reported by other investigators using interferon-based regimens to treat HCV.[37,74,76,77] In a cross-sectional study of 552 HCV-infected patients, there was a fivefold decrease in CKD in those who were treated with an interferon-based regimen during a 7-year follow-up.[37] Among 650 HCV-infected patients treated with interferon with or without ribavirin, the failure to achieve a SVR was associated with a 2.67-fold greater risk of developing CKD.[76] Among 12,534 HCV-infected patients treated with pegylated interferon and ribavirin and followed for a mean of 3.3 years, antiviral therapy was associated with a lower risk of ESRD in adjusted analysis (HR 0.15).[74] Consistent with these observations, Park et al.[77] observed a 30% reduction in the risk of developing CKD among 55,000 newly diagnosed HCV-infected individuals treated with interferon with or without ribavirin or boceprevir, telaprevir, sofosbuvir, or simeprevir plus pegylated interferon and ribavirin or all oral therapy.

Similar benefits have been described among patients treated exclusively with DAA therapies.[58,78,79] Sise et al.[58] treated 98 HCV-infected patients with stages 1–3 CKD with a sofosbuvir-based regimen. In those with an eGFR less than 60 mL/min/1.73 m^2 at baseline, a multivariate linear regression model indicated that SVR was associated with a 9.3 mL/min/1.73 m^2 improvement in GFR over a 6-month posttreatment follow-up period. In contrast, no change in eGFR was observed in those with stage 1 or stage 2 CKD at baseline. However, this study did not include an untreated control group. Medeiros et al.[79] also observed an increase in eGFR in HCV-infected patients 1 year after treatment with a sofosbuvir-based regimen.

In contrast, other studies show no improvement in renal outcome after DAA therapy and SVR.[43,80,81] A pooled analysis of phase 3 clinical trials of therapy with ombitasvir/paritaprevir/ritonavir or dasbuvir with or without ribavirin involving 5539 genotype 1 HCV-infected patients with stages 2–5 CKD and 464 placebo-treated controls followed for 52 weeks post treatment showed no significant change in eGFR from baseline, assessed 52 weeks after therapy.[81] However, those patients with stage 1 CKD at baseline experienced a significant decline in eGFR. One year after treatment of 523 HCV-infected patients with mostly sofosbuvir-containing DAA regimens, the rate of decline in eGFR in those who achieved SVR was not different from untreated HCV-infected patients but was less than in treated patients who failed to achieve SVR.[80] Rossi et al.[43] also failed to find an association between SVR and the rate of eGFR decline in HCV/HIV coinfected patients.

First-generation DAAs have been associated with transient AKI during therapy, and in the case of telaprevir, with long-term reductions in eGFR.[82,83] Several trials of second-generation DAAs report an increased, albeit low, incidence of AKI during therapy, which may occur more frequently with sofosbuvir-containing regimens and in those with more advanced CKD at baseline.[43,84–88] However, this signal has not been observed in other trials.[58,89] The use of different criteria among various trials to define adverse renal events confounds interpretation of data. A persistent reduction in eGFR measured 12 weeks after the end of therapy with second-generation DAAs as compared with baseline values has also been reported in many studies.[85,86,90,91] Saxena et al.[84] reported AKI, identified by administrative codes, in 2% of all patients treated with a sofosbuvir-containing regimen. However, the rate of AKI rose to 15% in those with an eGFR less than 45 mL/min/1.73 m^2 at baseline. Among 43 HCV-infected patients treated with sofosbuvir-containing regimens, eGFR fell more than 6 mL/min/1.73 m^2 at the end of therapy and, in those with cirrhosis, failed to recover 24 weeks after therapy. A meta-analysis of 13 trials which included 6884 HCV-infected subjects

found that DAA therapy was associated with renal functional deterioration in those with advanced CKD at baseline.[92] In contrast, the incidence of sosofovir-induced AKI was not increased among 98 HCV-infected patients with stages 1–3 CKD at baseline who were treated with a sosofovir-based regimen.[58] Although nearly 7% of patients experienced a transient episode of AKI with full recovery of renal function, in all but one case, the investigators deemed all these episodes to be unrelated to sofosbuvir therapy.

Several studies suggest that therapy of HCV-infected liver transplant recipients with antiviral therapy has a beneficial effect on renal outcomes.[93–95] Satapathy et al.[94] treated 204 liver transplant recipients with interferon and/or DAA and followed them for a median of 5.5 years. They found an 88% lower risk of CKD, a less steep rate of decline of eGFR over time and an 85% lower risk of ESRD in treated patients. Similarly, in a study of 99 HCV-infected liver transplant recipients with stage 2 CKD at baseline who were treated with pegylated interferon and ribavirin and followed for up to 5 years, SVR was associated with a 16 mL/min/1.73 m^2 improvement in eGFR compared with nonresponders.[93] However, among 31 treated patients with stage 3 CKD at baseline, there was no difference in eGFR between responders and nonresponders.

The decision whether or not to treat an HCV-infected individual suffering from late-stage CKD with a second-generation DAA entails consideration of the individual's kidney transplantation status. Immediate therapy may be warranted in living donor kidney transplant candidates, CKD due to HCV-related glomerulonephritis or in those suffering from advanced liver disease at high risk for decompensated liver failure. However, successful treatment of an HCV-positive candidate for a deceased donor kidney may result in a substantial delay or a lost opportunity for transplantation. The wait list for a kidney harvested from a deceased HCV-positive donor is on average one year shorter, and up to several years shorter, than for a HCV-negative deceased donor, giving HCV-positive recipients a substantial advantage in securing a kidney transplant.[96] Thus, deferring DAA therapy until after kidney transplantation may result in a substantial reduction in wait time. This advantage is greater in geographic regions with a high prevalence of anti-HCV seropositive deceased kidney donors and in those regions with a long wait list. Of course, patient preference and whether or not the local kidney transplant center accepts anti-HCV seropositive deceased donor kidneys are of paramount importance. Other considerations include HIV coinfection, which may increase the risk of decompensated liver failure, dialysis vintage which determines accumulated wait time credit, the average wait time for a deceased donor kidney in the local geographic area, and the HCV genotype which determines the complexity of treatment.

HEPATITIS B VIRUS INFECTION

Controversy also surrounds the relationship between CKD and HBV infection. A meta-analysis of four longitudinal studies which included 184,937 subjects, 36,192 of whom were infected with HBV, found that HBV infection was associated with incident ESRD (HR 3.78 [1.48,6.25]) as well as incident CKD, however, the latter association did not achieve statistical significance.[97] In contrast, the meta-analysis found no relationship between HBV infection and the prevalence of CKD in seven cross-sectional or case-control studies which included 109,889 subjects, 8023 of whom were infected with HBV. The meta-analysis also found no relationship between HBV infection and the prevalence of proteinuria. More recently, several large studies have confirmed the association of HBV with CKD. Si et al.[98] found an association between HBV infection and incident CKD, identified by administrative codes, among 469,459 subjects followed for 9.1 years, of which 14,871 were seropositive for HB surface antigen. Similarly, Hong et al.[99] found an association between HBV infection and incident proteinuria, but not incident eGFR <60 mL/min/1.73 m^2, among 299,913 subjects followed for 5.6 years, of which 11,209 were seropositive for HB surface antigen. Unlike the aforementioned meta-analysis, Kim et al.[100] found an association between HBV infection and prevalent eGFR <60 mL/min/1.73 m^2 and proteinuria among 265,086 subjects, of which 10,048 were seropositive for HB surface antigen.

Many of the same limitations identified in studies of HCV infection and CKD also apply to studies that address the relationship between HBV infection and CKD. Similarly, the mechanisms invoked to explain the effects of HBV infection on the development and progression of CKD are analogous to those postulated to mediate the effects of HCV infection on CKD. Proposed mediators include enhanced oxidative stress, upregulation of inflammatory cytokines, insulin resistance, modulation of immune responses, and cytopathic effects of HBV on renal tissue.

Therapy of HBV-associated glomerulonephritis with an interferon-based regimen or with lamivudine leads to remission of proteinuria in nearly two-thirds of cases and reduces the risk of progression to ESRD.[52,101–103] Eradication of HBV infection reduced the risk of incident ESRD in a propensity-matched cohort of HBV-infected subjects with CKD.[103] On the other hand, most of the nucleos(t)ide analogs used to treat HBV infection have

been associated with deterioration of renal function, likely related to the nephrotoxicity of these agents.[104] The sole exception is tebivudine which was associated with an increase in eGFR in treated patients which persisted after 4–6 years of follow-up. The mechanisms responsible for this effect are unclear insofar as no relationship was observed between sustained viral response and the improvement in eGFR.[104]

NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (NAFLD) represents a burgeoning public health concern of enormous importance. NAFLD is defined by the accumulation of liver fat exceeding 5% of liver weight in the absence of significant alcohol intake or other secondary causes of chronic liver disease.[105–111] NAFLD encompasses a spectrum of liver injury ranging from simple steatosis to the more severe inflammatory form, nonalcoholic steatohepatitis (NASH), and ultimately advanced fibrosis and cirrhosis.[105–111] 20–30% of the adult population of western countries are estimated to suffer from NAFLD.[105–111] The prevalence of NALFD is even greater among the obese and among diabetics. NAFLD is generally regarded as the hepatic manifestation of the metabolic syndrome.

Complex interrelationships have been proposed to explain cross talk between the liver and kidney in NAFLD. Cross talk may be mediated by the synthesis and systemic release of proinflammatory and procoagulant factors released by steatotic, necrotic, and apoptotic hepatocytes, nonparenchymal Kupffer cells and hepatic stellate cells. Cross talk may also be mediated by insulin resistance or dyslipidemia associated with NAFLD. Specifically, NAFLD has been associated with increased circulating levels of inflammatory cytokines and other inflammatory mediators (TNF-α, TGF-β, IL-6, and C-reactive protein), a procoagulant profile (increased plasminogen activator inhibitor-1, decreased tissue plasminogen activator, and decreased fibrinolytic factors), and evidence of increased oxidative stress.[105–111] Increased production of fetuin A by the liver in NAFLD promotes insulin resistance by inhibiting insulin signal transduction and by reducing adiponectin levels in adipose tissue and in plasma.[105–111] A fall in adiponectin levels reduces activation of the energy sensor, 5′ adenosine monophosphate activation protein kinase, which in turn acts to decrease insulin sensitivity and induce insulin resistance and dyslipidemia. These effects are mediated by the influx of free fatty acids into the liver to increase liver gluconeogenesis, lipogenesis, and fatty acid oxidation.[105–111] These actions promote hepatic inflammation, cell proliferation, and fibrosis. An increase in proinflammatory cytokines and a decrease in protective adipokines released from inflamed visceral adipose tissue may also contribute to both liver and kidney injury.[105–111] These metabolic alterations make the liver both a target and a contributor to a systemic inflammatory response in which the kidney is also a target. In addition, endothelial dysfunction and activation of the renin–angiotensin system have been postulated to play a role in liver-kidney cross talk in NAFLD.

Despite the elucidation of intricate pathways that might mediate liver-kidney cross talk in this disorder, the clinical data supporting the role of NAFLD in promoting CKD remains controversial. Recent studies have demonstrated an association between NAFLD and CKD which survives multivariate analysis, leading to the suggestion that NAFLD may be an independent risk factor for the development and progression of CKD.[105–111] However, NAFLD and CKD share multiple common risk factors, and both have been associated with abdominal obesity, hypertension, diabetes mellitus, dyslipidemia, and insulin resistance.[105–111] The paramount issue revolves around the role that common pathogenic mechanisms and shared risk factors play, and whether or not the purported effects of NAFLD on the progression of CKD are truly independent of these shared risk factors.

Most studies demonstrate an association between the presence and the severity of NAFLD and the risk and severity of CKD after adjusting for traditional risk factors. In these cohorts, the prevalence of CKD in patients with NAFLD ranges from 10% to 20%.[112] In addition, most liver biopsy cohorts have shown a correlation between the histologic severity of NASH and renal dysfunction.[112]

Musso et al.[112] performed a meta-analysis of 20 cross-sectional and 13 longitudinal studies that included nearly 64,000 screened individuals. Patient-level data were available in nearly half of the subjects. Prevalent CKD was over twice as common in NAFLD compared with controls, and incident CKD was 1.8 times more common in NAFLD compared with controls. The severity of NAFLD was associated with the severity of CKD. In adjusted analyses of liver biopsy studies, the presence of NASH increased the prevalence of CKD by 2.5-fold, and increased the incidence of CKD by over 2-fold compared with simple steatosis. The presence of advanced fibrosis increased the prevalence of CKD by 5.2-fold and increased the incidence of CKD by 3.3-fold compared with nonadvanced fibrosis.

Mantovani et al.[113] performed a meta-analysis of nine prospective or retrospective observational cohorts consisting of nearly 100,000 subjects followed for a mean of 5.2 years. They found that NAFLD was associated with a 40% increase in the incidence of CKD. Furthermore, increased severity of NAFLD was associated with an increased risk of developing CKD.

Newer noninvasive techniques to detect NAFLD have recently been employed to study the relationship between CKD and NAFLD. The use of transient elastography to generate a controlled attenuation parameter score to quantitate steatosis and a liver stiffness score to quantitate fibrosis led to the observation that over 85% of patients with CKD had NAFLD, and that the severity of CKD correlated with the severity of hepatic steatosis.[114] Similar findings have been reported by other investigators.[115,116]

The limitations of the studies that report an association between NAFLD and CKD are significant and arguably compromise the validity of conclusions drawn from the accumulated data. The observational nature of these studies does not allow for a conclusion of causality. Despite utilization of multivariate analysis, residual unmeasured confounding factors cannot be excluded. Studied cohorts have been heterogeneous and vary by age, ethnicity, duration of follow-up, and prevalence of diabetes and hypertension. In addition, there is heterogeneity of kidney disease outcome parameters. Most population-based cohort studies rely on liver enzyme abnormalities or ultrasound examination to diagnose NAFLD without liver biopsy confirmation. Even liver biopsy diagnosis is subject to sampling error, because NAFLD may be patchy in distribution. Moreover, cohorts that underwent liver biopsies have been small in size, generally lack a control group, and suffer from selection bias. Misclassification of NAFLD cases due to the low sensitivity of liver enzyme abnormalities and ultrasound examination may obscure relationships between NAFLD and CKD. Ultrasound-based diagnosis is subjective and qualitative in nature and in cases where less than 30% of hepatocytes are steatotic, the sensitivity is limited to 60–90%.[105–111] However, in more severe NAFLD, the sensitivity rises to 85–94% with a specificity in the mid-90s range. Use of abnormal liver enzymes as a surrogate marker for NAFLD lacks both sensitivity and specificity. In fact, liver enzyme tests may be normal in up to 50% of patients with NAFLD.[105–111]

Misclassification of CKD cases due to overestimation of kidney function in liver disease may also obscure relationships between NAFLD and CKD. The equations used to estimate GFR overestimate renal function in severe liver disease and underestimate the incidence and prevalence of CKD in this population, which may mask relationships between NAFLD and CKD. Although patients with cirrhosis were excluded from most studies, S[Cr] tends to be lower in patients with severe liver disease due to muscle wasting, reduced hepatic generation of creatinine from creatine, and increased tubular secretion of creatinine.

MECHANISMS OF KIDNEY-LIVER CROSS TALK

The existence of renal-hepatic cross talk has been clearly established in animal models of CKD. However, to what extent these experimental observations in animal models of CKD can be extrapolated to CKD in humans is not clear. Unilateral nephrectomy promotes liver injury and the development of steatohepatitis. Unilateral nephrectomy is associated with dysregulation of lipid metabolism, insulin resistance, hyperglycemia, and a redistribution of fat from adipose to nonadipose tissue.[117] There is evidence of ectopic fat deposition in the liver and kidney and increased oxidative stress and upregulation of TGF-β in both organs. These metabolic alterations are mediated by the renin–angiotensin system insofar as angiotensin-converting enzyme inhibitors reverse these effects.

Studies performed by Park et al.[118] have implicated inflammatory cytokines as the primary mediators of remote hepatic injury associated with renal disease. Bilateral nephrectomy in the rat was associated with elevated transaminase levels and hepatocellular injury characterized by apoptosis and inflammation. These distant effects on the liver were attributed to increased synthesis and release of IL-17A by intestinal Paneth cells. Increased systemic delivery of IL-17A to the liver by circulating macrophages induced hepatic neutrophil infiltration, hepatic cellular necrosis and apoptosis, transaminitis, and increased hepatic expression and release of IL-6 and TNF-α. The latter cytokines magnified tissue injury. Administration of neutralizing antibodies to IL-17A, genetic deficiency of IL-17A, or genetic or pharmacologic depletion of Paneth cells reduced hepatic injury after bilateral nephrectomy, supporting the putative role of IL-17A in mediating the remote effects of renal injury on the liver. Also of interest is the observation that bilateral nephrectomy exacerbated hepatic injury after hepatic ischemia reperfusion.

Studies by other investigators have focused on the role of oxidative stress in mediating remote hepatic injury associated with renal disease.[119–121] Following bilateral nephrectomy in rats, hepatic lipid peroxidation products increased, whereas levels of the antioxidant molecule glutathione decreased.[121] Enzyme markers of liver injury were transiently increased in association with histologic evidence of hepatic cellular injury including apoptosis, leukocyte infiltration, and vascular congestion. Levels of TNF-α and the antiinflammatory cytokine IL-10 were elevated. An important role for increased oxidant stress in mediating these remote effects on the liver was suggested by the ability of infused reduced glutathione to partially prevent hepatic injury

and blunt hepatic lipid peroxidation. An important role for increased oxidative stress in mediating kidney/liver cross talk was also demonstrated in a protein overload nephropathy model.[119,120]

HEPATIC DRUG METABOLISM

CKD alters the pharmacokinetics of over 75 drugs whose elimination depends on nonrenal, predominantly hepatic, clearance. In general, CKD is associated with reduced hepatic drug clearance, although in some cases hepatic clearance is enhanced. The magnitude of the change in hepatic drug clearance generally correlates with the degree of renal functional impairment.

Cytochrome P450 (CYP) enzymes are a superfamily of hemoproteins that play a key role in the metabolism of endogenous substrates, therapeutic agents, and environmental chemicals.[116,122–128] The CYP3 family is responsible for most CYP-mediated drug metabolism. These enzymes are present in a variety of organs but are most abundant in the liver.[116,122–128] Experimental evidence suggests CKD influences CYP-mediated hepatic drug metabolism by multiple different mechanisms: by directly inhibiting CYP enzyme activity, by influencing CYP gene transcription, and by acting at posttranslational and epigenetic levels.[116,122–128] The remote effects of CKD on CYP enzymes are likely mediated by both the accumulation of uremic toxins and by the generation of cytokine mediators.[116,122–128] Although CKD generally inhibits CYP enzyme activity and suppresses CYP protein expression, CYP inducibility is retained, with important clinical implications.[129,130]

The effect of subtotal nephrectomy on hepatic drug clearance pathways has been studied by several investigators. Leblond et al.[129,130] found a reduction in total hepatic microsomal CYP activity associated with a reduction in the protein expression of several hepatic CYP proteins. These changes paralleled a reduction in the clearance of drugs that are known substrates for these hepatic CYP enzymes. The reduction in CYP activity correlated with the severity of renal functional impairment in this as well as in other studies.[129–133] Although total hepatic microsomal CYP activity was reduced, inducibility by dexamethasone and phenobarbital was retained.[129,130] The reduction in CYP protein expression was transcriptionally mediated, as evidenced by a parallel reduction in mRNA levels. The relationship between subtotal nephrectomy and CYP activity and protein expression has been replicated by other investigators, although the pattern of CYP alterations has not been entirely consistent.[131–135]

The metabolic activity of hepatic CYP2D was assessed in an isolated rat liver preparation using a specific CYP substrate as a probe. Hepatic drug clearance declined when normal rat livers or livers from rats made uremic with uranyl nitrate were perfused with uremic blood.[136] Hepatic drug clearance was restored when livers from uremic rats were perfused with normal blood. The rapidity of onset of the effects of uremic serum suggests a direct and reversible inhibitory effect of a circulating uremic toxin on CYP enzyme activity.

Michaud et al.[137] showed that incubation of normal rat hepatocytes with serum from patients with CKD had a widespread suppressive effect on CYP enzyme activity and protein expression, and that these effects were mediated at a transcriptional level. Several small molecular weight uremic toxins have been identified that inhibit CYP activity *in vitro* at concentrations achieved in humans with CKD.[131,138] Yoshitani et al.[138] found that incubation of hepatic microsomal preparations from normal livers with uremic serum obtained from rats with bilateral ureteral ligation reduced the metabolism of a specific CYP substrate probe, and that this effect was reproduced by exposure of the microsomal preparations to the putative uremic toxin indoxyl sulfate. Barnes et al.[131] found a potent suppressive effect of several known uremic toxins on CYP activity in human liver microsomes. These data support the hypothesis that circulating uremic toxins mediate the inhibitory effects of CKD on CYP activity, protein expression, and mRNA levels. It would follow that removal of these toxins by RRT or kidney transplantation would restore hepatic drug metabolism. Several studies have demonstrated that both RRT and kidney transplantation reverse the inhibitory effects of uremic serum on the hepatic clearance of drugs that are specific substrates for hepatic CYP enzymes, as well as on hepatic CYP protein expression and mRNA levels in hepatocyte microsomal preparations and in isolated hepatocytes.[139,140]

The inhibitory factor in CKD serum has been isolated to a serum fraction that contained parathyroid hormone and proinflammatory cytokines.[137] Several investigators have suggested that proinflammatory cytokines such as IL-6, TNF-α, and NF-κB mediate the effects of CKD on CYP activity and protein expression. The NF-κB signaling pathway may be the final common pathway transducing the suppressive effects of other proinflammatory cytokines. Michaud et al.[139] proposed that the inhibitory effects of uremic human serum on CYP expression in normal rat hepatocytes were mediated by NF-κB, because inhibition of NF-κB reversed these effects. Michaud et al.[141] also suggested a prominent role for elevated parathyroid hormone levels in mediating the suppressive effects of uremic sera on CYP activity and protein synthesis and went on to hypothesize that this effect is mediated through NF-κB. The suppressive effects of serum from rats made uremic with subtotal nephrectomy on CYP protein expression, mRNA levels,

and enzyme activity in preparations of normal rat hepatocytes correlated with parathyroid levels. These effects were reversed by parathyroidectomy or depletion of parathyroid hormone by immunoadsorption and were restored by administration of exogenous parathyroid hormone. Inhibition of NF-κB prevented the effects of exogenous parathyroid hormone on CYP activity. However, other investigators failed to find a correlation between CYP activity and parathyroid hormone levels.[140]

In a subtotal nephrectomy model, Velenosi et al.[142] proposed that the effects of CKD on hepatic CYP activity, protein expression, and mRNA levels occur both at transcriptional and epigenetic levels. Several CYP isoforms are transcriptionally regulated by the nuclear receptors pregnane X receptor and hepatic nuclear factor 4α. These investigators demonstrated reduced nuclear receptor binding and decreased histone acetylation of CYP promoter regions in CKD animals. Interestingly, Gu et al.[143] have shown that the ability of TNF-α to suppress CYP3A4 is mediated by NF-κB. NF-κB prevents the association of the pregnane X receptor with the retinoid X receptor, which in turn prevents the heterodimer from binding to the promoter region of CYP3A4. Watanabe et al.[144] reported that CYP3A was downregulated in rat primary hepatoctyes by parathyroid hormone through multiple signal transduction pathways. Increased intracellular cyclic adenosine monophosphate levels led to activation of phosphatidylinositol 3-kinase-protein kinase B/protein kinase C/protein kinase A/NF-κB pathways which ultimately suppressed pregnane X receptor activity. They further demonstrated that administration of a calcimimetic partially reversed CYP inhibition in a subtotal nephrectomy model. Thus, the NF-κB pathway may be crucial to interactions between CKD and hepatic CYP activity and may represent a final common pathway for the effects of proinflammatory cytokines and PTH on CYP activity.

Using specific hepatic CYP substrates as probes to assess hepatic CYP activity in humans, investigators have confirmed that experimental observations on interactions between CKD and CYP activity translate to clinical practice.[116,122–128] Reductions in CYP activity observed in experimental models parallel increased bioavailability of numerous drugs known to be specific CYP substrates in humans with both dialysis-dependent and nondialysis-dependent CKD.[116,122–128] The magnitude of the effects of CKD on hepatic drug metabolism correlates with renal function, and the effects are reversed by RRT or kidney transplantation.

Active transport of drugs across the sinosoidal membrane of hepatocytes to access hepatic metabolic enzymes is mediated by transporters such as the organic anion transporting polypeptide family of transporters, expressed on the sinosoidal surface of hepatocytes.[116,122–128] P-glycoprotein and multidrug resistance-associated protein-2 are energy-dependent efflux transporters on the canalicular membrane of hepatocytes, responsible for extrusion of drug metabolites into bile canaliculi.[116,122–128] Drug uptake and efflux transporters regulate intracellular exposure of substrates to hepatic CYP and may be rate-limiting for hepatic drug metabolism. These transporters are also expressed on renal proximal tubules and enterocytes.[116,122–128]

Hepatic organic anion transporting polypeptide protein-mediated uptake of specific drug probes is reduced in humans with ESRD.[126] In addition, organic anion transporting polypeptide activity is inhibited *in vitro* by uremic toxins.[145] In a subtotal nephrectomy model and in *in vitro* studies of normal rat hepatocytes incubated with uremic rat serum, Naud et al.[146] showed reduced organic anion transporting polypeptide protein expression in the absence of changes in mRNA levels. However, data on the effects of CKD on P-glycoprotein and multidrug resistance-associated protein expression and mRNA levels in the subtotal nephrectomy model have been inconsistent.[146,147]

Although the majority of drug metabolized by the liver undergoes oxidation, the hepatic elimination of other drugs is mediated by conjugation reactions, including glucuronidation and acetylation, mediated by the enzyme uridine diphosphate-glucuronosyl transferase, and N-acetyl-transferase, respectively.[122,123,126,148] Using drug probes, investigators have demonstrated reduced hepatic acetylation in humans with ESRD.[122,123] Reversal of the uremic milieu by renal transplantation restores hepatic clearance of drugs whose elimination is dependent on acetylation.[122,123] Similarly, normal rat hepatocytes incubated with uremic serum from rats which had undergone subtotal nephrectomy show reduced N-acetyl-transferase activity and protein expression mediated at a transcriptional level.[148] These effects were reversed by parathyroidectomy and reproduced by incubation of rat hepatocytes with exogenous parathyroid hormone. Using drug probes, investigators have also demonstrated reduced hepatic drug glycuronidation in humans with CKD, the magnitude of which correlated with the level of renal function.[126] P-cresol, a putative uremic toxin, inhibited uridine diphosphate-glucuronosyl transferase activity in human liver microsomes.[131] However, other experimental data have yielded inconsistent results. No changes in uridine diphosphate-glucuronosyl

transferase activity or in protein expression were observed in a subtotal nephrectomy model of CKD in the rat.[149]

Adding further complexity to the situation is the fact that effects of CKD on hepatic CYP and drug transporter protein function may not necessarily translate into the change in serum drug concentration that might be expected from the observed changes in hepatic metabolism. CKD may have effects on CYP and drug transporter protein activity in the intestine or kidney than are opposite to those seen in the liver. Furthermore, CKD may have additional effects on organ perfusion, drug plasma protein binding and volume of distribution, renal clearance, and extrahepatic metabolism that offset or magnify the effects of CKD on the hepatic metabolism of a given drug. Thus, the net effect on drug pharmacokinetics is a complex interplay between all these competing or complementary actions, and further translational research will be critical.

CONCLUSIONS

Accumulating evidence derived from basic science and clinical studies supports the existence of bidirectional cross talk between the kidney and the liver. These studies suggest that chronic liver disease promotes the development and accelerates the progression of CKD, and that CKD accelerates the progression of chronic liver disease. The data are most robust for interactions between the kidney and decompensated liver disease in the context of HRS-CKD, in HCV-related liver disease and in NAFLD. Upregulation of proinflammatory cytokines plays a paramount role in mediating these interactions. CKD also alters hepatic drug metabolism *via* effects on hepatic CYPs and hepatic drug transporter proteins, mediated by the accumulation of uremic toxins and release of proinflammatory cytokines. These interactions significantly influence drug dosing in patients with combined liver and renal disease. Opportunities for future research may be directed toward enhancing our understanding of the molecular pathways that mediate liver-kidney cross talk. Elucidation of the complex interactions between the liver and kidney may lead to therapeutic interventions directed toward slowing the progression of both liver and kidney disease and may provide novel therapeutic strategies, directed primarily toward the liver, to retard the progression of CKD in patients with combined liver and kidney disease. The emergence of newer DAAs warrant a reappraisal of the effects of sustained viral remission on the progression of CKD, to better inform our therapeutic decisions in HCV-infected patients with CKD.

References

1. Davenport A, Sheikh MF, Lamb E, Agarwal B, Jalan R. Acute kidney injury in acute-on-chronic liver failure: where does hepatorenal syndrome fit? *Kidney Int* 2017;**92**(5):1058–70.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018;**69**(2):406–60.
3. Gines P, Sola E, Angeli P, Wong F, Nadim MK, Kamath P. Hepatorenal syndrome. *Nat Rev Dis Primers* 2018;**4**(1):23.
4. Golestaneh L, Neugarten J. Dual organ duel: the hepatorenal axis. *Adv Chron Kidney Dis* 2017;**24**(4):253–60.
5. Sole C, Pose E, Sola E, Gines P. Hepatorenal syndrome in the era of acute kidney injury. *Liver Int* 2018;**38**(11):1891–901.
6. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol* 2015;**62**(4):968–74.
7. Wong F, Nadim MK, Kellum JA, Salerno F, Bellomo R, Gerbes A, et al. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. *Gut* 2011;**60**(5):702–9.
8. Kostreva DR, Castaner A, Kampine JP. Reflex effects of hepatic baroreceptors on renal and cardiac sympathetic nerve activity. *Am J Physiol* 1980;**238**(5):R390–4.
9. Koyama S, Nishida K, Terada N, Shiojima Y, Takeuchi T. Reflex renal vasoconstriction on portal vein distension. *Jpn J Physiol* 1986;**36**(3):441–50.
10. Platt JF, Ellis JH, Rubin JM, Merion RM, Lucey MR. Renal duplex Doppler ultrasonography: a noninvasive predictor of kidney dysfunction and hepatorenal failure in liver disease. *Hepatology* 1994;**20**(2):362–9.
11. Maroto A, Gines A, Salo J, Claria J, Gines P, Anibarro L, et al. Diagnosis of functional kidney failure of cirrhosis with Doppler sonography: prognostic value of resistive index. *Hepatology* 1994;**20**(4 Pt 1):839–44.
12. Mindikoglu AL, Dowling TC, Wong-You-Cheong JJ, Christenson RH, Magder LS, Hutson WR, et al. A pilot study to evaluate renal hemodynamics in cirrhosis by simultaneous glomerular filtration rate, renal plasma flow, renal resistive indices and biomarkers measurements. *Am J Nephrol* 2014;**39**(6):543–52.
13. Claria J, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, et al. Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. *Hepatology* 2016;**64**(4):1249–64.
14. Navasa M, Follo A, Filella X, Jimenez W, Francitorra A, Planas R, et al. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. *Hepatology* 1998;**27**(5):1227–32.
15. Fagundes C, Pepin MN, Guevara M, Barreto R, Casals G, Sola E, et al. Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. *J Hepatol* 2012;**57**(2):267–73.
16. Bairaktari E, Liamis G, Tsolas O, Elisaf M. Partially reversible renal tubular damage in patients with obstructive jaundice. *Hepatology* 2001;**33**(6):1365–9.
17. van Slambrouck CM, Salem F, Meehan SM, Chang A. Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction. *Kidney Int* 2013;**84**(1):192–7.
18. Angeli P, Piano S. Is type 2 hepatorenal syndrome still a potential indication for treatment with terlipressin and albumin? *Liver Transplant* 2015;**21**(11):1335–7.
19. Rodriguez E, Henrique Pereira G, Sola E, Elia C, Barreto R, Pose E, et al. Treatment of type 2 hepatorenal syndrome in patients awaiting transplantation: effects on kidney function and transplantation outcomes. *Liver Transplant* 2015;**21**(11):1347–54.

20. Testino G, Ferro C, Sumberaz A, Messa P, Morelli N, Guadagni B, et al. Type-2 hepatorenal syndrome and refractory ascites: role of transjugular intrahepatic portosystemic stent-shunt in eighteen patients with advanced cirrhosis awaiting orthotopic liver transplantation. *Hepatogastroenterology* 2003;**50**(54):1753–5.
21. Desai N, Neugarten J, Dominguez M, Golestaneh L. Hepatic vein pressure predicts GFR in cirrhotic patients with hemodynamic kidney dysfunction. *Phys Rep* 2017;**5**(11).
22. Chang Y, Qi X, Li Z, Wang F, Wang S, Zhang Z, et al. Hepatorenal syndrome: insights into the mechanisms of intra-abdominal hypertension. *Int J Clin Exp Pathol* 2013;**6**(11):2523–8.
23. http://www.who.int/news-room/fact-sheets/detail/hepatitis-c.
24. www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1.
25. Fabrizi F, Marcelli D, Bacchini G, Guarnori I, Erba G, Locatelli F. Antibodies to hepatitis C virus (HCV) in chronic renal failure (CRF) patients on conservative therapy: prevalence, risk factors and relationship to liver disease. *Nephrol Dial Transplant* 1994; **9**(7):780–4.
26. Fabrizi F, Donato FM, Messa P. Association between hepatitis C virus and chronic kidney disease: a systematic review and meta-analysis. *Ann Hepatol* 2018;**17**(3):364–91.
27. Tartof SY, Hsu JW, Wei R, Rubenstein KB, Hu H, Arduino JM, et al. Kidney function decline in patients with CKD and untreated hepatitis C infection. *Clin J Am Soc Nephrol* 2018; **13**(10):1471–8.
28. Fabrizi F, Dixit V, Martin P, Messa P. Hepatitis C virus increases the risk of kidney disease among HIV-positive patients: systematic review and meta-analysis. *J Med Virol* 2016;**88**(3): 487–97.
29. Moe SM, Pampalone AJ, Ofner S, Rosenman M, Teal E, Hui SL. Association of hepatitis C virus infection with prevalence and development of kidney disease. *Am J Kidney Dis* 2008;**51**(6): 885–92.
30. Asrani SK, Buchanan P, Pinsky B, Rey LR, Schnitzler M, Kanwal F. Lack of association between hepatitis C infection and chronic kidney disease. *Clin Gastroenterol Hepatol* 2010;**8**(1):79–84.
31. Kurbanova N, Qayyum R. Association of hepatitis C virus infection with proteinuria and glomerular filtration rate. *Clin Transl Sci* 2015;**8**(5):421–4.
32. Tsui JI, Vittinghoff E, Shlipak MG, O'Hare AM. Relationship between hepatitis C and chronic kidney disease: results from the third national health and nutrition examination survey. *J Am Soc Nephrol* 2006;**17**(4):1168–74.
33. Rogal SS, Yan P, Rimland D, Lo Re 3rd V, Al-Rowais H, Fried L, et al. Incidence and progression of chronic kidney disease after hepatitis C seroconversion: results from ERCHIVES. *Dig Dis Sci* 2016;**61**(3):930–6.
34. Molnar MZ, Alhourani HM, Wall BM, Lu JL, Streja E, Kalantar-Zadeh K, et al. Association of hepatitis C viral infection with incidence and progression of chronic kidney disease in a large cohort of US veterans. *Hepatology* 2015;**61**(5):1495–502.
35. Tsui J, Vittinghoff E, Anastos K, Augenbraun M, Young M, Nowicki M, et al. Hepatitis C seropositivity and kidney function decline among women with HIV: data from the Women's Interagency HIV Study. *Am J Kidney Dis* 2009;**54**(1):43–50.
36. Tsui JI, Vittinghoff E, Shlipak MG, Bertenthal D, Inadomi J, Rodriguez RA, et al. Association of hepatitis C seropositivity with increased risk for developing end-stage renal disease. *Arch Intern Med* 2007;**167**(12):1271–6.
37. Satapathy SK, Lingisetty CS, Williams S. Higher prevalence of chronic kidney disease and shorter renal survival in patients with chronic hepatitis C virus infection. *Hepatol Int* 2012;**6**(1): 369–78.
38. Lai TS, Lee MH, Yang HI, You SL, Lu SN, Wang LY, et al. High hepatitis C viral load and genotype 2 are strong predictors of chronic kidney disease. *Kidney Int* 2017;**92**(3):703–9.
39. Lai TS, Lee MH, Yang HI, You SL, Lu SN, Wang LY, et al. Hepatitis C viral load, genotype, and increased risk of developing end-stage renal disease: REVEAL-HCV study. *Hepatology* 2017;**66**(3): 784–93.
40. Peters L, Grint D, Lundgren JD, Rockstroh JK, Soriano V, Reiss P, et al. Hepatitis C virus viremia increases the incidence of chronic kidney disease in HIV-infected patients. *AIDS* 2012;**26**(15): 1917–26.
41. Butt AA, Wang X, Fried LF. HCV infection and the incidence of CKD. *Am J Kidney Dis* 2011;**57**(3):396–402.
42. Mocroft A, Neuhaus J, Peters L, Ryom L, Bickel M, Grint D, et al. Hepatitis B and C co-infection are independent predictors of progressive kidney disease in HIV-positive, antiretroviral-treated adults. *PLoS One* 2012;**7**(7):e40245.
43. Rossi C, Saeed S, Cox J, Vachon ML, Martel-Laferriere V, Walmsley SL, et al. Hepatitis C virus cure does not impact kidney function decline in HIV co-infected patients. *AIDS* 2018;**32**(6): 751–9.
44. Lucas GM, Jing Y, Sulkowski M, Abraham AG, Estrella MM, Atta MG, et al. Hepatitis C viremia and the risk of chronic kidney disease in HIV-infected individuals. *J Infect Dis* 2013;**208**(8): 1240–9.
45. Barsoum RS. Hepatitis C virus: from entry to renal injury–facts and potentials. *Nephrol Dial Transplant* 2007;**22**(7):1840–8.
46. Barsoum RS, William EA, Khalil SS. Hepatitis C and kidney disease: a narrative review. *J Adv Res* 2017;**8**(2):113–30.
47. Gopalani A, Ahuja TS. Prevalence of glomerulopathies in autopsies of patients infected with the hepatitis C virus. *Am J Med Sci* 2001;**322**(2):57–60.
48. Arase Y, Ikeda K, Murashima N, Chayama K, Tsubota A, Koida I, et al. Glomerulonephritis in autopsy cases with hepatitis C virus infection. *Intern Med* 1998;**37**(10):836–40.
49. McGuire BM, Julian BA, Bynon Jr JS, Cook WJ, King SJ, Curtis JJ, et al. Brief communication: glomerulonephritis in patients with hepatitis C cirrhosis undergoing liver transplantation. *Ann Intern Med* 2006;**144**(10):735–41.
50. Tong X, Spradling PR. Increase in nonhepatic diagnoses among persons with hepatitis C hospitalized for any cause, United States, 2004-2011. *J Viral Hepat* 2015;**22**(11):906–13.
51. El-Serag HB, Hampel H, Yeh C, Rabeneck L. Extrahepatic manifestations of hepatitis C among United States male veterans. *Hepatology* 2002;**36**(6):1439–45.
52. Available from: www.cdc.gov/diabetes/statistics/esrd.
53. Kasuno K, Ono T, Matsumori A, Nogaki F, Kusano H, Watanabe H, et al. Hepatitis C virus-associated tubulointerstitial injury. *Am J Kidney Dis* 2003;**41**(4):767–75.
54. Wornle M, Schmid H, Banas B, Merkle M, Henger A, Roeder M, et al. Novel role of toll-like receptor 3 in hepatitis C-associated glomerulonephritis. *Am J Pathol* 2006;**168**(2):370–85.
55. Chen YC, Chiou WY, Hung SK, Su YC, Hwang SJ. Hepatitis C virus itself is a causal risk factor for chronic kidney disease beyond traditional risk factors: a 6-year nationwide cohort study across Taiwan. *BMC Nephrol* 2013;**14**:187.
56. Perico N, Cattaneo D, Bikbov B, Remuzzi G. Hepatitis C infection and chronic renal diseases. *Clin J Am Soc Nephrol* 2009; **4**(1):207–20.
57. Carvalho-Filho RJ, Feldner AC, Silva AE, Ferraz ML. Management of hepatitis C in patients with chronic kidney disease. *World J Gastroenterol* 2015;**21**(2):408–22.
58. Sise ME, Backman E, Ortiz GA, Hundemer GL, Ufere NN, Chute DF, et al. Effect of sofosbuvir-based hepatitis C virus therapy on kidney function in patients with CKD. *Clin J Am Soc Nephrol* 2017;**12**(10):1615–23.
59. Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko S, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *N Engl J Med* 2015;**373**(27):2608–17.

60. Foster GR, Mangia A, Sulkowski M. Sofosbuvir and velpatasvir for patients with HCV infection. *N Engl J Med* 2016;**374**(17):1687–8.
61. Struble K, Chan-Tack K, Qi K, Naeger LK, Birnkrant D. Benefit-risk assessment for sofosbuvir/velpatasvir/voxilaprevir based on patient population and hepatitis C virus genotype: U. S. Food and Drug Administration's evaluation. *Hepatology* 2018; **67**(2):482–91.
62. Desnoyer A, Pospai D, Le MP, Gervais A, Heurgue-Berlot A, Laradi A, et al. Pharmacokinetics, safety and efficacy of a full dose sofosbuvir-based regimen given daily in hemodialysis patients with chronic hepatitis C. *J Hepatol* 2016;**65**(1):40–7.
63. Goel A, Bhadauria DS, Kaul A, Verma P, Mehrotra M, Gupta A, et al. Daclatasvir and reduced-dose sofosbuvir: an effective and pangenotypic treatment for hepatitis C in patients with eGFR <30 mL/min. *Nephrology (Carlton)* 2019;**24**(3):316–21.
64. Taneja S, Duseja A, De A, Mehta M, Ramachandran R, Kumar V, et al. Low-dose sofosbuvir is safe and effective in treating chronic hepatitis C in patients with severe renal impairment or end-stage renal disease. *Dig Dis Sci* 2018;**63**(5):1334–40.
65. Choudhary NS, Kumar A, Bodh V, Bansal SB, Sharma R, Jain M, et al. Efficacy and safety of sofosbuvir-based regimens in chronic hepatitis C patients on dialysis. *Indian J Gastroenterol* 2017;**36**(2): 113–6.
66. Kumar MNS, Gupta E, Kataria A, Sarin SK. Generic sofosbuvir-based direct-acting antivirals in heptitis C virus-infected patients with chronic kidney disease. *Liver Int* 2018;**38**:2137–48.
67. Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, Monsour Jr H, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. *Lancet* 2015; **386**(10003):1537–45.
68. Papudesu C, Kottilil S, Bagchi S. Elbasvir/grazoprevir for treatment of chronic hepatitis C virus infection. *Hepatol Int* 2017; **11**(2):152–60.
69. Pockros PJ, Reddy KR, Mantry PS, Cohen E, Bennett M, Sulkowski MS, et al. Efficacy of direct-acting antiviral combination for patients with hepatitis C virus genotype 1 infection and severe renal impairment or end-stage renal disease. *Gastroenterology* 2016;**150**(7):1590–8.
70. Gane E, Lawitz E, Pugatch D, Papatheodoridis G, Brau N, Brown A, et al. Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. *N Engl J Med* 2017;**377**(15):1448–55.
71. Liver EAftSot. EASL recommendations on treatment of hepatitis C 2018. *J Hepatol* 2018;**69**(2):461–511.
72. Feng B, Eknoyan G, Guo ZS, Jadoul M, Rao HY, Zhang W, et al. Effect of interferon-alpha-based antiviral therapy on hepatitis C virus-associated glomerulonephritis: a meta-analysis. *Nephrol Dial Transplant* 2012;**27**(2):640–6.
73. Rutledge SM, Chung RT, Sise ME. Treatment of hepatitis C virus infection in patients with mixed cryoglobulinemic syndrome and cryoglobulinemic glomerulonephritis. *Hemodial Int* 2018; **22**(Suppl. 1):S81–96.
74. Hsu YC, Ho HJ, Huang YT, Wang HH, Wu MS, Lin JT, et al. Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. *Gut* 2015; **64**(3):495–503.
75. Chen YC, Hwang SJ, Li CY, Wu CP, Lin LC. A Taiwanese nationwide cohort study shows interferon-based therapy for chronic hepatitis C reduces the risk of chronic kidney disease. *Medicine (Baltim)* 2015;**94**(32):e1334.
76. Arase Y, Suzuki F, Kawamura Y, Suzuki Y, Kobayashi M, Matsumoto N, et al. Development rate of chronic kidney disease in hepatitis C virus patients with advanced fibrosis after interferon therapy. *Hepatol Res* 2011;**41**(10):946–54.
77. Park H, Chen C, Wang W, Henry L, Cook RL, Nelson DR. Chronic hepatitis C virus (HCV) increases the risk of chronic kidney disease (CKD) while effective HCV treatment decreases the incidence of CKD. *Hepatology* 2018;**67**(2):492–504.
78. Anty RFG, Coilly A, Rossignol E, Houssel-Debry P, Duvoux C, De Ledinghen V, Di Martino V, Leroy V, Radenne S, Kamar N, Canva V, D'Aleroche L, Durand F. Safety of sofosbuvir-based regimens after liver transplantation: longitudinal assessment of renal function in the prospective ANRS CO23 CUPILT study. *Aliment Pharmacol Ther* 2017;**47**:1682–9.
79. Medeiros T, Rosario NF, Saraiva GN, Andrade TG, Silva AA, Almeida JR. Renal safety after one year of sofosbuvir-based therapy for chronic hepatitis C: a Brazilian "real-life" study. *J Clin Pharm Ther* 2018;**43**(5):707–13.
80. Aby ES, Dong TS, Kawamoto J, Pisegna JR, Benhammou JN. Impact of sustained virologic response on chronic kidney disease progression in hepatitis C. *World J Hepatol* 2017;**9**(36): 1352–60.
81. Mehta DA, Cohen E, Charafeddine M, Cohen DE, Bao Y, Sanchez Gonzalez Y, et al. Effect of hepatitis C treatment with ombitasvir/paritaprevir/R + dasabuvir on renal, cardiovascular and metabolic extrahepatic manifestations: a post-hoc analysis of phase 3 clinical trials. *Infect Dis Ther* 2017;**6**(4):515–29.
82. Sise ME, Backman ES, Wenger JB, Wood BR, Sax PE, Chung RT, et al. Short and long-term effects of telaprevir on kidney function in patients with hepatitis C virus infection: a retrospective cohort study. *PLoS One* 2015;**10**(4):e0124139.
83. Mauss S, Hueppe D, Alshuth U. Renal impairment is frequent in chronic hepatitis C patients under triple therapy with telaprevir or boceprevir. *Hepatology* 2014;**59**(1):46–8.
84. Saxena V, Koraishy FM, Sise ME, Lim JK, Schmidt M, Chung RT, et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. *Liver Int* 2016;**36**(6):807–16.
85. Chen J, Zhang X, Luo H, Wu C, Yu M, Liu D, et al. Changes in renal function indices in cirrhotic chronic hepatitis C patients treated with sofosbuvir-containing regimens. *Oncotarget* 2017; **8**(53):90916–24.
86. Taramasso L, Di Biagio A, Bovis F, Nicolini LA, Antinori A, Milazzo L, et al. Trend of estimated glomerular filtration rate during ombistasvir/paritaprevir/ritonavir plus dasabuvir +/- ribavirin in HIV/HCV co-infected patients. *PLoS One* 2018; **13**(2):e0192627.
87. Dashti-Khavidaki S, Khalili H, Nasiri-Toosi M. Potential nephrotoxicity of sofosbuvir-based treatment in patients infected with hepatitis C virus: a review on incidence, type and risk factors. *Expert Rev Clin Pharmacol* 2018;**11**(5):525–9.
88. Butt AA, Ren Y, Puenpatom A, Arduino JM, Kumar R, Abou-Samra AB. Effectiveness, treatment completion and safety of sofosbuvir/ledipasvir and paritaprevir/ritonavir/ombitasvir + dasabuvir in patients with chronic kidney disease: an ERCHIVES study. *Aliment Pharmacol Ther* 2018;**48**(1):35–43.
89. Dumortier J, Bailly F, Pageaux GP, Vallet-Pichard A, Radenne S, Habersetzer F, et al. Sofosbuvir-based antiviral therapy in hepatitis C virus patients with severe renal failure. *Nephrol Dial Transplant* 2017;**32**(12):2065–71.
90. Alvarez-Ossorio MJ, Sarmento ECR, Granados R, Macias J, Morano-Amado LE, Rios MJ, et al. Impact of interferon-free regimens on the glomerular filtration rate during treatment of chronic hepatitis C in a real-life cohort. *J Viral Hepat* 2018;**25**(6): 699–706.
91. Butt AA, Ren Y, Marks K, Shaikh OS, Sherman KE, study E. Do directly acting antiviral agents for HCV increase the risk of hepatic decompensation and decline in renal function? Results from ERCHIVES. *Aliment Pharmacol Ther* 2017;**45**(1):150–9.

92. Kao CC, Lin YS, Chu HC, Fang TC, Wu MS, Kang YN. Association of renal function and direct-acting antiviral agents for HCV: a network meta-analysis. *J Clin Med* 2018;**7**(10).
93. Ble M, Aguilera V, Rubin A, Garcia-Eliz M, Vinaixa C, Prieto M, et al. Improved renal function in liver transplant recipients treated for hepatitis C virus with a sustained virological response and mild chronic kidney disease. *Liver Transplant* 2014;**20**(1): 25–34.
94. Satapathy SK, Joglekar K, Molnar MZ, Ali B, Gonzalez HC, Vanatta JM, et al. Achieving sustained virological response in liver transplant recipients with hepatitis C decreases risk of decline in renal function. *Liver Transplant* 2018;**24**(8):1040–9.
95. Beig J, Orr D, Harrison B, Gane E. Hepatitis C virus eradication with new interferon-free treatment improves metabolic profile in hepatitis C virus-related liver transplant recipients. *Liver Transplant* 2018;**24**(8):1031–9.
96. Kucirka LM, Singer AL, Ros RL, Montgomery RA, Dagher NN, Segev DL. Underutilization of hepatitis C-positive kidneys for hepatitis C-positive recipients. *Am J Transplant* 2010;**10**(5): 1238–46.
97. Fabrizi F, Donato FM, Messa P. Association between hepatitis B virus and chronic kidney disease: a systematic review and meta-analysis. *Ann Hepatol* 2017;**16**(1):21–47.
98. Si J, Yu C, Guo Y, Bian Z, Qin C, Yang L, et al. Chronic hepatitis B virus infection and risk of chronic kidney disease: a population-based prospective cohort study of 0.5 million Chinese adults. *BMC Med* 2018;**16**(1):93.
99. Hong YS, Ryu S, Chang Y, Cainzos-Achirica M, Kwon MJ, Zhao D, et al. Hepatitis B virus infection and development of chronic kidney disease: a cohort study. *BMC Nephrol* 2018;**19**(1):353.
100. Kim SE, Jang ES, Ki M, Gwak GY, Kim KA, Kim GA, et al. Chronic hepatitis B infection is significantly associated with chronic kidney disease: a population-based, matched case-control study. *J Korean Med Sci* 2018;**33**(42):e264.
101. Fabrizi F, Dixit V, Martin P. Meta-analysis: anti-viral therapy of hepatitis B virus-associated glomerulonephritis. *Aliment Pharmacol Ther* 2006;**24**(5):781–8.
102. Tang S, Lai FM, Lui YH, Tang CS, Kung NN, Ho YW, et al. Lamivudine in hepatitis B-associated membranous nephropathy. *Kidney Int* 2005;**68**(4):1750–8.
103. Chen YC, Li CY, Tsai SJ, Chen YC. Nationwide cohort study suggests that nucleos(t)ide analogue therapy decreases dialysis risk in Taiwanese chronic kidney disease patients acquiring hepatitis B virus infection. *World J Gastroenterol* 2018; **24**(8):917–28.
104. Gane EJ, Deray G, Liaw YF, Lim SG, Lai CL, Rasenack J, et al. Telbivudine improves renal function in patients with chronic hepatitis B. *Gastroenterology* 2014;**146**(1):138–146 e5.
105. Ix JH, Sharma K. Mechanisms linking obesity, chronic kidney disease, and fatty liver disease: the roles of fetuin-A, adiponectin, and AMPK. *J Am Soc Nephrol* 2010;**21**(3):406–12.
106. Marcuccilli M, Chonchol M. NAFLD and chronic kidney disease. *Int J Mol Sci* 2016;**17**(4):562.
107. Musso G, Cassader M, Cohney S, De Michieli F, Pinach S, Saba F, et al. Fatty liver and chronic kidney disease: novel mechanistic insights and therapeutic opportunities. *Diabetes Care* 2016;**39**(10): 1830–45.
108. Musso G, Cassader M, Cohney S, Pinach S, Saba F, Gambino R. Emerging liver-kidney interactions in nonalcoholic fatty liver disease. *Trends Mol Med* 2015;**21**(10):645–62.
109. Orlic L, Mikolasevic I, Bagic Z, Racki S, Stimac D, Milic S. Chronic kidney disease and nonalcoholic fatty liver disease-is there a link? *Gastroenterol Res Pract* 2014;**2014**:847539.
110. Targher G, Chonchol M, Zoppini G, Abaterusso C, Bonora E. Risk of chronic kidney disease in patients with non-alcoholic fatty liver disease: is there a link? *J Hepatol* 2011;**54**(5):1020–9.
111. Targher G, Chonchol MB, Byrne CD. CKD and nonalcoholic fatty liver disease. *Am J Kidney Dis* 2014;**64**(4):638–52.
112. Musso G, Gambino R, Tabibian JH, Ekstedt M, Kechagias S, Hamaguchi M, et al. Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. *PLoS Med* 2014;**11**(7):e1001680.
113. Mantovani A, Zaza G, Byrne CD, Lonardo A, Zoppini G, Bonora E, et al. Nonalcoholic fatty liver disease increases risk of incident chronic kidney disease: a systematic review and meta-analysis. *Metabolism* 2018;**79**:64–76.
114. Mikolasevic I, Racki S, Bubic I, Jelic I, Stimac D, Orlic L. Chronic kidney disease and nonalcoholic fatty liver disease proven by transient elastography. *Kidney Blood Press Res* 2013;**37**(4–5): 305–10.
115. Yeung MW, Wong GL, Choi KC, Luk AO, Kwok R, Shu SS, et al. Advanced liver fibrosis but not steatosis is independently associated with albuminuria in Chinese patients with type 2 diabetes. *J Hepatol* 2018;**68**(1):147–56.
116. Zeng J, Sun C, Sun WL, Chen GY, Pan Q, Yan SY, et al. Association between non-invasively diagnosed hepatic steatosis and chronic kidney disease in Chinese adults on their health check-up. *J Dig Dis* 2017;**18**(4):229–36.
117. Zhao HL, Sui Y, Guan J, He L, Zhu X, Fan RR, et al. Fat redistribution and adipocyte transformation in uninephrectomized rats. *Kidney Int* 2008;**74**(4):467–77.
118. Park SW, Chen SW, Kim M, Brown KM, Kolls JK, D'Agati VD, et al. Cytokines induce small intestine and liver injury after renal ischemia or nephrectomy. *Lab Invest* 2011;**91**(1):63–84.
119. Sheng X, Nakajima T, Wang L, Zhang X, Kamijo Y, Takahashi K, et al. Attenuation of kidney injuries maintains serum sulfatide levels dependent on hepatic synthetic ability: a possible involvement of oxidative stress. *Tohoku J Exp Med* 2012;**227**(1): 1–12.
120. Zhang X, Nakajima T, Kamijo Y, Li G, Hu R, Kannagi R, et al. Acute kidney injury induced by protein-overload nephropathy down-regulates gene expression of hepatic cerebroside sulfotransferase in mice, resulting in reduction of liver and serum sulfatides. *Biochem Biophys Res Commun* 2009;**390**(4): 1382–8.
121. Golab F, Kadkhodaee M, Zahmatkesh M, Hedayati M, Arab H, Schuster R, et al. Ischemic and non-ischemic acute kidney injury cause hepatic damage. *Kidney Int* 2009;**75**(8):783–92.
122. Dreisbach AW. The influence of chronic renal failure on drug metabolism and transport. *Clin Pharmacol Ther* 2009;**86**(5): 553–6.
123. Dreisbach AW, Lertora JJ. The effect of chronic renal failure on drug metabolism and transport. *Expert Opin Drug Metabol Toxicol* 2008;**4**(8):1065–74.
124. Ladda MA, Goralski KB. The effects of CKD on cytochrome P450-mediated drug metabolism. *Adv Chron Kidney Dis* 2016;**23**(2): 67–75.
125. Lane K, Dixon JJ, MacPhee IA, Philips BJ. Renohepatic crosstalk: does acute kidney injury cause liver dysfunction? *Nephrol Dial Transplant* 2013;**28**(7):1634–47.
126. Momper JD, Venkataramanan R, Nolin TD. Nonrenal drug clearance in CKD: searching for the path less traveled. *Adv Chron Kidney Dis* 2010;**17**(5):384–91.
127. Nolin TD, Frye RF, Matzke GR. Hepatic drug metabolism and transport in patients with kidney disease. *Am J Kidney Dis* 2003; **42**(5):906–25.
128. Nolin TD, Naud J, Leblond FA, Pichette V. Emerging evidence of the impact of kidney disease on drug metabolism and transport. *Clin Pharmacol Ther* 2008;**83**(6):898–903.
129. Leblond F, Guevin C, Demers C, Pellerin I, Gascon-Barre M, Pichette V. Downregulation of hepatic cytochrome P450 in chronic renal failure. *J Am Soc Nephrol* 2001;**12**(2):326–32.

130. Leblond FA, Giroux L, Villeneuve JP, Pichette V. Decreased in vivo metabolism of drugs in chronic renal failure. *Drug Metab Dispos* 2000;**28**(11):1317–20.
131. Barnes KJ, Rowland A, Polasek TM, Miners JO. Inhibition of human drug-metabolising cytochrome P450 and UDP-glucuronosyltransferase enzyme activities in vitro by uremic toxins. *Eur J Clin Pharmacol* 2014;**70**(9):1097–106.
132. Uchida N, Kurata N, Shimada K, Nishimura Y, Yasuda K, Hashimoto M, et al. Changes of hepatic microsomal oxidative drug metabolizing enzymes in chronic renal failure (CRF) rats by partial nephrectomy. *Jpn J Pharmacol* 1995;**68**(4): 431–9.
133. Velenosi TJ, Fu AY, Luo S, Wang H, Urquhart BL. Down-regulation of hepatic CYP3A and CYP2C mediated metabolism in rats with moderate chronic kidney disease. *Drug Metab Dispos* 2012;**40**(8):1508–14.
134. Leber HW, Schutterle G. Oxidative drug metabolism in liver microsomes from uremic rats. *Kidney Int* 1972;**2**(3):152–8.
135. Okabe H, Hasunuma M, Hashimoto Y. The hepatic and intestinal metabolic activities of P450 in rats with surgery- and drug-induced renal dysfunction. *Pharm Res* 2003;**20**(10): 1591–4.
136. Terao N, Shen DD. Reduced extraction of I-propranolol by perfused rat liver in the presence of uremic blood. *J Pharmacol Exp Ther* 1985;**233**(2):277–84.
137. Michaud J, Dube P, Naud J, Leblond FA, Desbiens K, Bonnardeaux A, et al. Effects of serum from patients with chronic renal failure on rat hepatic cytochrome P450. *Br J Pharmacol* 2005; **144**(8):1067–77.
138. Yoshitani T, Yagi H, Inotsume N, Yasuhara M. Effect of experimental renal failure on the pharmacokinetics of losartan in rats. *Biol Pharm Bull* 2002;**25**(8):1077–83.
139. Michaud J, Nolin TD, Naud J, Dani M, Lafrance JP, Leblond FA, et al. Effect of hemodialysis on hepatic cytochrome P450 functional expression. *J Pharmacol Sci* 2008;**108**(2):157–63.
140. Nolin TD, Appiah K, Kendrick SA, Le P, McMonagle E, Himmelfarb J. Hemodialysis acutely improves hepatic CYP3A4 metabolic activity. *J Am Soc Nephrol* 2006;**17**(9):2363–7.
141. Michaud J, Naud J, Chouinard J, Desy F, Leblond FA, Desbiens K, et al. Role of parathyroid hormone in the downregulation of liver cytochrome P450 in chronic renal failure. *J Am Soc Nephrol* 2006; **17**(11):3041–8.
142. Velenosi TJ, Feere DA, Sohi G, Hardy DB, Urquhart BL. Decreased nuclear receptor activity and epigenetic modulation associates with down-regulation of hepatic drug-metabolizing enzymes in chronic kidney disease. *FASEB J* 2014;**28**(12): 5388–97.
143. Gu X, Ke S, Liu D, Sheng T, Thomas PE, Rabson AB, et al. Role of NF-kappaB in regulation of PXR-mediated gene expression: a mechanism for the suppression of cytochrome P-450 3A4 by proinflammatory agents. *J Biol Chem* 2006;**281**(26): 17882–9.
144. Watanabe H, Sugimoto R, Ikegami K, Enoki Y, Imafuku T, Fujimura R, et al. Parathyroid hormone contributes to the down-regulation of cytochrome P450 3A through the cAMP/PI3K/PKC/PKA/NF-kappaB signaling pathway in secondary hyperparathyroidism. *Biochem Pharmacol* 2017;**145**: 192–201.
145. Sun H, Huang Y, Frassetto L, Benet LZ. Effects of uremic toxins on hepatic uptake and metabolism of erythromycin. *Drug Metab Dispos* 2004;**32**(11):1239–46.
146. Naud J, Michaud J, Leblond FA, Lefrancois S, Bonnardeaux A, Pichette V. Effects of chronic renal failure on liver drug transporters. *Drug Metab Dispos* 2008;**36**(1):124–8.
147. Laouari D, Yang R, Veau C, Blanke I, Friedlander G. Two apical multidrug transporters, P-gp and MRP2, are differently altered in chronic renal failure. *Am J Physiol Renal Physiol* 2001;**280**(4): F636–45.
148. Simard E, Naud J, Michaud J, Leblond FA, Bonnardeaux A, Guillemette C, et al. Downregulation of hepatic acetylation of drugs in chronic renal failure. *J Am Soc Nephrol* 2008;**19**(7): 1352–9.
149. Yu C, Ritter JK, Krieg RJ, Rege B, Karnes TH, Sarkar MA. Effect of chronic renal insufficiency on hepatic and renal udp-glucuronyltransferases in rats. *Drug Metab Dispos* 2006;**34**(4): 621–7.

QUESTIONS AND ANSWERS

Question 1

A 54-year-old man infected with HCV develops the acute onset of oliguric AKI in the setting of decompensated cirrhosis which fails to respond to diuretic withdrawal or intravenous albumin infusion. Which of the following statements about the patient is most likely to be correct?

A. The renin–angiotensin system is suppressed
B. Arginine vasopressin levels are reduced
C. Nitric oxide levels are low
D. Cardiac output is reduced
E. A beneficial effect of blockade of the renin–angiotensin system is anticipated

Answer: D

Cirrhosis is characterized by deranged liver architecture leading to increased intrahepatic vascular resistance which in turn leads to increased portal vein pressure.[1–5] Release of systemic vasodilators, classically thought to arise as a response to portal hypertension, leads to peripheral vasodilation and decreased vascular resistance. The recruitment of compensatory mechanisms to maintain renal perfusion in the face of reduced effective arterial volume constitutes the hallmark of the HRS. These compensatory mechanisms include release of systemic vasoconstrictors, upregulation of the renin–angiotensin system, and activation of the sympathetic nervous system, increased nonosmotic release of vasopressin, and increased generation of potent vasoconstrictors. In early stages of cirrhosis, increased cardiac output maintains renal perfusion. However, in advanced cirrhosis, the ability of the heart to compensate is limited by cirrhotic cardiomyopathy and cardiac output declines.

Question 2

A 35-year-old woman with alcoholic cirrhosis develops the acute onset of oliguric AKI in the setting of decompensated cirrhosis which fails to respond to diuretic withdrawal or intravenous albumin infusion. Which of the following statements about the patient is most likely to be correct?

A. TNF-α levels are suppressed
B. Interleukin-6 levels are reduced
C. Urinary biomarkers of renal injury are absent
D. Circulating pathogen-associated molecular patterns are absent
E. An inflammatory state exists

Answer: E

It has recently been suggested that the primary factor responsible for the release of vasodilatory mediators in the HRS is increased circulating levels of cytokines and chemokines resulting from chronic inflammation associated with decompensated liver disease.[2,13] Cirrhosis is associated with increased gastrointestinal permeability, altered gastrointestinal microbiome, and translocation from the gastrointestinal tract of bacteria and bacterial products into the circulation. These bacterial products along with mediators released by apoptotic and necrotic hepatocytes stimulate the production of proinflammatory cytokines and chemokines, reactive oxygen species, and nitrogen species and activate immune cells. Decompensated cirrhosis is associated with increased levels of interleukin-6, interleukin-8, and TNF-α. Renal dysfunction in patients with decompensated liver failure has been correlated with circulating levels of proinflammatory cytokines.

Question 3

A 24-year-old woman with alcoholic cirrhosis develops a slowly progressive rise in the level of S[Cr] from 0.4 to 1.6 mg/dL over 3 weeks, which fails to respond to diuretic withdrawal or intravenous albumin infusion. Which of the following statements about the patient is most likely to be correct?

A. This is the most common clinical presentation of the HRS
B. This disorder is likely to show a sustained response to intravenous albumin and terlipressin
C. Post liver transplant renal outcomes are favorably influenced by therapy with intravenous albumin and terlipressin
D. This disorder is not associated with an inflammatory state
E. Even if intravenous albumin and terlipressin improve renal function in the short term, relapse is frequent

Answer: E

HRS-CKD is uncommon, accounting for only 5–11% of patients with cirrhosis and renal dysfunction. Treatment with intravenous albumin and terlipressin or noradrenaline can reverse HRS-CKD in more than half the cases.[18,19] However, responders experience a high relapse rate early after withdrawal of therapy. Relapse may occur in two-thirds of initial responders. Treatment of HRS-CKD with albumin volume expansion and vasoconstrictors is controversial and is not recommended by international practice guidelines due to inconsistent outcomes data.[2] After liver transplantation, there was no

difference in eGFR or in the development of CKD on follow-up, ranging up to 1 year, based on response to therapy.[19]

Question 4

A 69-year-old man with stage 5 chronic kidney disease is begun on therapy with warfarin, a drug that is subject to cytochrome P450 metabolism. Which of the following statements about the patient is most likely to be correct?

A. His chronic kidney disease status will have no effect on hepatic drug metabolism
B. The patient may require a lower dose of warfarin as a result of chronic kidney disease
C. Chronic kidney disease is associated with upregulation of most cytochrome P450 enzymes
D. Parathyroid hormone is not involved in cross talk between the kidney and hepatic drug metabolism
E. Chronic kidney disease does not influence gastrointestinal absorption of some drugs

Answer: B

CKD alters the pharmacokinetics of over 75 drugs whose elimination depends on nonrenal, predominantly hepatic clearance. In general, CKD is associated with reduced hepatic drug clearance, although in some cases hepatic clearance is enhanced. The magnitude of the change in hepatic drug clearance generally correlates with the degree of renal functional impairment. The remote effects of CKD on cytochrome P450 enzymes and drug transport proteins in the liver, kidney, and gastrointestinal tract are likely mediated by both the accumulation of uremic toxins including parathyroid hormone and by the generation of cytokine mediators.

Question 5

A 24-year-old HCV-infected man presents with microscopic hematuria and nephrotic syndrome. Which of the following statements about the patient is most likely to be correct?

A. Focal and segmental glomerulosclerosis is the most likely cause of nephrotic syndrome in this patient
B. Deposition of immune complexes containing viral antigens will not be demonstrated on kidney biopsy
C. HCV infection probably did not play a role in the development of glomerulonephritis in this patient
D. Interleukin-6 levels are reduced in this patient
E. Membranoproliferative glomerulonephritis is the most likely cause of nephrotic syndrome in this patient

Answer: E

Glomerular disease is a well-described extrahepatic manifestation of HCV infection.[45–47] A systemic immune response to HCV infection is thought to contribute to glomerular injury. Glomerular disease may be mediated by HCV-antibody immune complex deposition with or without cryoglobulin formation. Deposition of immune complexes containing viral antigens has been demonstrated in mesangial and subendothelial locations. The most common histologic pattern of glomerular injury is membranoproliferative glomerulonephritis; however, membranous glomerulopathy, focal and segmental glomerulosclerosis, IgA nephropathy, immunotactoid and fibrillary glomerulopathies, amyloidosis, and thrombotic microangiopathy have been described in HCV-infected patients.

Question 6

A 35-year-old HCV-infected man with stage 5 chronic kidney disease presents for antiviral therapy. Which of the following statements about the patient is most likely to be correct?

A. Sofosbuvir is approved by the Food and Drug Administration to treat this patient
B. Newer DAA agents may be expected to achieve a SVR in 25% of such cases
C. Transplantation status is not relevant to the decision whether or not to delay antiviral therapy in this patient
D. An interferon-based regimen is preferred due to the patient's age
E. A regimen containing grazoprevir and elbasvir is approved by the Food and Drug Administration to treat this patient

Answer: E

In the past, interferon and ribavirin constituted the only treatment option for HCV, and outcomes were suboptimal because of adherence issues related to toxicity.[56] Research into the HCV life cycle identified new opportunities to arrest viral replication and infectivity within hepatocytes. The four types of DAAs that were developed include (1) NS3/4A protease inhibitors, (2) NS5A inhibitors, (3) NS5B nonnucleoside polymerase inhibitors, and (4) NS5B nucleoside polymerase inhibitors.[57] They are given for a finite duration, usually in combination, avoid the difficult adverse effects of interferon-based therapies, and are curative. The current DAA regimens approved for use in patients with advanced CKD (stages 4 and 5) include Zepatier (combination of grazoprevir and elbasvir), Viekira (combination of ombitasvir, paritaprevir, dasabuvir, and ritonavir), and Mavyret

(combination of glecaprevir and pibrentasvir). FDA approval of sofosbuvir is limited to individuals with a GFR>30 mL/min/m^2. The decision whether or not to treat an HCV-infected individuals suffering from late-stage CKD with a second-generation DAA entails consideration of the individual's kidney transplantation status. Successful treatment of an HCV-positive candidate for a deceased donor kidney may result in a substantial delay or a lost opportunity for transplantation.[96]

CHAPTER

54

Chronic Kidney Disease and Heart Failure—A Nephrologic Approach

Andrew A. House[a], *Claudio Ronco*[b,c], *Charles A. Herzog*[d]

[a]Division of Nephrology, Department of Medicine, Western University and London Health Sciences Centre, London, ON, Canada; [b]Università degli Studi di Padova, Padova, Italy; [c]Department of Nephrology, Dialysis and Transplantation, San Bortolo Hospital, Vicenza, Italy; [d]Division of Cardiology, Department of Medicine, Hennepin County Medical Center and University of Minnesota, Minneapolis, MN, United States

Abstract

Increasing stages of chronic kidney disease are associated with increasing incidence and prevalence of congestive heart failure. After adjustment for multiple risk factors, even modest degrees of chronic kidney disease and/or albuminuria are associated with a significant increase in the adjusted hazard ratio of incident heart failure, underscoring the important relationship between the kidneys and the heart. Evidence supports the hypothesis that chronic kidney disease, through a variety of proposed mechanisms, contributes to significant functional and structural changes to the heart culminating in the clinical phenotype we recognize as congestive heart failure. Furthermore, chronic kidney disease and heart disease commonly coexist and may have shared pathophysiology and risk factors. In this chapter, the epidemiological association between chronic kidney disease and heart failure is examined, pathophysiology is briefly reviewed, and strategies to prevent and treat heart failure in this population are presented, both from the viewpoint of improved cardiovascular outcomes, and improved renal outcomes.

BACKGROUND

Owing to the high prevalence of heart disease in patients with chronic kidney disease (CKD), nephrologists must be well versed in the recognition and management of heart disease in this population. Cardio-renal syndrome type 4, or chronic renocardiac syndrome, has been defined as "chronic abnormalities in renal function leading to cardiac disease."[1] Within this broad category of patients, who suffer an inordinate burden of excess cardiovascular events and arrhythmias,[2] there is a significant proportion with incident and prevalent heart failure. The definition and classification of cardio-renal syndromes is presented in Table 54.1.[1] The European Society for Cardiology (ESC) defines heart failure as "a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress."[3] Within this are categories that differ significantly in terms of ejection fraction (EF), clinical phenotype, pathophysiology, and response to treatment, namely heart failure with preserved ejection fraction, ≥50% (HFpEF); reduced ejection fraction, <40% (HFrEF); and mid-range ejection fraction, 40–49% (HFmrEF).

The characterization of a patient as having cardiorenal syndrome type 4 is predicated on the ability to temporally place the kidney disease before the development of heart failure, which is not always a straightforward task. A remaining problem to be resolved is the clinical conundrum of what actually constitutes congestive heart failure in this population. For example, a patient with advanced stage 5 CKD who consumes a large helping of pepperoni pizza may develop "cardiogenic pulmonary edema" with all of the ESC clinical and radiologic stigmata of heart failure (including elevated serum natriuretic peptides), but the main cause is really circulatory congestion. Moreover, an anuric dialysis patient (who is exquisitely sensitive to alterations in interdialytic volume status), might present to the hospital after consuming said pepperoni pizza with conventionally labeled Class IV New York Heart

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00054-1

TABLE 54.1 Definition and Classification of the Cardio-Renal Syndromes Workgroup Statements from the Seventh ADQI Consensus Conference.

CARDIO-RENAL SYNDROMES (CRS) GENERAL DEFINITION
Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other
ACUTE CARDIO-RENAL SYNDROME (TYPE 1)
Acute worsening of cardiac function leading to renal dysfunction
CHRONIC CARDIO-RENAL SYNDROME (TYPE 2)
Chronic abnormalities in cardiac function leading to renal dysfunction
ACUTE RENO-CARDIAC SYNDROME (TYPE 3)
Acute worsening of renal function causing cardiac dysfunction
CHRONIC RENO-CARDIAC SYNDROME (TYPE 4)
Chronic abnormalities in renal function leading to cardiac disease
SECONDARY CARDIO-RENAL SYNDROMES (TYPE 5)
Systemic conditions causing simultaneous dysfunction of the heart and kidney

Association congestive heart failure—yet following a single ultrafiltration treatment they may be reclassified as "Class I." In dialysis patients, current heart failure classification schemas are too blunt an instrument for meaningful clinical understanding of heart failure in this special group of patients.

Clearly, it is not always possible to dissect out the temporal order of advanced CKD and (clinical) heart failure. Observational studies of CKD and heart failure often assemble a cohort of patients defined by the presence of one disease and then establish the prevalence of the other. For example, the Acute Decompensated Heart Failure National Registry evaluated over 100,000 hospitalizations for decompensated heart failure for evidence of concurrent CKD,[4] whereas a landmark study of patients newly starting on dialysis examined participants for evidence of concurrent heart failure.[5,6] This naturally leads to highly disparate estimates of coexisting CKD and heart failure. For many patients presenting with both disorders, it may be difficult to determine which of the disease processes is primary, and which is secondary, or whether in fact both are the result of shared pathophysiology or risk factors (for example hypertension or diabetes mellitus). It has been suggested that the term cardio-renal syndrome type 2/4 be used,[7] as an amalgam of type 2, (chronic abnormalities in cardiac function leading to renal dysfunction[1]) and type 4. Figures 54.1 and 54.2 (from references 8,9) illustrate the great burden of cardiovascular disease (CVD) in elderly CKD patients, particularly related to congestive heart failure.

Although these distinctions may seem somewhat artificial or arbitrary, they do assist in the interpretation of epidemiological studies and have helped focus clinical and basic investigation into the pathophysiology and treatment of heart failure in patients with CKD. In this chapter, the epidemiological association between CKD and heart failure will be examined, pathophysiology will be briefly reviewed, and strategies for the prevention and treatment of heart failure in patients with CKD will be presented, both from the viewpoint of improved cardiovascular outcomes, and improved renal outcomes. At the time of writing of this chapter, there

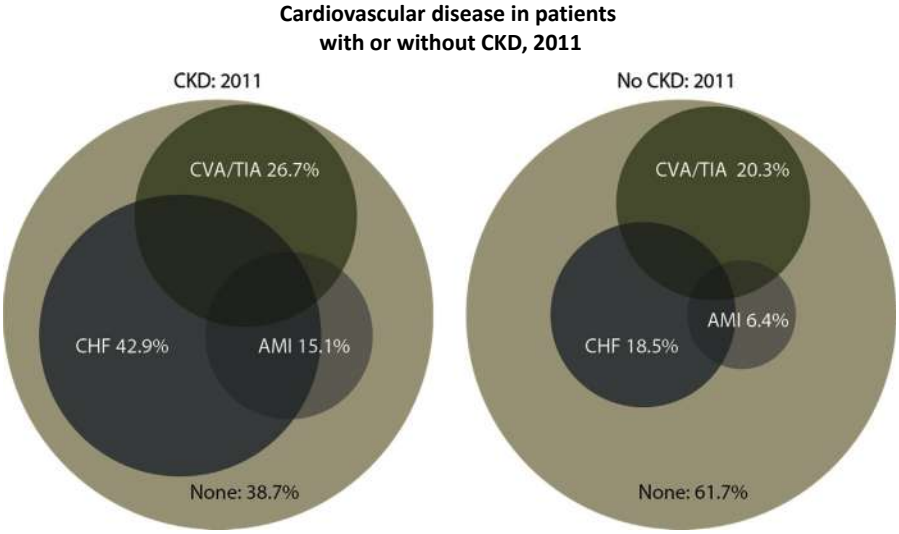


FIGURE 54.1 Cardiovascular disease burden in elderly Medicare enrollees based on presence or absence of CKD. Note that congestive heart failure is more than twice as prevalent in the CKD population. *AMI*, acute myocardial infarction; *CKD*, chronic kidney disease; *CHF*, congestive heart failure; *CVA*, cerebrovascular accident; *TIA*, transient ischemic attack. *Reproduced from reference 8. The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data and those of subsequent figures from USRDS are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.*

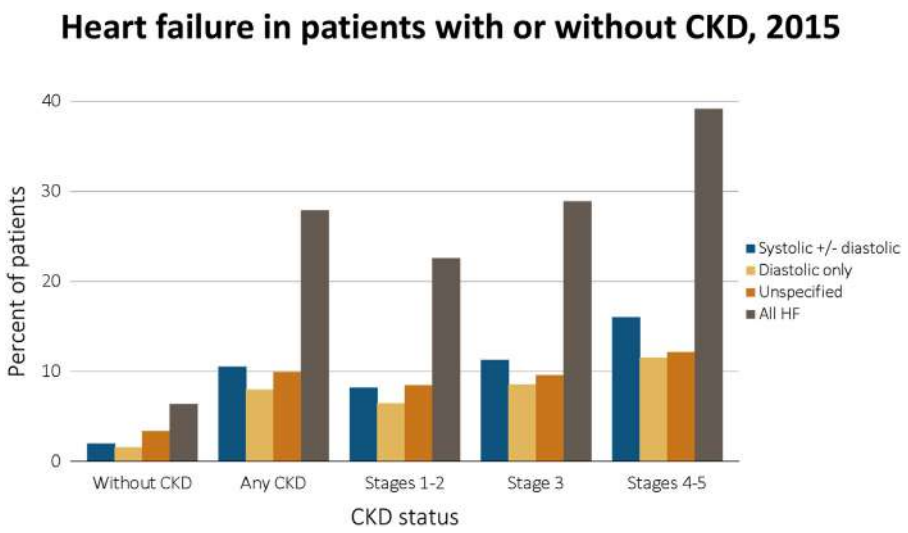


FIGURE 54.2 Prevalence of heart failure by subtype (systolic or reduced ejection fraction; diastolic or preserved ejection fraction) in elderly Medicare enrollees based on presence or absence of CKD. *CKD*, chronic kidney disease; *HF*, heart failure. *Reproduced from reference 9.*

remains a lack of any robust evidence for successfully modifying the grave outcome of HFpEF, including in the setting of CKD.[10] For this reason, discussion of prevention and treatment strategies generally refer to HFrEF, for which the strongest data are available. Although this textbook is primarily geared toward the various facets of CKD prior to reaching end-stage, there are a number of observations in dialysis patients that warrant brief discussion in this chapter.

EPIDEMIOLOGY

The independent association between CKD and the risk of CVD, events, and mortality has long been recognized. Early reports suggested that the risk associated with CKD and cardiovascular events was explained by comorbid conditions and cardiovascular risk factors.[11] As subsequent observational studies with larger numbers and greater statistical power emerged, it has become clearer that statistical adjustment for known risk factors can mitigate the association between renal function and cardiovascular events somewhat, but an independent association can be easily demonstrated. For example, a meta-analysis of nearly 1.4 million subjects found a progressive increase in all-cause mortality with declining glomerular filtration rate (GFR), and estimated relative odds of death increased in a stepwise manner to 1.9, 2.6, and 4.4 for GFR of 80, 60, and 40 mL/min respectively, compared with a reference group with GFR 100 mL/min.[12] A study by Go et al. found not only an increase in all-cause mortality but also that hospitalization for cardiovascular events, which included heart failure, coronary disease, stroke, and peripheral vascular disease, increased with each diminishing category of GFR.[13] These relationships held after sophisticated multivariable adjustment for all manner of potential confounding or influential variables. The burden of cardiovascular morbidity and mortality is particularly evident in patients with the most advanced stage of CKD, whether treated by hemodialysis, peritoneal dialysis, or kidney transplantation (Figure 54.3, from reference 8). Currently, it is believed that CVD is responsible for approximately 50% of deaths in CKD patients, regardless of age,[14] though most of these events are ischemic or arrhythmic in nature.

In the Kidney Early Evaluation Program, over 100,000 subjects screened for kidney disease self-reported the presence of a number of comorbid conditions, including congestive heart failure in 1.6% of respondents with estimated GFR >120 mL/min/1.73 m^2, increasing with every diminishing category of GFR to 14.9% for the respondents with GFR <30 mL/min/1.73 m^2.[15]

In a subset of the Chronic Renal Insufficiency Cohort Study,[16] investigators focused on 190 subjects who progressed from moderate CKD to end-stage renal disease (ESRD) and underwent serial echocardiography. Over a period of approximately 2 years where subjects progressed from advanced CKD to ESRD, there was a decrease in mean EF from 53% to 50% ($p = 0.002$), and the proportion of participants with an EF $\leq$50% increased from 29% to 48% ($p < 0.001$). During this period the frequency of self-reported congestive heart failure nearly doubled.

Lesser degrees of CKD have also been associated with development of heart failure. Investigators in the Atherosclerosis Risk in Communities (ARIC) study analyzed data from nearly 15,000 participants in a large, population-based study of adults who were followed with serial estimates of GFR.[17] Participants known to

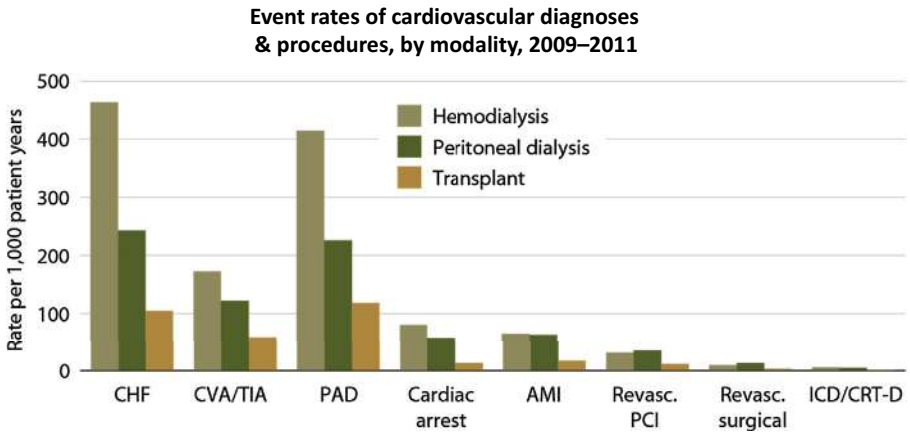


FIGURE 54.3 Rates of cardiovascular diagnoses and procedures in patients 20 years and older with end-stage renal disease treated by hemodialysis, peritoneal dialysis, or transplant. *AMI*, acute myocardial infarction; *CHF*, congestive heart failure; *CRT-D*, cardiac resynchronization therapy defibrillator; *CVA*, cerebrovascular accident; *ESRD*, end-stage renal disease; *ICD*, implantable cardiac defibrillator; *PAD*, peripheral arterial disease; *PCI*, percutaneous coronary intervention; *TIA*, transient ischemic attack. *From USRDS, reference 8.*

have preexisting heart failure were excluded, meaning that incident heart failure was captured in the analysis. They found a substantial increase in heart failure in participants with GFR <60 mL/min. Specifically, using participants with GFR ≥90 mL/min as reference, Cox proportional hazards modeling demonstrated an adjusted relative hazard of incident heart failure of 1.10 (95% CI 0.97–1.26) for participants in the range 60–89 mL/min, and 1.94 (95% CI 1.49–2.53) for participants <60 mL/min. In spite of multivariable adjustment for many known risk factors for CVD, the presence of a GFR consistent with stage 3 CKD or greater was associated with nearly a doubling in the risk of incident heart failure.

In a subsequent analysis of the ARIC study, investigators estimated GFR using not only serum creatinine concentration (S[Cr]) but also using serum cystatin C (GFRcys), and also quantified albuminuria using the albumin:creatinine ratio (ACR).[18] The addition of these biomarkers to the categorization of kidney disease strengthened the association with all-cause mortality, cardiovascular events, and incident heart failure. At every level of GFR, increasing ACR was associated with a greater adjusted hazard ratio of heart failure. Likewise within each category of ACR, decreasing GFR, particularly as estimated by cystatin C, was associated with a greater hazard of heart failure. Adjusted hazard ratios ranged from 5.6 for participants with an estimated GFRcys of 45–59 mL/min/1.73 m^2 and ACR of 30–299 mg/g to as high as 14.0 for participants with estimated GFRcys of 30–44 mL/min/1.73 m^2 and ACR ≥300 mg/g. This is illustrated graphically in Figure 54.4 (from reference 18).

These observations are all supportive of the hypothesis that CKD, through a number of posited mechanisms, can lead to significant functional and structural changes to the heart, leading eventually to the clinical phenotype of congestive heart failure. Not only is heart failure more prevalent but patients with CKD are also at higher mortality risk following the diagnosis of CVD, including heart failure. As shown in Figure 54.5 (from reference 9) there is a strong, graded relationship between heart failure mortality and CKD stage. Additional support for this association is found in a meta-analysis of 30 cohort studies comprising nearly 40,000 heart failure patients, from the Meta-Analysis Global Group in Chronic Heart Failure investigators.[19] In multivariable modeling, S[Cr] was found to be one of the five most powerful predictive variables associated with mortality, along with age, EF, New York Heart Association class, and diabetes mellitus, the association becoming evident at a S[Cr] as low as 1.25 mg/dL.

PATHOPHYSIOLOGY OF HEART FAILURE IN CKD

Various proposed mechanisms of CVD and heart failure are highlighted in Figure 54.6 (from reference 20). In brief, CKD of varying degrees can contribute to heart failure indirectly through its putative role in exacerbating ischemic heart disease, or more directly through pressure and volume overload, which increase proportionately with the decline in renal function and contribute to ventricular hypertrophy.[21] Marked hypertrophy has been shown to be highly prevalent by the time patients progress to dialysis-dependence. Ventricular hypertrophy is a frequent precursor to subsequent hospitalizations for heart failure.[22] Furthermore, the association between CKD and heart disease/heart failure may also be one of shared risk factors, such as diabetes and hypertension, or reflect widespread vascular disease and endothelial dysfunction. Pressure overload is

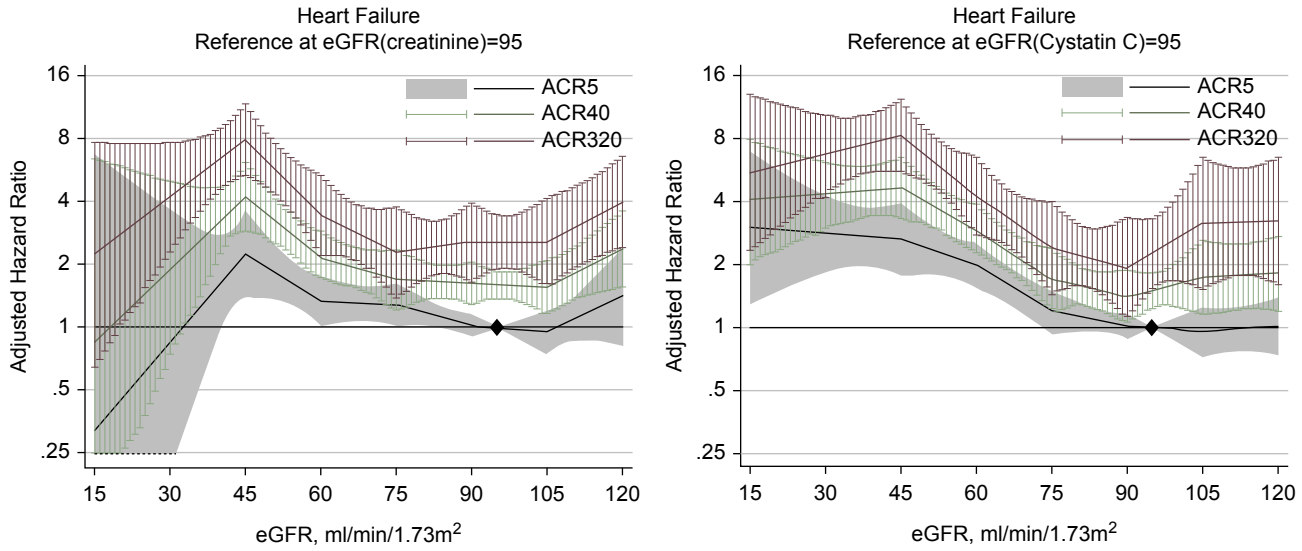


FIGURE 54.4 Hazard ratios with 95% confidence intervals of estimated glomerular filtration rate using creatinine-based or Cystatin C based estimates with heart failure in the Atherosclerosis Risk in Communities (ARIC) study. *ACR*, albumin:creatinine ratio; *eGFR*, estimated glomerular filtration rate. *Adapted from reference 18 with permission.*

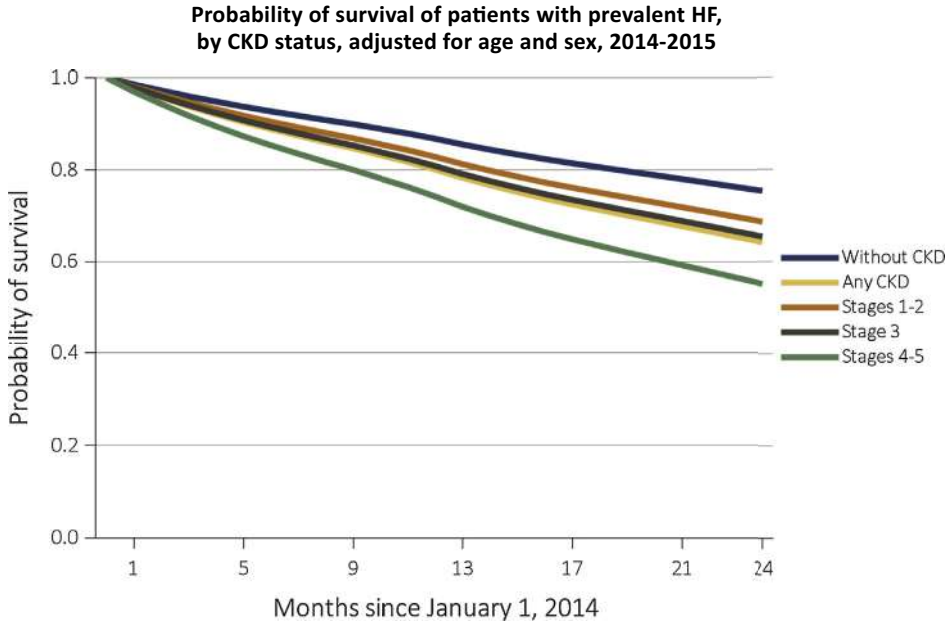


FIGURE 54.5 Probability of survival with prevalent heart failure based on stage of chronic kidney disease in elderly Medicare recipients. *CKD*, chronic kidney disease, *HF*, heart failure. *From USRDS, reference 9.*

the result of factors such as hypertension and cardiac valve calcification, which are extremely common in CKD and prevalent dialysis patients.[23,24] Phosphate retention, hyperparathyroidism, and related disorders falling under the umbrella term CKD mineral and bone disorder (CKD-MBD) lead to a progressive transformation of the vasculature and cardiac valves as they literally begin to ossify. Altered compliance of blood vessels resulting from chronic hypertension and potentially from CKD-MBD–related vascular calcification further contributes to pressure overload. Anemia and sodium retention, leading to excess extracellular fluid volume and hypertension, contribute to chronic volume overload and hypertrophy.[21] Volume overload may be further aggravated by the presence of an arteriovenous fistula or graft.[25]

With the ongoing exposure to pressure and volume overload, it is believed that increased cardiac workload

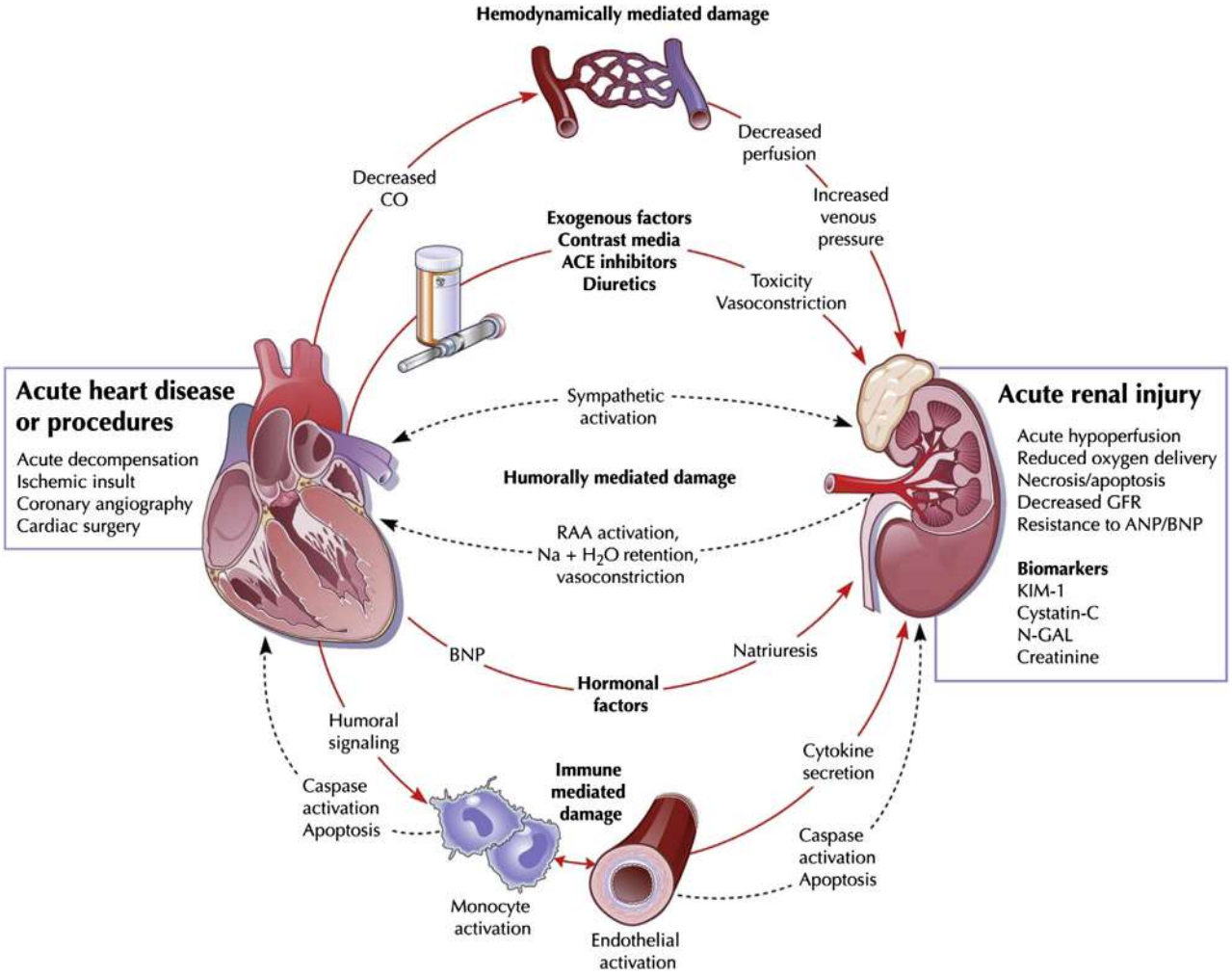


FIGURE 54.6 Pathophysiological interactions between heart and kidney in type 4 cardio-renal syndrome or "chronic reno-cardiac syndrome." *BMI*, body mass index; *CKD*, chronic kidney disease; *EPO*, erythropoietin; *LDL*, low-density lipoprotein. Figure illustration by Rob Flewell. *From reference 20 with permission.*

leads to compensatory ventricular hypertrophy. This has been shown in many other disease states to lead to the eventual outstripping of myocardial oxygen supply.[26] Myocyte death and cardiac fibrosis result, leading ultimately to chamber dilation and pump failure.[14,27] The failing heart, in turn, leads to activation of the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system, and other neurohormonal axes that themselves contribute both to worsening volume and pressure overload,[28] as well as playing a key role in progressive glomerulosclerosis and progressive kidney injury.[29,30] Finally, the recognition that some dialysis patients with severe cardiomyopathy improve following renal transplantation has led to speculation regarding some unidentified uremic myocardial depressant factor(s).[31,32]

PREVENTION AND TREATMENT OF HEART FAILURE IN CKD

The strategies of managing heart failure in CKD patients are limited by a paucity of relevant large-scale randomized controlled trials. Many pivotal trials of patients with established heart failure or myocardial infarction, with death or worsening heart failure as the primary outcome, purposefully excluded patients with significant CKD. Most studies of CKD patients typically employ composite cardiovascular endpoints as the primary outcome, where heart failure *per se* is a secondary outcome. Notwithstanding these limitations, management strategies include a selection of representative trials, both negative and positive, seeking to demonstrate the prevention of a new diagnosis of heart failure and

those treating existing heart failure. These trials are generally targeting factors described in the proposed pathogenesis of heart failure in CKD.

PREVENTION

As a general strategy to prevent incident heart failure, evidence from the SPRINT trial demonstrated that aggressive blood pressure control (targeting systolic BP to less than 120 mm Hg) could reduce new onset of heart failure in nondiabetic patients, even in the presence of CKD.[33] Similar findings in support of tight blood pressure control have been shown in patients regardless of the presence or absence of diabetes mellitus.[34]

In CKD patients, glycemic control is associated with the risk of incident heart failure.[35] Emerging evidence from the EMPA-REG OUTCOME study of around 7000 patients showed that the sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin reduced heart failure hospitalizations by approximately 35%.[36] This observation was also seen in patients with reduced eGFR and/or albuminuria.[37] These results were mirrored by the SGLT2 inhibitor canagliflozin in the CANVAS Program (CANVAS and CANVAS-R trials) of over 10,000 patients with type 2 diabetes mellitus.[38] It has been suggested that glycemic control was not the only factor responsible for reducing heart failure, as these drugs have diuretic effects as well as effects on the myocardium itself through cardiac Na+/H+ exchange, and changes in hematocrit had a greater association with outcome than measures of glycemic control.

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study was a double-blind, randomized, placebo-controlled study designed to evaluate the renoprotective effects of losartan in 1513 patients with type 2 diabetes and nephropathy, none of whom had heart failure at baseline.[39] Losartan resulted in a 16% reduction in the risk of the primary composite endpoint of doubling of S[Cr], ESRD, or death ($p = 0.02$). Of relevance to the prevention of heart failure in CKD patients, a significant reduction in the first hospitalization with heart failure was observed, occurring in 11.9% of the losartan group vs. 16.7% of the placebo group, a reduction of 32% ($p = 0.005$).

Similar to the RENAAL study, the Irbesartan Diabetic Nephropathy Trial (IDNT) was a double-blind, randomized, controlled study designed to evaluate the renoprotective effects of the angiotensin receptor blocker (ARB) irbesartan vs. amlodipine or placebo in 1715 patients with type 2 diabetes and nephropathy.[40] The patients in the irbesartan group had an unadjusted relative risk of reaching the primary composite endpoint of doubling of S[Cr], ESRD, or death that was 20% lower than that in the placebo group ($p = 0.02$) and 23% lower than that in the amlodipine group ($p = 0.006$). Baseline heart failure was not described, nonetheless the irbesartan group had a significantly lower incidence of congestive heart failure compared with placebo recipients (hazard ratio, 0.72 [CI, 0.52−1.00]; $p = 0.048$) or amlodipine recipients (hazard ratio, 0.65 [CI, 0.48−0.87]; $p = 0.004$).[41]

In more advanced CKD, the Fosinopril in Dialysis study was a randomized trial evaluating the safety and efficacy of angiotensin converting enzyme (ACE) inhibition with fosinopril on cardiovascular clinical outcomes in 397 hemodialysis patients with left ventricular hypertrophy.[42] Heart failure was included in the composite endpoint, which was not statistically significant between fosinopril and control groups, and heart failure outcomes alone were not reported.

TREATMENT

For CKD patients with established heart failure, the RAAS system has been an important target. For example, in the Valsartan in Heart Failure Trial (Val-HeFT), 5010 patients with class II, III, or IV heart failure were randomly assigned to receive the ARB valsartan or placebo in addition to optimal heart failure therapy, including ACE inhibition in 93% of patients.[43] Patients with S[Cr] >2.5 mg/dL were excluded from the trial, but nearly 60% of patients had an estimated GFR <60 mL/min, and 8% had dipstick positive proteinuria, allowing for a secondary analysis of the efficacy of valsartan in patients with CKD. Mortality and morbidity were highest in the patients with both reduced GFR and proteinuria, least in patients with normal GFR and no proteinuria, and intermediate in the remaining subgroups of patients. Although the addition of valsartan did not have an effect on overall mortality, the group with CKD who were randomized to valsartan did have a statistically lower rate of first morbid event (an outcome including death or heart failure hospitalization or intravenous vasoactive drug administration). An additional trial in 332 hemodialysis patients in which the ARB telmisartan was added to ACE inhibition in patients with left ventricular EF of ≤40% and followed for 3 years found a dramatic decrease in all-cause mortality and hospital admission for heart failure.[44] The former was decreased to 35.1% for the telmisartan group vs. 54.4% for control patients ($p < 0.001$). The latter was decreased to 33.9% for the telmisartan group compared with 55.1% for control patients ($p < 0.0001$).

In patients with both heart failure and CKD with eGFR 30−60 mL/min/1.73 m^2, mineralocorticoid receptor antagonists (MRAs) are generally as efficacious as they are in the absence of kidney disease.[45] Sadly, pivotal trials of MRAs in heart failure have excluded those with

more advanced CKD. The Randomized Aldactone Evaluation Study treated 1600 subjects with EF <35% using spironolactone or placebo but excluded patients with S[Cr] ≥ 2.5 mg/dL or S[K] > 5.0 mmol/L.[46] A reasonable number were included with eGFR <60 mL/min/1.73 m^2. They had similar positive outcomes in terms of mortality and heart failure hospitalization, coming at the expense of more hyperkalemia and worsening kidney function necessitating reduction or discontinuation.[47] Studies in advanced CKD are even more limited and include a large observational cohort from Taiwan indicating increased risk of death or hospitalization for heart failure among more than 1300 patients with eGFR <15 mL/min/1.73 m^2 receiving spironolactone.[48] At the time of this writing there is a randomized clinical trial of spironolactone in hemodialysis patients, which will hopefully answer questions regarding its safety and efficacy in dialysis patients with heart failure (ClinicalTrials.gov Identifier: NCT01848639).

Targeting the sympathetic nervous system in advanced CKD, a small study of 114 dialysis patients with dilated cardiomyopathy randomly compared carvedilol or placebo in addition to standard therapy. A first analysis was performed at one year and was a blinded trial. This was followed by an additional unblinded follow-up period of 12 months.[49] The primary endpoints included changes in left ventricular end-diastolic volume, end-systolic volume, EF, and clinical status 24 months after randomization. EF was 26% in both groups at baseline. Although the mean EF in the placebo group was essentially unchanged at 24% after 2 years, the carvedilol group had an early and sustained improvement to 37% ($p < 0.05$). Similar changes were seen in the other echocardiographic parameters. Heart failure symptoms were dramatically improved in the carvedilol group. At 2 years, 30 patients in the carvedilol group (51.7%) had died, compared with 41 (73.2%) in the placebo group ($p < 0.01$). There were significantly fewer all-cause cardiovascular deaths (29.3% vs. 67.9%, $p < 0.0001$) and heart failure hospitalizations (13.8% vs. 57.1%, $p < 0.0001$) among patients receiving carvedilol than among those receiving placebo.

Patients with less severe degrees of CKD have been included in several pivotal trials of beta-blockers in heart failure. For instance, the Metoprolol CR/XL Randomized Intervention Trial in Chronic HF randomized approximately 4000 symptomatic HFrEF patients to metoprolol or placebo, including approximately 500 patients with eGFR <45 mL/min/1.73 m^2. Metoprolol reduced mortality by nearly 60% for the CKD subgroup.[50] Similar results were seen in the Cardiac Insufficiency Bisoprolol Study II, which included patients with S[Cr] up to 300 μmol/L (3.4 mg/dL).[51]

A new class of agent targeting the RAAS system is the addition of a neprilysin inhibitor to an ARB, referred to as an Angiotensin Receptor and Neprilysin Inhibitor (ARNI). The first such agent LCZ696 combined sacubitril with valsartan. This agent is recommended as a replacement for an ACE inhibitor or ARB in HFrEF patients who remain symptomatic in spite of maximum optimized care. The study PARADIGM-HF (Prospective Comparison of ARNI with ACE Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial) compared enalapril with LCZ696. It was stopped early due to a large benefit of LCZ696 in terms of overall mortality, cardiovascular mortality, hospitalizations, and HF symptoms.[52] Fewer participants randomized to LCZ696 developed worsening kidney function or high S[K]. However, the study excluded patients with eGFR <30 mL/min/1.73 m^2 at baseline or during the run-in, or any patient who developed a decrease in eGFR of >35% or high S[K] during the run-in. This limits the ability to recommend this class of drug for HF patients with CKD stage 4 or higher.

Observational data in CKD patients are also consistent with a beneficial effect of RAAS and sympathetic nervous system blockade. As shown in Figure 54.7 (from reference 53), the use of both beta-blockers and ACE inhibitors or ARBs is associated with better outcomes in elderly heart failure patients, including those with CKD. A frequently encountered problem arises when patients (particularly those with more advanced CKD) are intolerant of RAAS blockade because of significant (i.e. >30%) and persistent deterioration of kidney function or frequent hyperkalemia. In the Cooperative North Scandinavian Enalapril Survival Study, heart failure patients randomized to enalapril vs. placebo experienced a marked reduction in mortality and improvement in symptoms.[54] In a *post hoc* analysis of the data,[55] subjects in the enalapril group experienced a rise in S[Cr] to about 10−15% above baseline (usually within the first 2 weeks), consistent with the known hemodynamic effects of ACE inhibition on GFR, after which S[Cr] rose to a similar degree to the placebo group. S[Cr] doubled in significantly more patients receiving enalapril, though intercurrent illness or hypotension explained most of these occurrences. In most subjects S[Cr] returned to within 30% of baseline, including a number of patients who were able to continue on ACE inhibition at a lower dose.

Although the subgroup of truly ACE inhibitor and ARB intolerant heart failure patients has not been subjected to specific study, in clinical practice these remain a significant challenge. The fixed-dose combination of isosorbide dinitrate and hydralazine has been studied in populations that do not exclude those with CKD. One such study, the African-American Heart Failure Trial, demonstrated an early and sustained benefit of this combination when added to standard therapy in a study of over 1000 black patients with New York Heart

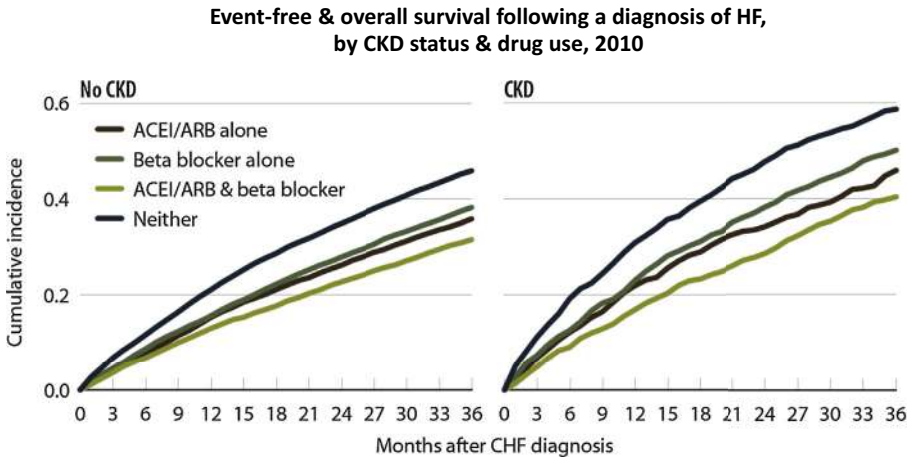


FIGURE 54.7 Survival following a diagnosis of congestive heart failure in Medicare recipients with and without a diagnosis of chronic kidney disease, accounting for use of beta blockers and renin–angiotensin blockade. *ACEI*, angiotensin converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *CHF*, congestive heart failure; *CKD*, chronic kidney disease. *From USRDS, reference 53.*

Association class III or IV heart failure.[56] The investigators found a 37% improvement in event-free survival ($p < 0.001$) and a 39% reduction in the risk for first hospitalization for heart failure ($p < 0.001$). The point estimates for risk reduction were similar in various subgroups, including patients with and without CKD, the former constituting approximately 17% of the study population. Although not as effective as the ACE inhibitor enalapril in terms of mortality and morbidity, the Vasodilator–Heart Failure Trials (V-HeFT I and II) did demonstrate that hydralazine and isosorbide dinitrate in combination confer a significant mortality benefit compared to placebo and caused less hyperkalemia and elevation of urea and S[Cr] than enalapril.[57,58] In practice, therefore, this seems a reasonable strategy to employ when RAAS blockade proves to be unsafe.

Given the link between CKD-MBD and heart outcomes in CKD patients, a number of studies have looked at agents targeting CKD-MBD. One such study, the DCOR (Dialysis Clinical Outcomes Revisited) trial, compared all-cause mortality and cause-specific mortality (cardiovascular mortality, infection, and other causes) in over 2100 hemodialysis patients treated with calcium-based phosphate binders vs. sevelamer,[59] 40% of whom were reported to have heart failure at baseline.[60] The primary outcome was not found to be different between groups, and heart failure outcomes were not described.

In the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial, nearly 4000 patients receiving dialysis were randomized to receive cinacalcet or placebo.[61] The primary composite endpoint was reached in 48.1% of subjects randomized to cinacalcet and 49.2% receiving placebo for a relative hazard of 0.93 (95% CI, 0.85–1.02; $p = 0.11$). Although the primary outcome was not statistically significant, there was a modest reduction in first episode of heart failure in favor of cinacalcet, which was statistically significant with a relative hazard of 0.82 (95% CI, 0.68–0.99; $p = 0.03$).

Previous observational studies and prospective trials have suggested a potential role for 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) in congestive heart failure. Unlike many cardioprevention trials, the TNT (Treating to New Targets) study did not exclude patients on the basis of S[Cr] levels, allowing for *post hoc* analysis of this study of intensive lipid lowering with high dose atorvastatin in patients with CKD.[62] Over 3000 patients in this study, which enrolled approximately 10,000 patients with known coronary heart disease, had estimated GFR <60 mL/min. This subgroup had a mean age of 65.5 years, two-thirds were male, and 9% were current smokers and they were predominantly white (95.2%) with body mass index of 28.5 kg/m^2. Roughly 12% of these CKD patients had heart failure at baseline. After a median follow-up of 5 years, a first major cardiovascular event was experienced by 9.3% of those receiving atorvastatin 80 mg daily and 13.4% of those receiving atorvastatin 10 mg daily, a 32% relative reduction in risk with intensive lipid lowering (HR 0.68; 95% CI 0.55–0.84; $p < 0.0003$). Hospitalization for congestive heart failure was reduced by 46% in the intensive lipid lowering group (HR 0.54; 95% CI 0.38–0.77) compared with the less-intensive group, a treatment effect much more pronounced than that in the normal GFR group ($p = 0.011$ for heterogeneity). This trial cannot discern whether the effects on heart failure were due to cholesterol lowering *per se*, or some pleiotropic effect of the statin therapy.

As ventricular hypertrophy is believed to be an important step in the sequence of events leading

ultimately to chamber dilatation and heart failure, it is interesting to examine the approach taken to control of volume and uremia in the most advanced stages of CKD. The Frequent Hemodialysis Network (FHN) study[63] randomized 245 dialysis patients to three times weekly (conventional) or six times weekly (frequent) hemodialysis for 12 months. The coprimary composite outcome of the trial was (1) death or change in left ventricular mass (determined by cardiac magnetic resonance imaging), and (2) death or change in the physical health composite score of the RAND 36-item health survey. The frequent group experienced benefits in both outcomes, with a hazard ratio for death or increased left ventricular mass of 0.61 (95% CI, 0.46−0.82). This study was not powered to examine differences in death or major cardiovascular events, and episodes of new or worsening heart failure were not described, but the improvement in ventricular mass means this intervention most certainly holds promise for prevention of heart failure and merits further study. Although this study cannot be readily extrapolated back to the nondialysis CKD population, it does underscore the importance of volume and/or uremic factors in progression of ventricular hypertrophy.

Another study in this population, the IDEAL trial,[64] used a different approach to control uremic toxins and volume overload by studying early vs. late initiation of conventional dialysis. A substudy of IDEAL examined 182 subjects randomized on the basis of estimated GFR to early (GFR 10−14 mL/min/1.73 m^2) or late (GFR 5−7 mL/min/1.73 m^2) start of dialysis and followed with echocardiography at baseline and 12 months. Left ventricular mass index was elevated at baseline, but there was no significant change within or between groups at 12 months. In addition, at baseline there were echocardiographic features consistent with significant diastolic dysfunction; however, there were no differences between groups at 12 months and no changes were observed for left ventricular volumes, left ventricular EF, stroke volume, and other echocardiographic parameters. It is difficult, as with FHN, to extrapolate these data to the nondialysis CKD population, though the negative results of this intervention may suggest that waiting for dialysis-dependence to intervene to prevent progression of left ventricular mass may simply be too late.

As a number of observational studies have identified a relationship between anemia and left ventricular mass[21,65] in CKD patients, treatment of anemia has been an obvious target for treatment trials in this population. In a 24-month randomized trial of immediate vs. delayed treatment of anemia with erythropoietin in 172 CKD patients not on dialysis, Levin et al. found no statistically significant difference between groups for the primary outcome of mean change in left ventricular mass index, despite an early and sustained difference in mean hemoglobin concentration throughout the trial.[66] A meta-analysis[67] of a number of related studies, involving over 1700 CKD patients (both predialysis and dialysis), suggested that treatment of severe anemia with conventional hemoglobin targets for erythropoietin therapy (<12 g/dL) is associated with a reduction in left ventricular mass index, although these studies lacked randomly assigned, untreated controls. Studies of patients with more moderate anemia and target hemoglobin above 12 g/dL did not demonstrate a significant beneficial impact on left ventricular mass. These data, coupled with randomized controlled evidence where higher hemoglobin targets have been associated with worse outcomes, do not support the use of erythropoiesis-stimulating agents to prevent or treat heart failure in CKD.

SUMMARY

Congestive heart failure and CKD commonly coexist, and CKD patients with heart failure suffer a tremendous burden of morbidity and excess mortality. As a patient population that has previously been targeted for exclusion from clinical trials, recognition of the importance of cardio-renal syndromes has led to recent advances in our understanding of the management of heart failure in CKD. In some instances one of these disorders clearly predates and likely contributes to the development of the other. In other instances this relationship is not so clear cut and certainly could represent coexistence of disease processes with shared pathophysiology and risk factors. Nonetheless, given the important role of volume and pressure overload, along with neurohormonal activation, available clinical trial evidence supports interruption of the RAAS system as the most critical primary target for the prevention and treatment of heart failure. Additional evidence supports beta-blockade. Indirect evidence indicates a potential role for hydralazine and isosorbide dinitrate in select patients. The role of the intensity and frequency of dialysis, but not the timing of its initiation, are supported by data examining the surrogate outcome of left ventricular mass, and there is some limited evidence to indicate that CKD-MBD and lipid management may also influence the course of heart failure in CKD patients. Despite observational data and sound biologic rationale for anemia management with erythropoiesis-stimulating agents to treat or delay cardiovascular complications, this has not been borne out in clinical trials, which do indicate the potential for significant harm.

The authors agree with the recommendations found in the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the

Evaluation and Management of Chronic Kidney Disease,[68] which highlight the importance of risk factor modification to prevent CVD in the CKD population. Specifically, we recommend for all patients with CKD the following: smoking cessation; exercise; weight reduction to optimal targets; lipid modification; control of diabetes (HbA1C <7%); control of blood pressure to <140/90 mm Hg or <130/80 mm Hg in those with diabetes and/or albuminuria; aspirin for secondary prevention and correction of anemia to individualized targets. We certainly favor the use of angiotensin-converting enzyme inhibitors (ACEIs) or ARBs, particularly in those with albuminuria. It is expected that these measures will not only reduce risk of cardiovascular events and progression of CKD but also to a certain degree the risk of *de novo* heart failure.

For those who manifest signs and symptoms of congestive heart failure, KDIGO suggests that the level of care for heart failure should be the same for those without CKD.[68] We concur and would add that ACEIs or ARBs should be used regardless of stage of CKD, provided renal function does not demonstrate a persistent and significant decline (i.e. delta GFR >30%), and S[K] is carefully monitored and maintained consistently below 5.0 mmol/L. In either of these instances, dose reduction with careful monitoring or the combination of hydralazine and isosorbide dinitrate may be considered as alternatives. We recommend the use of beta-blockers having an indication in congestive heart failure, where tolerated. MRAs should be considered, recognizing that clinical trials excluded patients with moderate CKD (S[Cr] $\geq$ 2.5 mg/dL or 220 μmol/L) or hyperkalemia >5.0 mmol/L.[46] Limited data on the use of ARNI in more advanced CKD make it difficult to make a recommendation pending further study. We reserve the use of other classes of diuretics to manage symptoms of pulmonary edema and to aid in achievement of blood pressure goals. Lower limb edema, by itself, without other signs or symptoms of volume overload or threatened skin integrity does not necessarily mandate increasing diuretics, as edema is multifactorial and may not reflect central hypervolemia. Loop diuretics are the preferred class of diuretic simply based on efficacy and potency in the CKD population.

References

1. House AA, Anand I, Bellomo R, Cruz D, Bobek I, Anker SD, et al. Definition and classification of cardio-renal syndromes: workgroup statements from the 7th ADQI consensus conference. *Nephrol Dial Transplant* 2010;**25**(5):1416–20. https://doi.org/10.1093/ndt/gfq136. PubMed PMID: 20228069.
2. House AA. Cardio-renal syndrome type 4: epidemiology, pathophysiology and treatment. *Semin Nephrol* 2012;**32**(1): 40–8. https://doi.org/10.1016/j.semnephrol.2011.11.006. PubMed PMID: 22365161.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; **18**(8):891–975. https://doi.org/10.1002/ejhf.592. PubMed PMID: 27207191.
4. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Card Fail* 2007;**13**(6):422–30. https://doi.org/10.1016/j.cardfail.2007.03.011. PubMed PMID: 17675055.
5. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The prognostic importance of left ventricular geometry in uremic cardiomyopathy. *J Am Soc Nephrol* 1995;**5**(12):2024–31. PubMed PMID: 7579050.
6. Harnett JD, Foley RN, Kent GM, Barre PE, Murray D, Parfrey PS. Congestive heart failure in dialysis patients: prevalence, incidence, prognosis and risk factors. *Kidney Int* 1995;**47**(3):884–90. PubMed PMID: 7752588.
7. Bagshaw SM, Cruz DN, Aspromonte N, Daliento L, Ronco F, Sheinfeld G, et al. Epidemiology of cardio-renal syndromes: workgroup statements from the 7th ADQI Consensus Conference. *Nephrol Dial Transplant* 2010;**25**(5):1406–16. https://doi.org/10.1093/ndt/gfq066. PubMed PMID: 20185818.
8. U.S. Renal Data System. *USRDS 2013 annual data report: Atlas of chronic kidney disease and end-stage renal disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2013.
9. U.S. Renal Data System. *USRDS 2017 annual data report: epidemiology of kidney disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2017.
10. Cleland JG, Pellicori P, Dierckx R. Clinical trials in patients with heart failure and preserved left ventricular ejection fraction. *Heart Fail Clin* 2014;**10**(3):511–23. https://doi.org/10.1016/j.hfc.2014.04.011. PubMed PMID: 24975913.
11. Garg AX, Clark WF, Haynes RB, House AA. Moderate renal insufficiency and the risk of cardiovascular mortality: results from the NHANES I. *Kidney Int* 2002;**61**(4):1486–94. https://doi.org/10.1046/j.1523-1755.2002.00270.x. PubMed PMID: 11918756.
12. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006;**17**(7):2034–47. https://doi.org/10.1681/asn.2005101085. PubMed PMID: 16738019.
13. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**(13):1296–305. https://doi.org/10.1056/NEJMoa041031. PubMed PMID: 15385656.
14. Shastri S, Sarnak MJ. Cardiovascular disease and CKD: core curriculum 2010. *Am J Kidney Dis* 2010;**56**(2):399–417. https://doi.org/10.1053/j.ajkd.2010.03.019. PubMed PMID: 20599309.
15. Stevens LA, Li S, Wang C, Huang C, Becker BN, Bomback AS, et al. Prevalence of CKD and comorbid illness in elderly patients in the United States: results from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2010;**55**(3 Suppl. 2):S23–33. https://doi.org/10.1053/j.ajkd.2009.09.035. PubMed PMID: 20172445; PubMed Central PMCID: PMCPMC4574484.
16. Bansal N, Keane M, Delafontaine P, Dries D, Foster E, Gadegbeku CA, et al. A longitudinal study of left ventricular function and structure from CKD to ESRD: the CRIC study. *Clin J Am Soc Nephrol* 2013;**8**(3):355–62. https://doi.org/10.2215/cjn.06020612. PubMed PMID: 23411431; PubMed Central PMCID: PMCPMC3586970.

17. Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, et al. Reduced kidney function as a risk factor for incident heart failure: the atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol* 2007;**18**(4):1307–15. https://doi.org/10.1681/asn.2006101159. PubMed PMID: 17344421.
18. Waheed S, Matsushita K, Sang Y, Hoogeveen R, Ballantyne C, Coresh J, et al. Combined association of albuminuria and cystatin C-based estimated GFR with mortality, coronary heart disease, and heart failure outcomes: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis* 2012;**60**(2):207–16. https://doi.org/10.1053/j.ajkd.2012.03.011. PubMed PMID: 22537422; PubMed Central PMCID: PMCPMC3582350.
19. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J* 2013;**34**(19):1404–13. https://doi.org/10.1093/eurheartj/ehs337. PubMed PMID: 23095984.
20. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008;**52**(19):1527–39. https://doi.org/10.1016/j.jacc.2008.07.051. PubMed PMID: 19007588.
21. Levin A, Singer J, Thompson CR, Ross H, Lewis M. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. *Am J Kidney Dis* 1996;**27**(3):347–54. PubMed PMID: 8604703.
22. Parfrey PS, Harnett JD, Griffiths SM, Taylor R, Hand J, King A, et al. The clinical course of left ventricular hypertrophy in dialysis patients. *Nephron* 1990;**55**(2):114–20. https://doi.org/10.1159/000185937. PubMed PMID: 2141918.
23. Lezaic V, Tirmenstajn-Jankovic B, Bukvic D, Vujisic B, Perovic M, Novakovic N, et al. Efficacy of hyperphosphatemia control in the progression of chronic renal failure and the prevalence of cardiovascular calcification. *Clin Nephrol* 2009;**71**(1):21–9. PubMed PMID: 19203546.
24. Raggi P, Bellasi A, Gamboa C, Ferramosca E, Ratti C, Block GA, et al. All-cause mortality in hemodialysis patients with heart valve calcification. *Clin J Am Soc Nephrol* 2011;**6**(8):1990–5. https://doi.org/10.2215/cjn.01140211. PubMed PMID: 21700824; PubMed Central PMCID: PMCPMC3359535.
25. MacRae JM, Pandeya S, Humen DP, Krivitski N, Lindsay RM. Arteriovenous fistula-associated high-output cardiac failure: a review of mechanisms. *Am J Kidney Dis* 2004;**43**(5):e17–22. PubMed PMID: 15112194.
26. De Boer RA, Pinto YM, Van Veldhuisen DJ. The imbalance between oxygen demand and supply as a potential mechanism in the pathophysiology of heart failure: the role of microvascular growth and abnormalities. *Microcirculation* 2003;**10**(2):113–26. https://doi.org/10.1038/sj.mn.7800188. PubMed PMID: 12700580.
27. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998;**32**(5 Suppl. 3):S112–9. PubMed PMID: 9820470.
28. Ichikawa I, Pfeffer JM, Pfeffer MA, Hostetter TH, Brenner BM. Role of angiotensin II in the altered renal function of congestive heart failure. *Circ Res* 1984;**55**(5):669–75. PubMed PMID: 6091942.
29. Entin-Meer M, Ben-Shoshan J, Maysel-Auslender S, Levy R, Goryainov P, Schwartz I, et al. Accelerated renal fibrosis in cardiorenal syndrome is associated with long-term increase in urine neutrophil gelatinase-associated lipocalin levels. *Am J Nephrol* 2012;**36**(2):190–200. https://doi.org/10.1159/000341651. PubMed PMID: 22889806.
30. Lekawanvijit S, Kompa AR, Zhang Y, Wang BH, Kelly DJ, Krum H. Myocardial infarction impairs renal function, induces renal interstitial fibrosis, and increases renal KIM-1 expression: implications for cardiorenal syndrome. *Am J Physiol Heart Circ Physiol* 2012;**302**(9):H1884–93. https://doi.org/10.1152/ajpheart.00967.2011. PubMed PMID: 22367506.
31. Horl WH, Riegel W. Cardiac depressant factors in renal disease. *Circulation* 1993;**87**(5 Suppl. l):Iv77–82. PubMed PMID: 8387405.
32. Weisensee D, Schnaars Y, Schoeppe W, Bereiter-Hahn J, Low-Friedrich I. Potential uremic toxins modulate energy metabolism of cardiac myocytes in vitro. *Exp Nephrol* 1997;**5**(3):194–200. PubMed PMID: 9208278.
33. Upadhya B, Rocco M, Lewis CE, Oparil S, Lovato LC, Cushman WC, et al. Effect of intensive blood pressure treatment on heart failure events in the systolic blood pressure reduction intervention trial. *Circ Heart Fail* 2017;**10**(4):e003613. https://doi.org/10.1161/CIRCHEARTFAILURE.116.003613. PubMed PMID: 28364091; PubMed Central PMCID: PMCPMC5384646.
34. Rahman M, Ford CE, Cutler JA, Davis BR, Piller LB, Whelton PK, et al. Long-term renal and cardiovascular outcomes in antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) participants by baseline estimated GFR. *Clin J Am Soc Nephrol* 2012;**7**(6):989–1002. https://doi.org/10.2215/CJN.07800811. PubMed PMID: 22490878; PubMed Central PMCID: PMCPMC3362309.
35. He J, Shlipak M, Anderson A, Roy JA, Feldman HI, Kallem RR, et al. Risk factors for heart failure in patients with chronic kidney disease: the CRIC (chronic renal insufficiency cohort) study. *J Am Heart Assoc* 2017;**6**(5). https://doi.org/10.1161/JAHA.116.005336. PubMed PMID: 28515118.
36. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**(22):2117–28. https://doi.org/10.1056/NEJMoa1504720. PubMed PMID: 26378978.
37. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. *Eur Heart J* 2016;**37**(19):1526–34. https://doi.org/10.1093/eurheartj/ehv728. PubMed PMID: 26819227; PubMed Central PMCID: PMCPMC4872285.
38. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**(7):644–57. https://doi.org/10.1056/NEJMoa1611925. PubMed PMID: 28605608.
39. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**(12):861–9. https://doi.org/10.1056/NEJMoa011161. PubMed PMID: 11565518.
40. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**(12):851–60. https://doi.org/10.1056/NEJMoa011303. PubMed PMID: 11565517.
41. Berl T, Hunsicker LG, Lewis JB, Pfeffer MA, Porush JG, Rouleau JL, et al. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes and overt nephropathy. *Ann Intern Med* 2003;**138**(7):542–9. PubMed PMID: 12667024.
42. Zannad F, Kessler M, Lehert P, Grunfeld JP, Thuilliez C, Leizorovicz A, et al. Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. *Kidney Int* 2006;**70**(7):1318–24. https://doi.org/10.1038/sj.ki.5001657. PubMed PMID: 16871247.
43. Anand IS, Bishu K, Rector TS, Ishani A, Kuskowski MA, Cohn JN. Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. *Circulation* 2009;**120**(16):1577–84. https://doi.org/10.1161/circulationaha.109.853648. PubMed PMID: 19805651.
44. Cice G, Di Benedetto A, D'Isa S, D'Andrea A, Marcelli D, Gatti E, et al. Effects of telmisartan added to Angiotensin-converting enzyme inhibitors on mortality and morbidity in hemodialysis patients with chronic heart failure a double-blind, placebo-controlled

trial. *J Am Coll Cardiol* 2010;**56**(21):1701–8. https://doi.org/10.1016/j.jacc.2010.03.105. PubMed PMID: 21070920.
45. Eschalier R, McMurray JJ, Swedberg K, van Veldhuisen DJ, Krum H, Pocock SJ, et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization and SurvIval Study in Heart Failure). *J Am Coll Cardiol* 2013;**62**(17):1585–93. https://doi.org/10.1016/j.jacc.2013.04.086. PubMed PMID: 23810881.
46. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**(10):709–17. https://doi.org/10.1056/NEJM199909023411001. PubMed PMID: 10471456.
47. Vardeny O, Wu DH, Desai A, Rossignol P, Zannad F, Pitt B, et al. Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). *J Am Coll Cardiol* 2012;**60**(20):2082–9. https://doi.org/10.1016/j.jacc.2012.07.048. PubMed PMID: 23083787.
48. Tseng WC, Liu JS, Hung SC, Kuo KL, Chen YH, Tarng DC, et al. Effect of spironolactone on the risks of mortality and hospitalization for heart failure in pre-dialysis advanced chronic kidney disease: a nationwide population-based study. *Int J Cardiol* 2017;**238**:72–8. https://doi.org/10.1016/j.ijcard.2017.03.080. PubMed PMID: 28363684.
49. Cice G, Ferrara L, D'Andrea A, D'Isa S, Di Benedetto A, Cittadini A, et al. Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. *J Am Coll Cardiol* 2003;**41**(9):1438–44. PubMed PMID: 12742278.
50. Ghali JK, Wikstrand J, Van Veldhuisen DJ, Fagerberg B, Goldstein S, Hjalmarson A, et al. The influence of renal function on clinical outcome and response to beta-blockade in systolic heart failure: insights from Metoprolol CR/XL Randomized Intervention Trial in Chronic HF (MERIT-HF). *J Card Fail* 2009;**15**(4):310–8. https://doi.org/10.1016/j.cardfail.2008.11.003. PubMed PMID: 19398079.
51. CIBIS-II Investigators. The cardiac insufficiency Bisoprolol study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**(9146):9–13. PubMed PMID: 10023943.
52. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**(11):993–1004. https://doi.org/10.1056/NEJMoa1409077. PubMed PMID: 25176015.
53. U.S. Renal Data System. *USRDS 2012 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
54. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;**316**(23):1429–35. https://doi.org/10.1056/nejm198706043162301. PubMed PMID: 2883575.
55. Ljungman S, Kjekshus J, Swedberg K. Renal function in severe congestive heart failure during treatment with enalapril (the Cooperative North Scandinavian Enalapril Survival Study [CONSENSUS] trial). *Am J Cardiol* 1992;**70**(4):479–87. PubMed PMID: 1642186.
56. Taylor AL, Ziesche S, Yancy CW, Carson P, Ferdinand K, Taylor M, et al. Early and sustained benefit on event-free survival and heart failure hospitalization from fixed-dose combination of isosorbide dinitrate/hydralazine: consistency across subgroups in the African-American Heart Failure Trial. *Circulation* 2007;**115**(13):1747–53. https://doi.org/10.1161/circulationaha.106.644013. PubMed PMID: 17372175.
57. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;**314**(24):1547–52. https://doi.org/10.1056/nejm198606123142404. PubMed PMID: 3520315.
58. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;**325**(5):303–10. https://doi.org/10.1056/nejm199108013250502. PubMed PMID: 2057035.
59. Suki WN, Zabaneh R, Cangiano JL, Reed J, Fischer D, Garrett L, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int* 2007;**72**(9):1130–7. https://doi.org/10.1038/sj.ki.5002466. PubMed PMID: 17728707.
60. St Peter WL, Liu J, Weinhandl E, Fan Q. A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: a secondary analysis of the Dialysis Clinical Outcomes Revisited (DCOR) randomized trial using claims data. *Am J Kidney Dis* 2008;**51**(3):445–54. https://doi.org/10.1053/j.ajkd.2007.12.002. PubMed PMID: 18295060.
61. Chertow GM, Block GA, Correa-Rotter R, Drueke TB, Floege J, Goodman WG, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012;**367**(26):2482–94. https://doi.org/10.1056/NEJMoa1205624. PubMed PMID: 23121374.
62. Shepherd J, Kastelein JJ, Bittner V, Deedwania P, Breazna A, Dobson S, et al. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. *J Am Coll Cardiol* 2008;**51**(15):1448–54. https://doi.org/10.1016/j.jacc.2007.11.072. PubMed PMID: 18402899.
63. Chertow GM, Levin NW, Beck GJ, Depner TA, Eggers PW, Gassman JJ, et al. In-center hemodialysis six times per week versus three times per week. *N Engl J Med* 2010;**363**(24):2287–300. https://doi.org/10.1056/NEJMoa1001593. PubMed PMID: 21091062; PubMed Central PMCID: PMCPMC3042140.
64. Whalley GA, Marwick TH, Doughty RN, Cooper BA, Johnson DW, Pilmore A, et al. Effect of early initiation of dialysis on cardiac structure and function: results from the echo substudy of the IDEAL trial. *Am J Kidney Dis* 2013;**61**(2):262–70. https://doi.org/10.1053/j.ajkd.2012.09.008. PubMed PMID: 23157937.
65. Matsumoto M, Io H, Furukawa M, Okumura K, Masuda A, Seto T, et al. Risk factors associated with increased left ventricular mass index in chronic kidney disease patients evaluated using echocardiography. *J Nephrol* 2012;**25**(5):794–801. https://doi.org/10.5301/jn.5000066. PubMed PMID: 22241636.
66. Levin A, Djurdjev O, Thompson C, Barrett B, Ethier J, Carlisle E, et al. Canadian randomized trial of hemoglobin maintenance to prevent or delay left ventricular mass growth in patients with CKD. *Am J Kidney Dis* 2005;**46**(5):799–811. https://doi.org/10.1053/j.ajkd.2005.08.007. PubMed PMID: 16253719.
67. Parfrey PS, Lauve M, Latremouille-Viau D, Lefebvre P. Erythropoietin therapy and left ventricular mass index in CKD and ESRD patients: a meta-analysis. *Clin J Am Soc Nephrol* 2009;**4**(4):755–62. https://doi.org/10.2215/cjn.02730608. PubMed PMID: 19339417; PubMed Central PMCID: PMCPMC2666431.
68. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:1–150.

QUESTIONS AND ANSWERS

Question 1

A 52-year-old man presents for management of Stage G3bA3 CKD secondary to diabetic nephropathy. His eGFR is 34 mL/min/1.73 m^2. He has increasing shortness of breath, orthopnea, and swelling of his lower extremities.

What are the main features of the evolution of cardio-renal syndrome type 4 when CKD progresses?

A. Worsening left ventricular hypertrophy
B. Progressive cardiac remodeling
C. Decreased ejection fraction
D. Congestive heart failure
E. All of the above

Answer: E

Cardio-renal syndrome type 4 is defined as chronic abnormalities in renal function leading to cardiac disease. In a cohort of 190 CKD patients, who progressed over a period of approximately 2 years from moderate CKD to ESRD and underwent serial echocardiography, there was a decrease in mean ejection fraction from 53% to 50% ($p = 0.002$).[16] The proportion of participants with an ejection fraction $\leq$50% increased from 29% to 48% ($p < 0.001$). During this period the frequency of self-reported congestive heart failure nearly doubled. CKD, through a number of mechanisms, can lead to significant functional and structural changes to the heart, leading eventually to the clinical phenotype of congestive heart failure. Not only is heart failure more prevalent, but patients with CKD are also at higher mortality risk following the diagnosis of CVD, including heart failure.

Question 2

Which ONE of the following is NOT true regarding the association between CKD and heart disease?

A. CKD patients are at higher mortality risk following the diagnosis of CVD
B. CVD is responsible for 10% of deaths in CKD patients
C. CKD is a predictor of CVD independent of other cardiovascular risk factors
D. Decreased GFR is associated with hospitalization for events that include heart failure, coronary disease, stroke, and peripheral vascular disease

Answer: B

Answer B is not true and therefore is the correct answer for this question. CVD is responsible for approximately 50% of deaths in CKD patients, regardless of age.[14] Most of these events are ischemic or arrhythmic. **Answer A** is correct as CKD patients are at higher risk for mortailty following the diagnosis of CVD. **Answer C** is correct as observational studies have demonstrated that CKD predicts CVD independent of other risk factors. For example, a meta-analysis of nearly 1.4 million subjects found a progressive increase in all-cause mortality with declining GFR, and estimated relative odds of death increased in a stepwise manner to 1.9, 2.6, and 4.4 for GFR of 80, 60, and 40 mL/min, respectively, compared with a reference group with GFR 100 mL/min.[12]

Go et al. found not only an increase in all-cause mortality but also that hospitalization for events that included heart failure, coronary disease, stroke, and peripheral vascular disease increased with each diminishing category of GFR making **Answer D** correct.[13]

Question 3

A 62-year-old man with CKD secondary to diabetic nephropathy presented for management of congestive heart failure. His current S[Cr] is 3.8 mg/dL and eGFR is 16 mL/min/1.73 m^2.

Which ONE of the following has NOT resulted in improvement of cardiovascular outcomes in CKD patients?

A. ARB
B. Isordil
C. Beta blockers
D. Calcium-based phosphate binders

Answer: D

Answer D, calcium-based phosphate binders, has not been demonstrated to improve cardiovascular outcomes. Given the link between CKD-MBD and heart outcomes in CKD patients, the DCOR trial, compared all-cause mortality and cause-specific mortality (cardiovascular mortality, infection, and other causes) in over 2100 HD patients treated with calcium-based phosphate binders vs. sevelamer,[59] 40% of whom were reported to have heart failure at baseline.[60] The primary outcome was not found to be different between groups, and heart failure outcomes were not described. The other treatments, ARB, isordil, and beta blockers have been demonstrated in different trials to improve cardiovascular outcomes.[39–41,49,50,56]

Question 4

Which ONE of the following answers is a pathogenic factor in the development of cardio-renal syndrome type 4 in CKD patients?

A. Ischemia due to advanced vascular abnormalities
B. Sodium retention
C. Mineral and bone disorders (CKD-MBD)
D. All of the above

Answer: D

Answer D is correct as ischemia, anemia, and MBD can all contribute to the pathogenesis of cardio-renal syndrome type 4. CKD can contribute to heart failure through its role in exacerbating ischemic heart disease, or more directly through pressure and volume overload, which increase proportionately to the decline in renal function and contribute to ventricular hypertrophy.[21,22] Left ventricular hypertrophy is highly prevalent in patients with advanced CKD and dialysis-dependence.[27] Furthermore, the association between CKD and heart disease/heart failure may depend on atherosclerotic vascular disease and endothelial dysfunction. Cardiac valve calcification is extremely common in CKD due to phosphate retention, hyperparathyroidism, and related disorders falling under the umbrella term CKD mineral and bone disorder.[23,24] Sodium retention, leading to excess extracellular fluid volume and hypertension, contributes to chronic volume overload and hypertrophy. These factors and others contribute to myocyte death and cardiac fibrosis with heart dilation and pump failure.

Question 5

A 71-year-old woman with CKD Stage G4A3 secondary to diabetic nephropathy is admitted with congestive heart failure. Her estimated GFR is 20 mL/min/1.73 m^2.

Which ONE of the following is NOT true regarding management of her congestive heart failure?

A. ARBs can reduce the incidence of heart failure in diabetic CKD patients

B. ARBs improve cardiovascular outcomes in CKD patients with established heart failure

C. ARBs should not be used for CKD patients with congestive heart failure because of the risk of hyperkalemia

D. S[Cr] is likely to increase in CKD patients with heart failure started on an ACEI

Answer: C

Answer C is not true and is therefore the correct answer for this question. Patients may develop hyperkalemia making monitoring of S[K] an important component of management of these patients. However, in most patients the benefits of ARBs outweigh the risks. Both the RENAAL and IDNT studies demonstrated a decreased incidence of heart failure in diabetic CKD patients making **Answer A** true.[39,40] The Val-HeFT study targeted CKD patients with class II, III, or IV heart failure. Patients were randomly assigned to receive the ARB valsartan or placebo in addition to optimal heart failure therapy, including ACE inhibition in 93% of patients.[43] Although the addition of valsartan did not have an effect on overall mortality, the group with CKD who were randomized to valsartan had a statistically significant lower rate of first morbid event (an outcome including death or heart failure hospitalization or intravenous vasoactive drug administration) making **Answer B** true. The majority of patients treated with an ACEI (or ARB) will have a 10−15% increase in S[Cr] above baseline, usually within the first 2 weeks of starting treatment, consistent with the known hemodynamic effects of ACEIs on GFR, after which S[Cr] stabilizes, making **Answer D** true.[55] This small increase in S[Cr] is not an indication to stop treatment.

CHAPTER

55

Cancer and Chronic Kidney Disease

Kenar D. Jhaveri[a], *Mitchell H. Rosner*[b]

[a]Division of Kidney Diseases and Hypertension, North Shore University Hospital and Long Island Jewish Medical Center, Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY, United States; [b]Divison of Nephrology, University of Virginia, Charlottesville, VA, United States

Abstract

Nephrologists will encounter patients who develop kidney disease associated with malignancy or its treatment or will be faced with the challenges of treating patients with chronic kidney disease and cancer. To optimize clinical outcomes, knowledge regarding these issues is critically important. As the population age increases and as newer therapeutic options emerge, these issues will likely be more common and require the expertise of the nephrologist to optimize patient outcomes.

INTRODUCTION

The overall incidence of cancer is rising worldwide.[1] The relationship between cancer and chronic kidney disease (CKD) is complex. Cancer is associated with the development of numerous forms of CKD, and CKD affects cancer risk and outcomes. Although the overall incidence of CKD in cancer patients is unknown, it is known that elderly patients with cancer are at the highest risk for both *de novo* development of CKD related to the cancer, as well as having baseline CKD that may influence therapeutic decisions and outcomes associated with cancer treatment.[2]

Acute kidney injury (AKI) is common in cancer patients and can be associated with the subsequent development of CKD. The 1-year risk of AKI (defined as a >50% rise in serum creatinine concentration [S[Cr]]) in patients with cancer is 17.5%, with a 27% risk over 5 years based on a Danish population study.[3] In another study done at M.D. Anderson Cancer Center in the US, the rate of AKI was higher than the rate in most noncancer settings and was associated with poorer clinical outcomes.[4] A more recent study of patients admitted to an ICU with underlying cancer demonstrated that 59% of these patients developed AKI, mostly related to sepsis (80%), hypovolemia (40%), and urinary tract obstruction (17%).[5] This high rate of AKI is important, as many cancer patients are left with CKD following such AKI events, which ultimately affects long-term outcomes.[4]

Very few studies have evaluated the incidence and prevalence of CKD among cancer patients. One retrospective study evaluated the causes of CKD in patients who had a diagnosis of cancer in their childhood. Over 700 childhood cancer survivors were followed for changes in glomerular filtration rate (GFR).[6] The factors that were major predictors of diminished GFR later in life after experiencing treatment for childhood cancers were nephrectomy, abdominal radiation, and high-dose ifosfamide or cisplatin exposure. CKD following cancer can be a result of insults leading to ischemia, acute tubular necrosis (either due to nephrotoxins or in the setting of ischemia or sepsis), tumor infiltration of the renal parenchyma, and/or vascular, tubular, interstitial, or glomerular toxicities of chemotherapy agents. Toxicities from chemotherapy are likely the most common causes of CKD in cancer patients. In addition, because many of these patients are living longer, they are not exempt from developing CKD associated with common risk factors such as hypertension and diabetes mellitus.

CKD has a significant impact on cancer therapy and outcomes. The CANcer and DialYsis (CANDY) study, which retrospectively evaluated treatment patterns and clinical outcomes in patients undergoing chronic dialysis who subsequently developed cancer, showed that chemotherapy was omitted or prematurely stopped in many cases, or was often not adequately prescribed. Survival was poor in this cohort of patients.[7] This study highlights the challenges facing oncologists treating patients with cancer who are maintained on chronic dialysis. Unfortunately, no such study exists for CKD

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00055-3

patients not receiving dialysis. Although one French study demonstrated that few patients in their centers required dose adjustments for chemotherapy agents due to a prior diagnosis of CKD, another analysis of patients from Belgium noted that the prevalence of patients with cancer and estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 was 64%.[7–9] These are important findings suggesting that GFR needs to be carefully assessed in patients with cancer.

Furthermore, for many chemotherapeutic and targeted therapy protocols, dose adjustments for suboptimal GFR are poorly defined and not evidence-based. A recent analysis demonstrated that 85% of recent trials of therapies for the five most common malignancies excluded patients with CKD.[10]

The risk of cancer in CKD patients is higher than in the general population, and CKD patients have a higher cancer-associated mortality rate.[11,12] Wong et al. analyzed a cohort of over 3000 patients over a mean of 10 years and found that men and patients with stage 3 or higher CKD had an increased risk of cancer.[11] The risk increased with GFRs starting at 55 mL/min/1.73 m^2. There was an increased risk of 29% for every 10 mL/min/1.73 m^2 decrement in eGFR.[11] The major cancers associated with CKD were of urinary origin and lung cancers. It is unclear why women had a lower risk. Weng et al. published the largest study to date analyzing cancer specific mortality in CKD.[13] In this study, CKD was significantly associated with liver cancer, kidney cancer, and urinary tract cancers. In kidney and urological cancers, increased mortality was associated with lower GFR.[13] Based on these data, there is increased risk of certain cancers with CKD. In addition, CKD appears to be a risk factor for poorer outcomes with cancer. Although not clear, an underlying proinflammatory state, altered host immunity, and poor nutritional status might be major contributors to this association. Furthermore, alterations in potentially curative therapeutic regimens may occur in the setting in CKD, which may limit efficacy.

LYMPHOMATOUS INFILTRATION OF THE KIDNEY AND CKD

A variety of cancers have been associated with infiltration of the kidney causing AKI, and much less commonly CKD. Lymphomas and leukemias have the highest risk of renal infiltration. Autopsy series have found the incidence of renal parenchymal infiltration to be 13%–40%.[14,15] However, most of these cases are not associated with changes in kidney function. Interestingly, glomerular diseases have been also noted in association with tumor infiltration of the kidney. The most common glomerular diseases in this setting have been membranoproliferative glomerulonephritis (MPGN) and MN.[16] Treatment of the underlying cancer is the most important part of management, and outcomes can be good with improvement in GFR.[17]

CHEMOTHERAPY AND TARGETED THERAPY INDUCED CKD

Many chemotherapeutic agents are associated with nephrotoxicity. Risk factors that can increase nephrotoxicity include patient age, preexisting CKD, exposure to other nephrotoxins (such as aminoglycoside antibiotics and iodinated contrast agents), and volume depletion. Most commonly, chemotherapy agents lead to electrolyte disorders or AKI, but there is significant risk of CKD from some agents. Table 55.1 lists some of the more common renal toxicities of chemotherapy agents.[18,19]

Cisplatin is a potent tubular toxin, associated with many tubulopathies.[20,21] These changes are mild and transient in most patients. Sustained elevations in S[Cr] are less common. In one study of 54 patients followed for more than 3 months, only one developed late onset azotemia.[22] Although long-term follow-up studies indicate that renal function either remains stable or improves over time, some patients may have a significant reduction in creatinine clearance despite normal S[Cr] levels.[23]

Alkylating agents such as ifosfamide, cyclophosphamide, and melphalan are used for many cancer treatments. Of these, ifosfamide is most often associated with nephrotoxicity.[24] Moderate to severe renal injury occurs when doses are above 100 g/m^2. In addition, ifosfamide may lead to long-term reductions in GFR. Farry et al. studied long-term follow-up of adult patients who received ifosfamide at a single center. There was a 15 mL/min decrease in GFR in the first year of treatment and then 22 mL/min in the next 4 years after treatment.[25]

Nitrosoureas have been noted to cause CKD. Semustine, carmustine, and lomustine are lipid-soluble alkylating agents used in treatment of brain tumors.[26,27] All three of these agents produce dose-related nephrotoxicity that can progress to CKD. In one study of over 150 patients treated with semustine and or carmustine, all patients who received more than 10 doses developed CKD.[27] Typically in these cases the urinary sediment is bland with not much proteinuria. In many patients, S[Cr] may not rise till months after treatment. Biopsy findings show extensive glomerular and interstitial fibrosis and tubular atrophy.[26]

Targeted therapies have recently evolved as promising agents for treatment of various cancers. Tyrosine kinase inhibitors and vascular endothelial growth factor

TABLE 55.1 Chemotherapy, Targeted Therapy and Immunotherapy Associated Kidney Dysfunction

Compartment of the Kidney	Toxicity	Chemotherapy Agent
Glomerular	Membranoproliferative glomerulonephritis	Gemcitabine, sirolimus
	Minimal change disease	Interferon alpha, beta and gamma, pamidronate, doxorubicin (adriamycin), daunorubicin (daunomycin), sirolimus, nivolumab
	Focal segmental glomerulosclerosis	sirolimus, temsirolimus, everolimus, doxorubicin (adriamycin), daunorubicin (daunomycin)
	Collapsing Glomerulopathy	Interferon alpha, beta and gamma, pamidronate, gefitinib, sirolimus, doxorubicin (adriamycin), daunorubicin (daunomycin), clofarabine
	Membranous nephropathy	Sirolimus
	Lupus-like nephritis	Ipilimumab
	IgA nephropathy	Sirolimus
Vascular	Thrombotic microangiopathy	Antiangiogenic agents (bevacizumab and tyrosine kinase inhibitors), gemcitabine, cisplatin, mitomycin and interferons, pembrolizumab, and nivolumab
Prerenal azotemia	Capillary leak syndrome	IL-2, denileukin diftitox, chimeric antigen receptor T-cell therapy
Tubular/interstitial	Acute tubular necrosis	Platinums, zoledronate, ifosfamide, mithramycin, pentostatin, imatinib, diaziquone, pemetrexed, clofarabine, arsenic trioxide
	Fanconi syndrome	Cisplatin, ifosfamide, azacitidine, diaziquone, imatinib, pemetrexed
	Salt Wasting	Cisplatin, azacitidine
	Magnesium wasting	Cisplatin, cetuximab, panitumumab
	Nephrogenic Diabetes Insipidus	Cisplatin, ifosfamide, pemetrexed
	Syndrome of inappropriate antidiuretic hormone	Cyclophosphamide, vincristine
	Acute interstitial nephritis	Sorafenib, sunitinib, (but can be any chemotherapy)
		Checkpoint inhibitors (ipilimumab, pembrolizumab, nivolumab)
	Crystal nephropathy	methotrexate

inhibitors are examples of such therapies. Tyrosine kinase inhibitors are classically associated with thrombotic microangiopathy (TMA). One case series reported that over time there is a chronic interstitial insult that leads to CKD in patients receiving these drugs.[28] Both sunitinib and sorafenib have been associated with acute interstitial damage and ultimately with chronic interstitial damage.[28] In addition, alectinib, a second-generation anaplastic lymphoma kinase tyrosine kinase inhibitor, has been reported to be rarely associated with progressive CKD.[29]

Many antiangiogenic agents and tyrosine kinase inhibitors lead to renal limited or systemic TMA[30] (Table 55.1). In addition, in one study examining sorafenib, among 54 patients initiating therapy, 93% had an increase in systemic blood pressure by day 6, and most experienced an increase in blood pressure by 24 hours of treatment initiation.[31] Hypertension improves when treatment is interrupted.[31] Hypertension if left untreated and severe may lead to the development of CKD. Renal limited TMA may go undiagnosed. It requires a high degree of clinical suspicion for confirmation by kidney biopsy. However, if diagnosed early, the syndrome can be reversible in some cases with cessation of the offending agent. Unfortunately, development of CKD is not unusual in patients with this syndrome.[32] In addition, all glomerular toxicities of chemotherapy agents can be potential causes of CKD if the insult is ongoing and long-term. Thus, for all agents with any potential nephrotoxicity, monitoring of GFR and urine studies should

be mandatory. Early diagnosis and rapid cessation of offending medications is critical to limit renal fibrosis and the eventual development of CKD.

Newer immunotherapies include checkpoints inhibitors such as anticytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and anti-programmed death 1 (PD-1).[33] These agents have revolutionized the treatment of malignancies by engaging the patient's own immune system against the tumor, rather than targeting the cancer directly. Drugs of this class include ipilimumab, pembrolizumab, and nivolumab. These drugs have been associated with AKI that is generally immune-mediated and consistent with acute interstitial nephritis.[34] The onset of kidney injury seen with PD-1 inhibitors is usually late (3–10 months) compared to CTLA-4 antagonist–related renal injury, which happens earlier (2–3 months).[34] Glomerular diseases such as minimal change disease (MCD), MN, TMA, and lupus-like nephritis also have been rarely reported with these agents. PD-1, as opposed to CTLA-4 inhibitors, has been associated with kidney rejection in transplantation.[33] Steroids appear to be effective in treating the immune-related adverse effects noted with these agents.[33] Whether these drugs are associated with CKD is not yet clear, but vigilance in monitoring GFR over time is warranted.

PARANEOPLASTIC GLOMERULAR DISEASES AND CKD

Various kinds of cancers have been associated with glomerular diseases. The pathophysiology underlying this association in most cases is not clear. Both solid and hematological malignancies can produce abnormal tumor cell products that could lead to paraneoplastic glomerular disease. Table 55.2 summarizes the solid and hematologic malignancies that have been associated with glomerular diseases.

MN is the most commonly reported glomerular disease in patients with solid tumors.[35,36] The prevalence of malignancy in 240 patients with biopsy proved MN was around 10%.[37] Only half of these patients had cancer-related symptoms at the time of their biopsy. Most were diagnosed with cancer within a year of being diagnosed with MN.[37] The finding of nephrotic-range proteinuria in a patient with cancer or the development of proteinuria within a few months of diagnosis of cancer should raise strong suspicion of glomerular disease, especially MN.

Differentiating primary from secondary/cancer associated MN has been a great challenge for nephrologists and nephropathologists. Various studies have evaluated different parameters that could help make this distinction. These parameters could be clinical or historical clues, serological markers, or histopathological findings on the kidney biopsy.

Podocyte transmembrane glycoprotein M-type phospholipase A2 receptor (PLA2R) autoantibodies were first identified by Beck et al. in 2009.[38] It was postulated that these circulating antibodies were mainly found in patients with primary MN. Similarly, glomerular deposition of IgG4 on kidney biopsy is also a feature that has been predominantly described in patients with primary MN.[38] A study analyzed 10 patients with solid tumors and MN. Of these 10 patients, 3 had both elevated levels of anti–PLA2R antibodies and moderate glomerular IgG4 deposition on kidney biopsy. These findings suggest an underlying primary MN in these patients with solid tumors.[39] These three patients had persistence or relapse of proteinuria despite tumor resection, further supporting the notion that these were indeed patients with primary MN. Hoxha et al. showed enhanced staining of PLA2R in glomeruli of patients with primary MN compared with normal staining in tumor-associated MN.[40] Ohani et al. showed increased glomerular deposition of both IgG1 and IgG2 subtypes in patients with cancer-associated MN compared to those with primary MN.[41] Although the presence of circulating anti–PLA2R antibodies or enhanced glomerular PLA2R staining or the predominance of IgG4 in the glomeruli of patients with MN suggests primary MN even in the presence of cancer, caution is warranted in excluding malignancy solely on the basis of anti-PLA2R antibodies. A recent study by Radice and colleagues analyzed 252 consecutive MN patients and found that 7 patients with cancer were anti-PLA2R positive.[42] Thus, anti-PLA2R positivity in a patient with MN should not be considered sufficient to refrain from seeking a secondary cause, especially in patients with risk factors for neoplasia. The presence of increased inflammatory cells (more than 8 cells per glomeruli) was shown to be more suggestive of cancer-associated MN than primary MN.[37] Table 55.3 outlines features that help differentiate primary from secondary cancer-associated MN.

MCD has been associated with hematologic malignancies such as Hodgkin lymphoma, non-Hodgkin lymphoma, and other leukemias. Of all the lymphoid malignancies, MCD is classically associated with Hodgkin lymphoma, occurring in about 1% of Hodgkin's patients. MCD seems to be more frequent in Hodgkin lymphoma that exhibits a mixed cellularity and is of nodular sclerosing subtype. In one case series, the diagnosis of MCD preceded the diagnosis of lymphoma by several months; 71% of patients with Hodgkin lymphoma and MCD had systemic symptoms (i.e. fever, weight loss, and night sweats), and 90% had positive laboratory parameters suggesting an inflammatory syndrome (as

TABLE 55.2 Solid and Hematologic Malignancies Associated with Different Glomerular Diseases

Malignancy	Glomerular Diseases Reported
Lung cancer*	MN, MCD, MPGN, IgAN, FSGS, CGN, TMA
Colon cancer	MN, MCD, CGN
Stomach cancer	MN
Pancreas cancer	MN, MCD, IgAN
Bladder cancer	MCD
Renal cell cancer	AAA, CGN, IgAN, MCD,FSGS, MPGN
Prostate cancer	MN, CGN
Breast cancer	MN, FSGS, MPGN,TMA
Esophageal cancer	MPGN, FSGS
GI stromal tumor	AAA
Gastric cancer	MPGN, CGN, TMA
Spleen sarcoma	AAA
Head and neck cancer	MN, IgAN
Wilm's tumor	MN, MPGN
Teratoma	MN
Ovarian cancer	MN,MCD
Cervical cancer	MN
Endometrial cancer	MN
Tongue cancer	IgAN
Mesothelioma	MCD
Melanoma	MN, MPGN
Skin cancers(basal, squamous cell)	MN
Pheochromocytoma	MN
Thymoma	MCD, FSGS, CGN, MPGN
Hodgkin's disease	MCD, MN, MPGN, IgAN, FSGS,CGN, AAA, Anti GBM
Non-Hodgkin disease	MN, MCD, MPGN, IgAN, FSGS
Chronic lymphocytic leukemia	MN, MCD, MPGN, FSGS, CGN
Acute myelogenous leukemia	MN, FSGS
Chronic myelogenous leukemia	MN, MCD, MPGN
Monoclonal gammopathy of unclear significance	MPGN
T cell leukemia	FSGS

AAA, AA amyloidosis; *CGN*, crescentic glomerulonephritis; *FSGS*, focal segmental global sclerosis; *GBM*, glomerular basement membrane; *IgAN*, IgA nephropathy; *MCD*, minimal change disease; *MN*, membranous nephropathy; *MPGN*, membranoproliferative glomerular nephritis; *TMA*, thrombotic microangiopathy.
* *Includes small cell, nonsmall cell, squamous cell and bronchogenic cancers.*
Adapted from reference 18.

assessed by C-reactive protein level, sedimentation rate, and fibrinogen level).[43] Lymphoma-associated MCD is usually associated with a high frequency of steroid (50%) and cyclosporine resistance.[43] A poor response to the treatment of MCD should prompt an investigation for an underlying lymphoma. In this case series, the simultaneous diagnosis of Hodgkin lymphoma and MCD was associated with the remission of proteinuria in response to chemotherapy.[43] MCD-associated nephrotic syndrome usually relapses simultaneously with the hematologic malignancy and remains highly responsive to specific treatment for the malignancy. MCD can occur at the time of relapse even if it was initially absent, emphasizing the need to evaluate proteinuria during the follow-up of patients with Hodgkin lymphoma.

A case series of five patients described the glomerular histopathology of kidney biopsies in patients with lymphocytic leukemia and/or non-Hodgkin lymphoma.[38] Two cases of MPGN and one case each of MN, diffuse proliferative glomerular disease, and infiltrative disease were found.[44] They also reviewed 42 reported cases of glomerular diseases associated with chronic lymphocytic leukemia (CLL) from prior literature.[44] Of these 42 patients, 36 had nephrotic-range proteinuria, with the most common glomerular lesions being MPGN (35.7%) and MN (19%).

MPGN may be a subtle clue to a developing or undiagnosed lymphoplasmacytic malignancy. A study suggested an association between MPGN and monoclonal gammopathy of unclear significance (MGUS).[45] Twenty-eight patients with monoclonal gammopathy were analyzed and had bone marrow and kidney biopsies. Sixteen of them had normal bone marrow biopsies and were classified as MGUS. However, kidney biopsies from these patients showed granular immune deposits. There has been no proven relationship between the presence of monoclonal proteins and the development of MPGN. Although current observations suggest this possibility, more studies are needed to prove a causal association. This study also showed that monoclonal gammopathy in the presence of MPGN can be seen in various lymphoplasmacytic diseases, including low-grade B cell lymphoma, CLL, and multiple myeloma.[45]

There is also an association of increased cancer risk in patients with glomerulonephritis (GN). In a recent Danish study in 5594 patients with GN, 911 cancers were diagnosed.[46] Of these, 35% were prevalent at the time of kidney biopsy. Increased cancer rates were seen for minimal change disase, focal segmental glomerulosclerosis, mesangioproliferative glomeulonephritis, MN, membranoproliferative glomeulonephritis, ANCA-associated vasculitis, and lupus nephritis. Increased cancer rates were seen for lung, prostate, renal, non-Hodgkin lymphoma, myeloma, leukemia, and skin. The increased

TABLE 55.3 Differentiating Features between Primary and Solid Tumor-Associated Membranous Nephropathy (MN)

Membranous Nephropathy	Primary MN	Solid Tumor-Associated MN
Clinical Clues	Younger age, no history of smoking	Age over 65 years, smoking more than 20 pack-years
Serological	Presence of circulating anti-PLA2R autoantibodies	Absence of circulating anti-PLA2R autoantibodies
Histopathological/kidney biopsy findings	**1.** Predominance of glomerular IgG4 deposition	**1.** Predominance of glomerular IgG1/IgG2 deposition
	2. Enhanced glomerular PLA2R staining	**2.** Normal glomerular PLA2R staining
	3. Fewer than 8 inflammatory cells per glomeruli	**3.** Presence of more than 8 inflammatory cells per glomeruli

incidence was mainly limited to −1 to 1 year after biopsy, but skin cancer showed an increased risk over time. The diagnosis with the highest risk for cancer was membranoproliferative glomeulonephritis.

CKD ASSOCIATED WITH HEMATOPOETIC STEM CELL TRANSPLANTATION

CKD is now an increasingly important complication following hematopoetic stem cell transplantation (HSCT). Hingorani et al. found that CKD was identified in 23% of recipients surviving at least 3 months after HSCT.[47] AKI and graft vs. host disease (GVHD) were noted as risk factors for the development of CKD. Another study found that the average fall in GFR in patients that develop CKD is 24.5 mL/min/1.73 m^2 over 24 months.[48] Approximately 16.6% patients who underwent HSCT developed CKD.[48] Most of these patients were treated with nonmyeloablative protocols. The growth in nonmyeloablative protocols may actually increase the risk of CKD as older patients with more comorbidities become candidates for this procedure. Calcineurin inhibitors (CNIs), which are used for prophylaxis and treatment of GVHD, have been associated with the development of nephrotoxicity and may contribute to the development of CKD. Hypertension and TMA are two comorbidities linked to the development of CKD.[49–51]

Myeloablative allogeneic HSCT protocols can lead to low-grade TMA that over time leads to CKD. This has also been termed bone marrow transplant nephropathy or radiation nephropathy, which resembles the hemolytic-uremic syndrome or thrombocytopenic thrombotic purpura (TTP).[49] Diagnostic criteria for HSCT-related TMA include >4% schistocytes in blood smears, *de novo* prolonged or progressive thrombocytopenia, sudden or persistent increase in lactate dehydrogenase levels, decreased hemoglobin concentration, and decrease in serum haptoglobin concentration.[50] Clinically, nonnephrotic proteinuria, worsening hypertension, and renal dysfunction are adequate to diagnose TMA in most of these patients. Hypertension is usually the first sign of beginnings of renal limited TMA in many of these cases. Thrombocytopenia may be a major hindrance in performing kidney biopsies in these patients. Classically, risk factors associated with the development of TMA following HSCT include use of CNIs, allogeneic transplantation, total body irradiation use, older age, female gender, acute GVHD, and high-dose chemotherapy.[50] Acute GVHD grade 2–4, hepatic GVHD and venoocclusive disease, adenovirus infection, older age, female gender, and total body irradiation greater than 12 Gy are likely risk factors for the development of TMA.[52,53] In immune-depleted (T cell-depleted) patients where GVHD does not exist nor does the use of CNIs, TMA was likely to still occur, but only in the group that received total body irradiation.[54] Some have considered HSCT-associated TMA an "endothelial" variant of GVHD. HSCT-associated TMA is usually treated supportively, including control of hypertension and proteinuria. Due to the absence of randomized controlled trials, plasma exchange cannot be considered a standard of care for patients with HSCT-associated TMA.[55,56] Other agents such as rituximab and eculizumab have limited data on treatment of HSCT-associated TMA.

Glomerular disease can be a cause of CKD following HSCT. In HSCT patients with nephrotic-range proteinuria, renal biopsy findings may include MN, MCD, and focal and segmental glomerulosclerosis (FSGS).[57] However, MN accounts for a majority of the cases of HSCT-associated glomerular diseases, whereas MCD accounts for most of the remaining cases.[57] Host and donor marrow chimerism in addition to the presence of host lymphocytes surviving conditioning may be risk factors for MN after HSCT.[58] Brukamp et al. conducted a meta-analysis of 46 cases who had HSCT and glomerular disease.[57] Their study revealed a close temporal relationship between the development of nephrotic syndrome shortly after cessation of immunosuppression and the diagnosis of chronic GVHD. The majority (61%) of these patients had MN and 22% had MCD.[51] Other causes included FSGS, IgA nephropathy, and mesangial proliferative disease.

In patients who receive low-intensity HSCT, there is a higher chance of glomerular GVHD.[59,60] Nonmyeloablative HSCT was identified as a risk factor for nephrotic syndrome in a cohort study.[59] Of 163 patients with nonmyeloablative HSCT, 7 developed nephrotic syndrome compared to none of the 118 patients in the myeloablative HSCT cohort. The etiology and pathogenesis of nephrotic syndrome after allogeneic HSCT were elucidated by Luo et al.[59] They compared 257 patients with nephrotic syndrome after allogeneic HSCT with nonnephrotic syndrome patients. They concluded that there was association of occurrence of chronic GVHD in patients with nephrotic syndrome after allogeneic HSCT.

In contrast to the above mentioned studies, a retrospective analysis of 95 cases showed that chronic GVHD in HSCT patients with glomerular disease was not different than what is observed in the overall HSCT population.[60] Autologous HSCT recipients also develop glomerular diseases but do not experience GVHD.[61] It is possible that immune dysregulation caused by the induction agents might cause nephrotic syndrome in this population. With improving life expectancy, it is also possible that these glomerular diseases are *de novo* and unrelated to HSCT. T cell-depleted HSCT recipients are highly unlikely to develop glomerular diseases, and no such instances have been reported so far.

CHRONIC KIDNEY DISEASE ASSOCIATED WITH RENAL CELL CARCINOMA

In the US, it is estimated that there will be over 64,000 incident cases and 13,700 cancer-related deaths from renal cell carcinoma (RCC) per year.[62] Given the age and comorbid conditions in this patient population, it is not surprising that 25% of patients with RCC have CKD.[63] In fact, approximately 10% of tumor nephrectomy specimens demonstrate features of diabetic nephropathy, 2–9% may have FSGS and another 20% show hypertensive nephrosclerosis.[64] In the past, radical nephrectomy was considered the treatment of choice for isolated RCC or solitary renal masses (SRM). However, there is increasing awareness that radical nephrectomy is associated with a higher risk of CKD. Therefore, there has been a shift to partial nephrectomy as the treatment of choice for RCC.[65–67] Huang et al. reported the probability of being free from a GFR less than 60 mL/min/1.73 m^2 5 years after the procedure was 67% and 23% for partial and complete nephrectomy respectively, with no difference in oncologic outcome.[68] Furthermore, the lower risk of CKD following partial nephrectomy has translated to improved overall survival for patients with localized RCC.[66,67,69,70] In a pooled analysis of 41,010 patients, partial nephrectomy was associated with a 61% risk reduction in developing CKD and 19% risk reduction for all-cause mortality.[71] The American Urological Association released a position statement in 2009 that partial nephrectomy (nephron-sparing surgery) is preferred for T1 tumors (less than 7 cm in size) as the oncologic outcomes are equivalent to radical nephrectomy and the preservation of kidney function is beneficial for long-term outcomes.[72] Most recently, the American Society of Clinical Oncology (ASCO) published guidelines on the management of small renal masses (incidentally image-detected, contrast-enhancing renal tumors $\leq$4 cm in diameter) that further highlights the recommendation for "nephron-sparing surgeries" such as partial nephrectomy over radical surgical approaches.[73] This guideline recommends that radical nephrectomy should only be considered for patients with anatomically complex small renal masses for whom partial nephrectomy might result in unacceptable morbidity.

A recent study also highlights that "surgically induced CKD" such as that occurring after nephrectomy is more stable than CKD due to medical causes such as diabetes.[74] This is especially true if the postoperative GFR is >45 mL/min/1.73 m^2. However, all patients undergoing either partial or radical nephrectomy should have close nephrology follow-up with close attention to treatment of risk factors for CKD progression.

KIDNEY DISEASE ASSOCIATED WITH PLASMA CELL DYSCRASIAS AND PARAPROTEINS

Plasma cell disorders encompass a spectrum of diseases that include multiple myeloma, immunoglobulin (Ig)-mediated amyloidosis, plasmacytomas, and the premalignant condition of MGUS. Kidney involvement in these disorders is common and abnormal GFR is seen in up to half of myeloma patients at the time of presentation.[75] Abnormal kidney function in patients with multiple myeloma significantly contributes to excessive mortality and can limit clinical outcomes associated with both systemic therapies and stem cell transplantation (SCT).[76]

Kidney injury associated with plasma cell cancers can be divided into Ig-dependent and Ig-independent mechanisms, although in any particular patient, several mechanisms may be operative.[77] Virtually all nephropathological syndromes have been observed with Ig-dependent kidney involvement (Table 55.4). However, three distinct syndromes account for the vast majority of Ig-mediated kidney disease: (1) cast nephropathy, in which proteinaceous deposits consisting of filtered monoclonal Igs in combination with other urinary

TABLE 55.4 Kidney Involvement with Plasma Cell Dyscrasias

Immunoglobulin Dependent	Immunoglobulin Independent
Cast nephropathy	Hypercalcemia
Monoclonal immunoglobulin deposition disease	Tumor lysis syndrome
AL amyloidosis	Medication-related toxicity: bisphosphonates, other drugs
Membranoproliferative, diffuse proliferative, crescentic and cryoglobulinemic glomerulonephritis	Renal invasion by plasma cells
Minimal change disease	Pyelonephritis
Membranous glomerulonephritis	
Immunotactoid and fibrillary glomerulonephritis	
IgA nephropathy	
Tubulointerstitial nephritis	
Thrombotic microangiopathy	

proteins (such as Tamm–Horsfall protein) obstruct the renal tubules as well as elicit an accompanying tubulointerstitial nephritis that typically results in AKI; (2) monoclonal Ig deposition disease (MIDD), characterized by the deposition of monoclonal proteins in the glomerulus and tubular basement membranes leading to local tissue injury; and (3) AL amyloidosis, where monoclonal light chains with specific physiochemical properties form β-pleated sheet structures that deposit in the glomeruli and lead to local tissue injury. Ig-independent mechanisms of kidney injury include volume depletion, sepsis, pyelonephritis, hypercalcemia, uric acid nephropathy, tumor lysis syndrome, rhabdomyolysis, direct parenchymal invasion by plasma cells, and drug-induced causes (including nonsteroidal anti-inflammatory agents, bisphosphonates, and renin–angiotensin system inhibitors).[77] The Ig-dependent processes typically are associated with more chronic presentations as well as with predominant glomerular pathologies. An exception is cast nephropathy that usually presents as AKI.

Given the wide spectrum of kidney disease associated with plasma cell disorders, kidney biopsy is recommended when any of these etiologies is suspected. Suspicion should be based on clinical findings such as fatigue, weight loss, bone pain, and orthostatic hypotension or the presence of autonomic neuropathy coupled with laboratory abnormalities such as anemia, hypercalcemia, proteinuria, Fanconi syndrome, and a low anion gap (due the presence of an excess of cationic light chain proteins). Urine dipstick analyses typically do not detect light chains, but tests of total urine protein are abnormal. Thus, a negative urine dipstick test for albumin and the simultaneous detection of significant urine total protein is highly suggestive of light chain proteinuria and requires further testing. Both MIDD and AL amyloidosis typically present with nephrotic-range proteinuria and albuminuria indicative of global glomerular damage.

Detection of Monoclonal Ig

Previously, the detection of monoclonal Ig proteins was with protein electrophoresis and immunofixation, which had significant limitations both in their diagnostic and prognostic abilities.[78] Newer free light chain (FLC) assays are much more sensitive in detecting kappa and lambda light chains in the serum and are complementary to the traditional detection methods.[79] Although elevations in FLCs can be seen in numerous inflammatory conditions, abnormalities in the kappa:lambda ratio indirectly suggest clonal expansion specifically seen with plasma cell disorders.[79] Furthermore, in newly diagnosed myeloma patients, high serum FLC levels are associated with an increased risk of kidney injury.[80] However, it is critically important to analyze the value of FLC ratios in the context of GFR. Because impaired GFR will lead to decreased clearance of FLCs, the normal values of FLC and their ratios are changed in patients with CKD. Therefore caution is warranted in interpreting these values when the GFR is abnormal.[81]

Although accumulation of FLCs has been observed in patients with CKD, the question arises regarding whether these polyclonal increases in kappa and lambda light chains may influence progression of CKD. Thus far, data in this area have not been conclusive.[82]

Monoclonal Ig Deposition Disease

Multiple myeloma is the most common underlying disease associated with MIDD (40–50% of cases). Biopsy proven MIDD can precede the clinical detection of a paraprotein in up to 15–30% of cases.[83] MIDD is typically

associated with kappa light chains, which may have atypical glycosylation or amino acid substitutions that promote misfolding and precipitation.[84] Although the majority of cases of MIDD are due to deposition of light chains, heavy chain and light and heavy chain deposition can also be found.[83] On light microscopy, MIDD demonstrates thickening of the tubular and glomerular basement membrane, as well as the presence of glomerular nodules very similar in appearance to the classic Kimmelstiel-Wilson lesions of diabetic nephropathy. Most patients with MIDD present with isolated renal involvement, although cardiac and liver disease occasionally can be seen as well. Patients are typically younger than those with multiple myeloma or amyloidosis, and males are more often affected than females. Presentation is typically with decreased GFR, hypertension, and nephrotic-range proteinuria with a rapidly progressive course in the absence of chemotherapy. Chemotherapy stabilized or improved renal function in two-thirds of patients with MIDD who presented with S[Cr] of <5.0 mg/dL, emphasizing the importance of early detection and therapy.[83] The prognostic significance of kidney involvement is highlighted by the fact that the initial S[Cr] is the strongest predictor of renal and patient survival in MIDD.[83]

AL Amyloidosis

AL amyloidosis results from extracellular deposition of fibril-forming monoclonal immunoglobulin light chains (most commonly of the lambda isotype), which are usually secreted by a small plasma cell clone.[85] Most patients have evidence of isolated monoclonal gammopathy or smoldering myeloma. The occurrence of AL amyloidosis in patients with symptomatic multiple myeloma is unusual. AL amyloidosis affects men slightly more often than women. The average age of diagnosed patients is 65 years and around 10% of patients are less than 50 years old.[86] The key event in the development of AL amyloidosis is the change in the secondary or tertiary structure of an abnormal monoclonal light chain, which results in a conformation that leads to assembly into monomers that stack together to form amyloid fibrils.

Clinical presentations can be varied because of the wide number of tissues or organs that may be affected. Kidney involvement is the most frequent, found in two-thirds of patients at the time of diagnosis. The characteristic presentation is with heavy proteinuria (composed mainly of albumin, with detectable urine monoclonal Ig light chains in most cases), with nephrotic syndrome and decreased GFR in 20–45% of cases.[87] As opposed to MIDD, hypertension and hematuria are usually absent.[88] Although it has been stated that increased kidney size is characteristic of AL amyloid nephropathy, this is not a constant feature.[89] The diagnosis of renal amyloidosis relies on the pathological demonstration of renal amyloid and/or, when a kidney biopsy is not available, on histological evidence from another tissue with proteinuria ≥0.5 g/day predominantly composed of albumin.[90] Cardiac involvement, which is present at diagnosis in more than 50% of patients, leads to restrictive cardiomyopathy.

The diagnosis of amyloid is based on the finding, by light microscopic examination, of amorphous extracellular Congo red positive deposits, which display characteristic dichroism and apple green birefringence under polarized light. Whenever possible, noninvasive biopsies of abdominal fat and minor salivary glands should be performed initially.[91] If these tissue biopsies fail to demonstrate amyloid deposition, or are insufficient for amyloid typing, biopsy of a clinically affected organ should be considered. When a kidney biopsy is performed in patients with renal involvement, it allows identification of Ig light chain amyloid deposits in more than 80% of cases.[87] Deposits predominate in the mesangium and along the glomerular basement membranes. Interstitial and vascular deposits are also frequently observed. Electron microscopy may be useful to confirm the presence of amyloid deposits, which typically display the ultrastructural appearance of randomly arranged fibrils, 7–10 nm in external diameter.[87]

Treatment of systemic AL amyloidosis relies mainly on chemotherapy aimed at suppressing the underlying plasma cell clone secreting amyloid-forming Ig light chains. The presence of significant cardiac involvement is the greatest predictor of poor long-term outcomes.[92]

Monoclonal Gammopathy of Unclear Significance and CKD

Both CKD and MGUS are common independent findings in patients over 50 years. There does not seem to be an association between the presence of FLCs and the risk of developing ESRD in these patients.[93] However, persistent or rising levels of monoclonal Ig combined with unexplained or worsening CKD may warrant a renal biopsy to document Ig deposition in the kidney. Such a syndrome has been termed monoclonal gammopathy of renal significance.[94] Both AKI and progressive CKD are reported prodromes for the development of multiple myeloma.[94] However, routine screening of the CKD population for multiple myeloma is of limited value and the decision to perform specific diagnostic testing for light chains should be guided by the presence of additional features consistent with myeloma.[95]

Treatment Issues in the Patient with CKD

Given the risk of rapid progression of monoclonal Ig-induced kidney injury, rapidly acting chemotherapeutic

agents need to be instituted as quickly as a diagnosis is established. The greatest likelihood of preserving kidney function is with early, effective therapy.

A cornerstone of therapy is the proteasome inhibitor bortezomib, which along with dexamethasone, is highly effective in treating plasma cell disorders when kidney injury is present.[96] A novel feature of bortezomib is that it inhibits the NF-κB and MAP kinase pathways, potent anti-inflammatory properties that may have beneficial effects in mitigating renal injury.[97] When bortezomib is combined in various regimens with dexamethasone, melphalan, doxorubicin, or thalidomide, 40–50% of patients who respond to therapy have significant improvement in kidney function within a few weeks.[98–100] Bortezomib does not require dosing adjustments for decreased GFR.

Another chemotherapeutic agent of benefit is thalidomide and its newer derivative lenalidomide, which are usually combined with dexamethasone. Thalidomide does not require dose adjustment with renal dysfunction, but lenalidomide does require reduction in dose. Myelosuppression is more common in patients with CKD treated with thalidomide or lenalidomide.[101] Thalidomide, lenalidomide, and dexamethasone are associated with a higher risk of thrombotic events, which can be exacerbated by nephrotic syndrome and/or erythropoietin use and may complicate the placement of arteriovenous access if needed for dialysis.[89]

Plasmapheresis remains a controversial therapy for monoclonal Ig-associated kidney diseases. An option to increase the removal of nephrotoxic FLCs is the addition of plasmapheresis or hemodialysis with a "high-cutoff" membrane, which allows for the removal of larger molecular weight proteins (up to 50 kDa). The goal is to rapidly decrease FLC levels. One study demonstrated that a 60% reduction in FLC levels by day 21 after diagnosis is associated with kidney recovery in 80% of cases.[102] Initial studies of the treatment of light chain nephropathy with plasmapheresis remains controversial and are not applicable to modern day bortezomib-based therapy.[103] Two recent clinical trials, the Studies in Patients with Multiple Myeloma and Renal Failure Due to Myeloma Cast Nephropathy (MYRE) and the European Trial of Free Light Chain Removal by Extended Hemodialysis in Cast Nephropathy (EuLITE) have reported using extracorporeal therapy in addition to bortezomib-based therapy in patients presenting with newly diagnosed myeloma and a need for acute dialysis.[104,105] The MYRE study randomized 98 patients to either standard high-flux hemodialysis (HF-HD) or to high-cutoff HD (HCO-HD). There was no difference in the primary endpoint of dialysis independence at 3 months between the HF-HD and HCO-HD groups (33% vs. 43%, respectively; $p = 0.31$). However, at 6 months, more patients in the HCO-HD arm than the control group were independent of dialysis (60% vs. 38%, respectively; $p = 0.03$). The difference at 6 months was tempered by concern that the renal response to bortezomib in the HF-HD group was less than had been seen in other studies, suggesting that this population may have been atypical.[104,105] The EuLITE study randomized 90 patients in a similar manner to the MYRE study to either HF-HD or HCO-HD in addition to bortezomib-based chemotherapy. However, the dialysis regimens in the EuLITE study were significantly different than the MYRE study, making comparisons difficult. However, at 3 months there was no difference in kidney recovery between the HF-HD and HCO-HD groups (55.8% vs. 51.6%, respectively; $p = NS$). Given that both studies were small, with equivocal results, the routine use of HCO-HD cannot be routinely recommended.

HSCT is an option for patients with myeloma and renal failure but requires dose-adjustment in conditioning regimens with an increased risk for toxicity.[106] There are small numbers of patients with myeloma and ESRD that have undergone combined kidney and allogeneic HSCT from an HLA-identical sibling without the requirement for immunosuppression.[107]

Most centers require that patients with myeloma achieve and maintain a durable remission for at least 3–5 years before being considered for transplantation.[108] Kidney transplantation is possible in highly selected patients with MIDD or AL amyloidosis once they have achieved hematologic remission, usually after HSCT.[109] For those patients with MGUS and ESRD, data on kidney transplantation are limited, but there is concern that the progression to myeloma may be accelerated by immunosuppression.[110] Thus, Ig levels should be monitored closely and should be stable before transplantation.

MANAGEMENT OF ANEMIA IN THE PATIENT WITH CKD AND CANCER

Erythropoiesis-stimulating agents (ESAs) have been extensively used to reduce transfusion requirements and improve quality of life (QOL) in both cancer and CKD patients.[111,112] However, the likelihood of response and duration of treatment differs in the two settings. In renal anemia, ESAs act as hormone-replacement therapy substituting for the loss of production of endogenous erythropoietin and are thus part of chronic therapy. In the cancer patient, although endogenous erythropoietin production may be suppressed by the tumor and particularly by the release of inflammatory mediators, anemia is usually a side effect of chemotherapy. Thus, ESAs are administered not as maintenance therapy but as an

aspect of acute patient support. Response to ESAs is slower and less certain in cancer patients than in those with CKD.[113] In both settings, early studies showed that reversal of severe anemia was accompanied by substantial improvement in QOL.[111,112] However, again in both settings, subsequent studies indicated that efforts to *normalize* hemoglobin might worsen outcomes, including survival.[114–118] This concern was reinforced by the suggestion that malignant cells had erythropoietin receptors and that administration of ESAs might therefore accelerate tumor growth. Moreover, cancer patients treated with ESAs are more susceptible to venous thrombosis.[119] The ASCO and the American Society of Hematology synthesized available data in its most recent practice guidelines, which are abstracted in Table 55.5.[120] When approaching the patient with CKD, the clinician should determine if the use of ESAs is due to underlying CKD or associated with chemotherapy-induced myelosuppression. In either case, an individualized approach that minimizes the risks of ESAs and targets a hemoglobin level that minimizes the need for transfusion should be instituted. Those patients with CKD and associated myelosuppression may not respond to ESA therapy. Careful monitoring with a time-limited trial is recommended. Those patients with chemotherapy-induced anemia may only require ESA support for a short period of time. However, those patients with significant CKD may require continued ESA support.

TABLE 55.5 Recommendations for erythropoiesis-stimulating agent (ESA) Use for Patients with Cancer

1. The use of epoetin or darbepoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and an Hb concentration that has decreased to less than 10 g/dL to decrease transfusions. RBC transfusion is also an option, depending on the severity of the anemia or clinical circumstances. Patients should be counseled on the specific risks and potential benefits of ESA use.
2. An optimal level to initiate ESA therapy in patients with anemia and Hb between 10 and 12 g/dL cannot be definitively determined from the available evidence. Under these circumstances, whether or not to initiate ESA treatment should be determined by clinical judgment, consideration of the risks and benefits of ESAs, and patient preference
3. Clinicians should carefully weigh the risks of thromboembolism in patients for whom epoetin or darbepoetin is prescribed
4. It is recommended that starting and modifying doses of ESA follow FDA guidelines
5. Continuing epoetin or darbepoetin treatment beyond 6–8 weeks in the absence of response (e.g. a 1–2 g/dL increase in Hb or no diminution of transfusion requirements) does not seem to be beneficial
6. Hb can be increased to the lowest concentration needed to avoid transfusions, which may vary by patient and condition. An optimal target Hb concentration cannot be definitively determined from the available literature. Modification to reduce the ESA dose is appropriate when Hb reaches a level sufficient to avoid transfusion or the increase exceeds 1 g/dL in any 2-week period to avoid excessive ESA exposure

Adapted from reference 120 with permission from the publisher.

CHEMOTHERAPY AND TARGETED THERAPY DOSING IN CKD

The kidneys are one of the major routes of elimination for most chemotherapy agents. Hence dose adjustments are required when most chemotherapy agents are administered to patients with CKD. It is often challenging, as these agents also have a very narrow therapeutic index. Many chemotherapy and targeted therapy trials have excluded patients with severe CKD. As a result, the patient with CKD may receive either too little or too much chemotherapy. Dosing guidelines often do not have a significant evidence basis for chemotherapy use in CKD patients. In addition, the method of calculating dose adjustments in patients with CKD, extrapolating from pharmacokinetic data, may not always conform with clinical practice. CKD status and the uremic milieu can lead to altered hepatic metabolism of drugs.[121] Despite these issues, CKD patients receiving chemotherapy or targeted therapies constitute a large group of patients that need proper dosing of agents. A list of common chemotherapy and targeted therapies agents requiring dose adjustments is presented in Table 55.6.[122–124]

SUMMARY: ONCONEPHROLOGY, A NEW FOCUS IN NEPHROLOGY

All nephrologists will encounter kidney disease in patients with cancer. The kidney disease may be preexisting and may affect dosing of chemotherapy, or the kidney disease may be a manifestation of the malignancy or its therapy. In each case, the nephrologist requires an understanding of the kidney diseases associated with malignancy. The nephrologist should also be a member of the team caring for patients with CKD and cancer, offering input into medication dosing and monitoring of GFR and electrolytes. Some have termed this intersection of kidney disease and cancer, onconephrology (encompassing both hematology and oncology related kidney diseases). The goal is that onconephrologists will help cancer care teams prevent kidney problems or resolve them as they arise and improve patient outcomes.

TABLE 55.6 Chemotherapy Dose Adjustments in Chronic Kidney Disease Patients

Chemotherapy Agents	Dose Adjustment Required for eGFR 10–50 mL/min (%)	Dose Adjustment Required when eGFR <10 mL/min (%)	Evidence Level
Capecitabine	75	50–75	B
Cisplatin	75	50, avoid if possible	A
Carboplatin	50 (AUC based)	50	D
Chlorambucil	75	50	B
Ifosfamide	100	75	B
Cyclophosphamide	100	75	D
Cytarabine	50	10	D
Dacarbazine	75 for eGFR 60–45	70	D
Doxorubicin	100	100	D
Daunorubicin	100	100	D
Epirubicin	100	100	D
Etoposide	75	50	B
Carmustine	75 for eGFR 30–60	Avoid if eGFR<30	D
Lomustine	70 for eGFR 30–60	Avoid if eGFR<30	B
Semustine	70 for eGFR 30–60	Avoid if eGFR<30	B
Streptozocin	75	50	D
Mitomycin C	100	75	B
Mithramycin	75	50	B
Azacitidine	100	100	B
Gemcitabine	100	100	B
Cytarabine	100	100	D
Methotrexate	50	Avoid	A
Pentostatin	60 for eGFR 30–60	Avoid when eGFR <30	B
Fludarabine	75	50	D
Cladribine	75	50	D
5-Fluorouracil	100	100	B
Melphalan	75	50	B
Oxaliplatin	100	50	A
Paclitaxel	100	100	A
Pemetrexed	100 if GFR 45–79 with oral folic acid and Vit B12	Avoid with eGFR <45	B
Temozolomide	100	100	B
Topotecan	75	50	A
Vincristine	100	100	B
Vinblastine	100	100	B
Sunitinib	100	100	B
Sorafenib	50	50	D
Erlotinib	100	100	B
Gefitinib	100	100	B
Imatinib	100	50	A

AUC, area under the curve; *eGFR*, estimated glomerular filtration rate; *GFR*, glomerular filtration rate. Strength of evidence: A, human trials; B, human case studies; C, *in vitro* data; D, Clinical opinion.
Adapted from reference 123.

References

1. American Cancer Society. *Cancer facts and figures 2012*. Atlanta, GA: American Cancer Society; 2012.
2. Feest TG, Round A, Hamad S. Incidence of severe acute renal failure in adults: results of a community based study. *BMJ* 1993;**306**: 481–3.
3. Christiansen CF, Johansen MB, Langeberg WJ, Feyzek JP, Sorensen HT. Incidence of acute kidney injury in cancer patients. A Danish population based cohort study. *Eur J Intern Med* 2011;**22**: 399–406.
4. Salahudeen AK, Doshi SM, Pawar T, Nowshad G, Lahoti A, Shah P. Incidence rate, clinical correlates, and outcomes of AKI in patients admitted to a comprehensive cancer center. *Clin J Am Soc Nephrol* 2012. https://doi.org/10.2215/CJN.03530412.
5. Kemlin D, Biard L, Kerhuel L, Zafrani L, Venot M, Texeira L, Schlemmer B, Azoulay E, Canet E. Acute kidney injury in critically ill patient with solid tumors. *Nephrol Dial Transplant* 2018. https://doi.org/10.1093/ndt/gfy051.
6. Dekkers IA, Blijdorp K, Cransberg K, Pluijm SM, Pieters R, Neggers SJ, van den Heuvel-Eibrink MM. Long-term nephrotoxicity in adult survivors of childhood cancer. *Clin J Am Soc Nephrol* 2013. https://doi.org/10.2215/CJN.09980912.
7. Janus N, Launay-Vacher V, Thyss A, Boulanger H, Moranne O, Islam MS, Durande JP, Ducret M, Juillard L, Soltani Z, Motte G, Rottembourg J, Deray G, Thariat J. Management of anticancer treatment in patients under chronic dialysis: results of the multicentric CANDY (CANcer and DialYsis) study. *Ann Oncol* 2013; **24**(2):501–7.
8. Launay-Vacher V, Oudard S, Janus N, Gligorov J, Pourrat X, Rixe O, Morere JF, Beuzeboc P, Deray G. Renal Insufficiency and Cancer Medications (IRMA) Study Group. Prevalence of renal insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. *Cancer* 2007;**110**(6):1376–84.
9. Janus N, Launay-Vacher V, Byloos E, Machiels JP, Duck L, Kerger J, Wynendaele W, Canon JL, Lybaert W, Nortier J, Deray G, Wildiers H. Cancer and renal insufficiency results of the BIRMA study. *Br J Cancer* 2010;**103**(12):1815–21.
10. Kitchlu A, Shapiro J, Amir E, Garg X, Kim SJ, Wald R, Harel Z. Representation of patients with chronic kidney disease in trials of cancer therapy. *J Am Med Assoc* 2018;**319**(23):2437–9.
11. Wong G, Hayen A, Chapman JR, Webster AC, Wang JJ, Mitchell P, Craig JC. Association of CKD and cancer risk in older people. *J Am Soc Nephrol* 2009;**20**(6):1341–50.
12. Na SY, Sung JY, Chang JH, Kim S, Lee HH, Park YH, Chung W, Oh KH, Jung JY. Chronic kidney disease in cancer patients: an independent predictor of cancer-specific mortality. *Am J Nephrol* 2011;**33**(2):121–3.
13. Weng PH, Hung KY, Huang HL, Chen JH, Sung PK, Huang KC. Cancer-specific mortality in chronic kidney disease: longitudinal follow-up of a large cohort. *Clin J Am Soc Nephrol* 2011;**6**(5): 1121–8.
14. Tomroth T, Heiro M, Marcussen N, Franssila K. Lymphomas diagnosed by percutaneous kidney biopsy. *Am J Kidney Dis* 2003;**42**: 960–71.
15. Schwartz JB, Shamsuddin AM. The effects of leukemic infiltrates in various organs in chronic lymphocytic leukemia. *Hum Pathol* 1981;**12**:432–40.
16. Kowalewska J, Nicosia RF, Smith KD, Kats A, Alpers CE. Patterns of glomerular injury in kidneys injury in kidneys infiltrated by lymphoplasmacytic neoplasms. *Hum Pathol* 2011;**42**:896–903.
17. Obrador GT, Price B, 0'Meara Y, Salant DJ. Acute renal failure due to lymphomatous infiltration of the kidneys. *J Am Soc Nephrol* 1997;**8**:1348–54.
18. Jhaveri KD, Shah HH, Calderon K, Campenot E, Radhakrishnan J. Glomerular diseases seen with cancer and chemotherapy: a narrative review. *Kidney Int* 2013. https://doi.org/10.1038/ki.2012.484.
19. Perazella MA. Onco nephrology: renal toxicities of chemotherapy agents. *Clin J Am Soc Nephrol* 2012;**7**:1713–21.
20. Madias N, Harrington J. Platinum nephrotoxicity. *Am J Med* 1987; **65**:307–14.
21. Blachley JD, Hill JB. Renal and electrolyte disorders associated with cisplatin. *Ann Intern Med* 1981;**95**:628–32.
22. Chiuten D, Vogl S, Kaplan B, Camacho F. Is there cumulative or delayed toxicity from cis-platinum? *Cancer* 1983;**52**:211–4.
23. Hansen S, Groth S, Daugaard G, Rossing N, Rorth M. Long term effects on renal function and blood pressure of treatment with cisplatin, vinblastine and bleomycin in patients with germ cell cancer. *J Clin Oncol* 1998;**6**:1728–31.
24. Skinner R, Sharkley IM, Pearson AD, Craft AW. Ifosfamide, mesna and nephrotoxicity in children. *J Clin Oncol* 1993;**11**:173–90.
25. Farry JK, Flombaum CD, Latcha S. Long term renal toxicity of ifosfamide in adult patients-a 5 year data. *Eur J Cancer* 2012;**48**: 1326–31.
26. Schacht RG, Feiner HD, Gallo GR, Lieberman A, Baldwin DS. Nephrotoxicity of nitrosoureas. *Cancer* 1981;**48**:1328–34.
27. Micetich KC, Jensen-Akula M, Mandard JC, Fisher RI. Nephrotoxicity of semustine in patients with malignant melanoma receiving adjuvant chemotherapy. *Am J Med* 1981;**71**:967–72.
28. Jhaveri KD, Flombaum CD, Kroog G, Glezerman IG. Nephrotoxities associated with the use of tyrosine kinase inhibitors: a single center experience and review of the literature. *Nephron Clin Pract* 2011;**117**(4):c312–9.
29. Nagai K, Ono H, Matsuura M, Hann M, Ueda S, Yoshimoto S, Tamaki M, Murakami T, Abe H, Ishikura H, Doi T. Progressive renal insufficiency related to ALK inhibitor, alectinib. *Oxf Med Case Reports* 2018;**2018**(4):omy009. https://doi.org/10.1093/omcr/omy009. eCollection.
30. Izzedine H, Brocheriou I, Deray G, Rixe O. Thrombotic microangiopathy and anti VEGF agents. *Nephrol Dial Transplant* 2007;**22**: 1481–2.
31. Maitland ML, Kasza KE, Karrison T, Moshier K, Sit L, et al. Ambulatory monitoring detects sorafenib-induced blood pressure elevations on the first day of treatment. *Clin Cancer Res* 2009;**15**: 6250–7.
32. Ermina V, Jefferson V, Kowalewska J, Hochster H, Haas M, et al. VEGF-inhibition and renal thrombotic microangiopathy. *N Engl J Med* 2008;**358**:1129–36.
33. Perazella MA. Checkmate: kidney injury associated with targeted cancer immunotherapy. *Kidney Int* 2016;**90**(3):474–6.
34. Cortazar FB, Marrone KA, Troxell ML, Ralto KM, Hoenig MP, Brahmer JR, Le DT, Lipson EJ, Glezerman IG, Wolchok J, Cornell LD, Feldman P, Stokes MB, Zapata SA, Hodi FS, Ott PA, Yamashita M, Leaf DE. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. *Kidney Int* 2016;**90**(3):638–47.
35. Ronco PM. Paraneoplastic glomerulonephritis: new insights into an old entity. *Kidney Int* 1999;**56**(1):355–77.
36. Bacchetta J, Juillard L, Cochat P, Droz JP. Paraneoplastic glomerular diseases and malignancies. *Crit Rev Oncol Hematol* 2009; **70**(1):39–58.
37. Lefaucheur C, Stengel B, Nochy D, Martel P, Hill GS, Jacquot C, Rossert J. Membranous nephropathy and cancer: epidemiologic evidence and determinants of high-risk cancer association. *Kidney Int* 2006;**70**(8):1510–7.
38. Beck Jr LH, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, Klein JB, Salant DJ. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009;**361**(1):11–21.

39. Qin W, Beck Jr LH, Zeng C, et al. Anti phospholipase A2 receptor antibody in membranous nephropathy. *J Am Soc Nephrol* 2011;**22**: 1137–43.
40. Hoxha E, Kneißler U, Stege G, et al. Enhanced expression of the M-type phospholipase A2 receptor in glomeruli correlates with serum receptor antibodies in primary membranous nephropathy. *Kidney Int* 2012. https://doi.org/10.1038/ki.2012.209.
41. Ohtani H, Wakui H, Komatsuda A, Okuyama S, Masai R, Maki N, Kigawa A, Sawada K, Imai H. Distribution of glomerular IgG subclass deposits in malignancy-associated membranous nephropathy. *Nephrol Dial Transplant* 2004;**19**(3):574–9.
42. Radice A, Pieruzzi F, Trezzi B, Ghiggeri G, Napodano P, D'Amico M, Stellato T, Brugnano R, Ravera F, Rolla D, Pesce G, Giovenzana ME, Londrino F, Cantaluppi V, Pregnolato F, Volpi A, Rombolà G, Moroni G, Ortisi G, Sinico RA. Diagnostic specificity of autoantibodies to M-type phospholipase A2 receptor (PLA2R) in differentiating idiopathic membranous nephropathy (IMN) from secondary forms and other glomerular diseases. *J Nephrol* 2018;**31**(2):271–8.
43. Audard V, Larousserie F, Grimbert P, et al. Minimal change nephrotic syndrome and classical Hodgkin's lymphoma: report of 21 cases and review of the literature. *Kidney Int* 2006;**69**: 2251–60.
44. Da'as N, Pollack A, Cohen Y, et al. Kidney involvement and renal manifestations in non-Hodgkin's lymphoma and lymphocytic leukemia: a retrospective study in 700 patients. *Eur J Haematol* 2001;**67**:158–64.
45. Sethi S, Zand L, Leung N, et al. Membranoproliferative glomerulonephritis secondary to monoclonal gammopathy. *Clin J Am Soc Nephrol* 2010;**5**(5):770–82.
46. Heaf JG, Hansen A, Laier GH. Quantification of cancer risk in glomerulonephritis. *BMC Nephrol* 2018;**19**(1):27. https://doi.org/10.1186/s12882-018-0828-2.
47. Hingorani S, Guthrie KA, Schoch G, Weiss NS, McDonald GB. Chronic kidney disease in long term survivors of hematopoetic cell transplant. *Bone Marrow Transplant* 2007;**39**:223–9.
48. Ellis MJ, Parikh CR, Inrig JK, Kanbay M, Patel UD. Chronic kidney disease after hematopoietic stem cell transplantation: a systemic review. *Am J Transplant* 2008;**8**:2378–90.
49. Cohen EP. Renal failure after bone marrow transplantation. *Lancet* 2001;**357**:6–7.
50. Ruutu T, Barosi G, Benjamin RJ, et al. Diagnostic criteria for hematopoietic stem cell transplant-associated microangiopathy: results of a consensus process by an international working group. *Haematologica* 2007;**92**(1):95–100.
51. Troxell M, Pilapil M, Miklos D, et al. Renal pathology in hematopoetic cell transplantation recipients. *Mod Pathol* 2008;**21**:396–406.
52. Chang A, Hingorani S, Kowalewska J, et al. Spectrum of renal pathology in hematopoietic cell transplantation: a series of 20 patients. *Clin J Am Soc Nephrol* 2007;**2**(5):1014–23.
53. Changsirikulchai S, Myerson D, Guthrie KA, et al. Renal Thrombotic microangiopathy after hematopoietic cell transplant: role of GVHD in pathogenesis. *Clin J Am Soc Nephrol* 2009;**4**(2):345–53.
54. Glezeman I, Jhaveri KD, Watson TH, et al. Chronic kidney disease, thrombotic microangiopathy, and hypertension following T cell depleted hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2010;**16**(7):976–84.
55. Ho VT, Cutler C, Carter S, et al. Blood and marrow transplant clinical trials network toxicity committee consensus summary: thrombotic microangiopathy after stem cell transplantation. *Biol Blood Marrow Transplant* 2005;**11**(8):571–5.
56. Hahn T, Alam AR, Lawrence D, et al. Thrombotic microangiopathy after allogeneic blood and marrow transplantation is associated with dose-intensive myeloablative conditioning regimens, unrelated donor and methylprednisolone T cell depletion. *Transplantation* 2004;**78**(10):1515–22.
57. Brukamp K, Dolye A, Bloom R, et al. Nephrotic syndrome after hematopoietic stem cell transplantation: do glomerular lesions represent renal graft versus host disease? *Clin J Am Soc Nephrol* 2006;**1**(14):685–94.
58. Srinivasan R, Balow JE, Sabnis S, Lundqvist A, Igarashi T, Takahashi Y, Austin H, Tisdale J, Barrett J, Geller N, Childs R. Nephrotic syndrome: an under-recognised immune-mediated complication of non-myeloablative allogeneic hematopoietic cell transplantation. *Br J Haematol* 2005;**131**:74–9.
59. Luo XD, Liu QF, Zhang Y, et al. Nephrotic syndrome after allogenic hematopoietic stem cell transplantation: etiology and pathogenesis. *Blood Cells Mol Dis* 2011;**46**(2):182–7.
60. Wang HH, Yang AH, Yang LY, et al. Chronic graft versus host disease complicated by nephrotic syndrome. *J Chin Med Assoc* 2011; **74**(9):419–22.
61. Hu S. The role of graft versus host disease in hematopoietic cell transplantation-associated glomerular disease. *Nephrol Dial Transplant* 2011;**26**(6):2025–31.
62. Siegel R, Naishadham D, Jernal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012;**62**:10–29.
63. Henriksen KJ, Meehan SM, Chang A. Nonneoplastic kidney diseases in adult tumor nephrectomy and nephroureterectomy specimens. Common, harmful, yet underappreciated. *Arch Pathol Lab Med* 2009;**133**:1012–25.
64. Henriksen KJ, Meehan SM, Chang A. Non-neoplastic renal diseases are often unrecognized in adult tumor nephrectomy specimens. A review of 246 cases. *Am J Surg Pathol* 2007;**31**:1703–8.
65. Kim SP, Thompson RH. Kidney function after partial nephrectomy: current thinking. *Curr Opin Urol* 2013;**23**:105–11.
66. Tan HJ, Norton EC, Ye Z, et al. Long-term survival following partial vs. radical nephrectomy among older patients with early stage kidney cancer. *J Am Med Assoc* 2012;**307**:1629–35.
67. Miller DC, Schoniau M, Litwin MS, et al. Renal and cardiovascular morbidity after partial or radical nephrectomy. *Cancer* 2008; **112**:511–20.
68. Huang WC, Levey AS, Seno AM, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumors: a retrospective cohort study. *Lancet Oncol* 2006;**7**:735–40.
69. MacLennan S, Imamura M, Lapitan MC, et al. Systematic review of oncological outcomes following surgical management of localized renal cancer. *Eur Urol* 2012;**61**:972–93.
70. MacLennan S, Imamura M, Lapitan MC, et al. Systematic review of perioperative and quality-of-life outcomes following surgical management of localized renal cancer. *Eur Urol* 2012;**61**:1097–117.
71. Kim SP, Thompson RH, Boorjian SA, et al. Comparative effectiveness for survival and renal function of partial and radical nephrectomy for localized renal tumors: a systematic review and meta-analysis. *J Urol* 2012;**188**:51–7.
72. Campbell SC, Novick AC, Belldegrun A, et al. Guideline for management of the clinical T1 renal mass. *J Urol* 2009;**182**:1271–9.
73. Finelli A, Ismaila N, Bro B, Durack J, Eggener S, Evans A, Gill I, Graham D, Huang W, Jewett MAS, Latcha S, Lowrance W, Rosner M, Shayegan B, Thompson RH, Uzzo R, Russo R. Management of small renal masses: American Society of Clinical Oncology Clinical Practice Guideline 2017;**35**(6):668–80.
74. Lane BR, Demirijian S, Derweesh IH, Takagi T, Zhang Z, Velet L, Ercole CE, Fergany AF, Campbell SC. Survival and functional

stability in chronic kidney disease due to surgical removal of nephrons: importance of the new baseline glomerular filtration rate. *Eur Urol* 2015;**68**(6):996–1003.
75. Knudsen LM, Hippe E, Hjorth M, Holmberg E, Westin J. Renal function in newly diagnosed multiple myeloma: a demographic study of 1353 patients. The Nordic Myeloma Study Group. *Eur J Hematol* 1994;**53**:207–12.
76. Knudsen LM, Hjorth M, Hippe E. Renal failure in multiple myeloma: reversibility and impact on the prognosis. Nordic Myeloma Study Group. *Eur J Hematol* 2000;**65**:175–81.
77. Heher E, Goes NB, Spitzer TR, Raje NS, et al. Kidney disease associated with plasma cell dyscrasias. *Blood* 2010;**116**:1397–404.
78. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma, and related disorders: a report of the International Myeloma Working Group. *Br J Hematol* 2003;**121**:749–57.
79. Bradwell AR, Carr-Smith HD, Mead GP, et al. Highly sensitive, automated immunoassay for immunoglobulin free light chains in serum and urine. *Clin Chem* 2001;**47**:673–80.
80. van Rhee F, Bolejack V, Hollmig K, et al. High serum-free light chain levels and their rapid reduction in response to therapy define an aggressive multiple myeloma subtype with poor prognosis. *Blood* 2007;**110**:827–32.
81. Hutchinson CA, Harding S, Hewins P, Mead GP, Townsend J, Bradwell AR, Cockwell P. Quantitative assessment of serum and urinary polyclonal light chains in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2008;**3**:1684–90.
82. Desjardins L, Liabeuf S, Lenglet A, Lemke H-D, Vanholder R, Choukroun G, Massy ZA, European Uremic Toxin (EUTox) Work Group. Association between free light chain levels and disease progression and mortality in chronic kidney disease. *Toxins* 2013;**5**(11):2058–73.
83. Lin J, Markowitz GS, Valeri AM, et al. Renal monoclonal immunoglobulin deposition disease: the disease spectrum. *J Am Soc Nephrol* 2001;**12**:1482–92.
84. Vidal R, Goni F, Stevens F, et al. Somatic mutations of the L12a gene in V-kappa(1) light chain deposition disease: potential effects on aberrant protein conformation and deposition. *Am J Pathol* 1999;**155**:2009–11.
85. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. *N Engl J Med* 2003;**349**:583–96.
86. Desport E, Bridoux F, Sirac C, et al. AL amyloidosis. *Orphanet J Rare Dis* 2012;**7**:1750–4.
87. Obici L, Perfetti V, Palladini G, Moratti R, Merlini G. Clinical aspects of systemic amyloid diseases. *Biochim Biophys Acta* 2005; **1753**:11–22.
88. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol* 1995;**32**:45–59.
89. Ekelund L. Radiological findings in renal amyloidosis. *Am J Roentgenol* 1977;**129**:851–3.
90. Gertz MA, Merlini G. Definition of organ involvement and response to treatment in AL amyloidosis: an updated consensus opinion. *Amyloid* 2010;**17**(Suppl. 1):48–9.
91. Libbey CA, Skinner M, Cohen AS. Use of abdominal fat tissue aspirate in the diagnosis of systemic amyloidosis. *Arch Intern Med* 1983;**143**:1549–52.
92. Bergesio F, Ciciani AM, Manganaro M, et al. Renal involvement in systemic amyloidosis: an Italian collaborative study on survival and renal outcome. *Nephrol Dial Transplant* 2008;**23**:941–51.
93. Haynes R, Hutchinson CA, Emberson J, et al. Serum free light chains and the risk of ESRD and death in CKD. *Clin J Am Soc Nephrol* 2011;**6**:2829–37.
94. Prakash J, Mandal AK, Vohra R, et al. Renal disease is a prodrome of multiple myeloma: an analysis of 50 patients from Eastern India. *Ren Fail* 2009;**31**:267–71.
95. Doyle A, Soutar R, Geddes CC. Multiple myeloma in chronic kidney disease. *Nephron Clin Pract* 2009;**111**:c7–11.
96. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005;**352**:2487–98.
97. Sarkozi R, Perco P, Hoichegger K, et al. Bortezomib-induced survival signals and genes in human proximal tubular cells. *J Pharmacol Exp Ther* 2008;**327**:645–56.
98. Jagannath S, Barlogie B, Berenson JR, et al. Bortezomib in recurrent and/or refractory multiple myeloma: initial clinical experience in patients with impaired renal function. *Cancer* 2005;**103**: 1195–200.
99. Chanan-Khan AA, Kaufman JL, Mehta J, et al. Activity and safety of bortezomib in multiple myeloma patients with advanced renal failure: a multicenter retrospective study. *Blood* 2007;**109**:2604–6.
100. Roussou M, Kastritis E, Migkou M, et al. Treatment of patients with multiple myeloma complicated by renal failure with bortezomib-based regimens. *Leuk Lymphoma* 2008;**49**:890–5.
101. Dimopoulos MA, Kastritis E, Rajkumar SV. Treatment of plasma cell dyscrasias with lenalidomide. *Leukemia* 2008;**22**:1343–53.
102. Hutchison CA, Cockwell P, Stringer S, et al. Early reduction of serum-free light chains associates with renal recovery in myeloma kidney. *J Am Soc Nephrol* 2011;**22**:1129–36.
103. Fabbrini P, Finkel K, Gallieni M, Capasso G, et al. Light chains removal by extracorporeal techniques in acute kidney injury due to multiple myeloma: a position statement of the Onconephrology Work Group of the Italian Society of Nephrology. *J Nephrol* 2016;**29**:735–46.
104. Bridoux F, Carron P-L, Pegourie B, et al. Effect of high-cutoff hemodialysis vs conventional hemodialysis on hemodialysis independence among patients with myeloma cast nephropathy. A randomized clinical trial. *J Am Med Assoc* 2017;**318**:2099–110.
105. Hutchison CA, Cook M, Heyne N, et al. European trial of free light chain removal by extended haemodialysis in cast nephropathy (EuLITE): a randomised control trial. *Trials* 2008;**9**:55.
106. Knudsen LM, Nielsen B, Gimsing P, Geisler C. Autologous stem cell transplantation in multiple myeloma: outcome in patients with renal failure. *Eur J Hematol* 2005;**75**:27–33.
107. Fudaba Y, Spitzer TR, Shaffer J, et al. Myeloma responses and tolerance following combined kidney and nonmyeloablative marrow transplantation: in vivo and in vitro analyses. *Am J Transplant* 2006;**6**:2121–33.
108. Kasiske BL, Cangro CB, Hariharan S, et al. The evaluation of renal transplant candidates: clinical practice guidelines. Recommendations for outpatient surveillance of renal transplantation. *Am J Transplant* 2001;(Suppl. 2):5–95.
109. Leung N, Griffith MD, Dispenzieri A, et al. Living donor kidney and autologous stem cell transplantation for primary systemic amyloidosis (AL) with predominant renal involvement. *Am J Transplant* 2005;**5**:1660–70.
110. Rostaing L, Modesto A, Abbai M, Durand D. Long-term follow-up of monoclonal gammopathy of undetermined significance in transplant patients. *Am J Nephrol* 1994;**14**:187–91.
111. Canadian Erythropoietin Study Group. Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. *BMJ* 1990;**300**:573–8.
112. Littlewood TJ, Bajetta E, Nortier JW, et al. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo controlled trial. *J Clin Oncol* 2001;**19**: 2865–74.
113. Locatelli F, Gascon P. Is nephrology more at ease than oncology with erythropoiesis-stimulating agents? Treatment guidelines and an update on benefits and risks. *Oncologist* 2009;**14**(Suppl. 1):57–62.

114. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;**355**: 2085–98.
115. Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006;**355**:2071–84.
116. Bennett CL, Silver SM, Djulbegovic B, Samaras AT, Blau CA, Gleason KJ, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *J Am Med Assoc* 2008;**299**:914–24.
117. Ludwig H, Crawford J, Osterborg A, Vansteenkiste J, Henry DH, Fleishman A, et al. Pooled analysis of individual patient-level data from all randomized, double-blind, placebo-controlled trials of darbepoetin alfa in the treatment of patients with chemotherapy-induced anemia. *J Clin Oncol* 2009;**27**:2838–47.
118. Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. *Lancet* 2009;**373**:1532–42.
119. Henke M, Mattern D, Pepe M, et al. Do erythropoietin receptors on cancer cells explain unexpected clinical findings? *J Clin Oncol* 2006;**24**:4708–13.
120. Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, et al. American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbopoetin in adult patients with cancer. *J Clin Oncol* 2010;**28**: 4996–5010.
121. Leblond F, Guevin C, Demers C, Pellerin I, Gascon-Barre M, Pichette V. Downregulation of hepatic cytochrome P450 in chronic renal failure. *J Am Soc Nephrol* 2001;**12**:326–32.
122. Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: dosing guidelines for altered renal function. *Cancer Treat Rev* 1995;**21**:33–64.
123. Flombaum C. Nephrotoxicity of chemotherapy agents and chemotherapy administration in patients with renal disease. In: Cohen EP, editor. *Cancer and the kidney: the frontier of nephrology and oncology.* Oxford, UK: Oxford University, Press; 2011. p. 115–75.
124. Sahni V, Chaudhary D, Ahmed Z. Chemotherapy associated renal dysfunction. *Nat Rev Nephrol* 2009;**5**:450–62.
125. Bollee G, Patey N, Cazajous G, Robert C, Goujon JM, Fakhouri F, et al. Thromobotic microangiopathy secondary to VEGF pathway inhibition by sunitinib. *Nephrol Dial Transplant* 2009; **24**:682–5.
126. Jhaveri KD, Flombaum CD, Kroog G, Glezerman IG. Nephrotoxicities associated with the use of tyrosine kinase inhibitors. A single center experience and review of the literature. *Nephron Clin Pract* 2011;**117**:c312–9.
127. Beck Jr LH. Membranous nephropathy and malignancy. *Semin Nephrol* 2010;**30**(6):635–44.
128. Lacy MG, Gertz MA. Acquired Fanconi's syndrome associated with monoclonal gammopathies. *Hematol Oncol Clin N Am* 1999; **13**:1273–80.

QUESTIONS AND ANSWERS

Question 1

A 56-year-old man with renal cell cancer receives chemotherapy with sunitinib. His baseline S[Cr] is 0.9 mg/dL. After 2 months of treatment, the oncologist notices that the S[Cr] is rising and currently is 2.0 mg/dL. The patient complains of lower extremity swelling. He has no known history of hypertension. He has normal vital signs except for slight new hypertension 145/90 mm Hg. His cardiac, lung, and abdomen exam is benign, but he has 1+ lower extremity edema bilaterally. His laboratory data are presented below:

Na 145 mEq/L, K 4.3 mEq/L, Cl 110 mEq/L, CO_2 19 mEq/L, BUN 30 mg/dL, S[Cr] 2.0 mg/dL, Albumin 2 g/dL.
Urinalysis with 2+ protein, no blood or cells
FeNa is 2%
CBC with WBC 14,000/mm^3, Hemoglobin 10 g/dL, Platelets 100/mm^3. Normal coagulation profile, haptoglobin is <10 mg/dL and LDH is 400 IU/L

Which **one** of the following is true regarding his condition:

A. Repeated exposure to sunitinib will lead chronic tubular damage
B. Repeated exposure to sunitinib will lead to a chronic thrombotic microangiopathy
C. Repeated exposure to sunitinib will lead to membranous nephropathy
D. Repeated exposure to sunitinib will less likely cause CKD

Answer: B

Renal TMA is a complication of all tyrosine kinase inhibitors such as sunitinib and sorafenib.[125] The classic syndrome includes hypertension, proteinuria, microangiopathic hemolytic anemia, and subacute decrease in GFR. Complement levels are usually normal and haptoglobin is usually low. Tubular toxicity is not a common finding with this drug class. Other findings such as acute and chronic interstitial nephritis with this agent have been reported.[126] Chronic tubular damage has not been consistently reported with this agent.

Question 2

A 45-year-old man treated with allogeneic HSCT for ALL develops nephrotic-range proteinuria. The serum albumin concentration is 2 g/dL. The patient has no prior history of renal disease. A kidney biopsy reveals membranous nephropathy. Which ONE of the following is the MOST likely cause of associated MN in patients with nephrotic syndrome after HSCT?

A. Drug-induced injury
B. Graft vs. host disease
C. Antipodocyte antibodies
D. Antiphospholipase receptor A2 antibodies
E. Renal vein thrombosis

Answer: B

Glomerular disease can be a cause of CKD following HSCT. Other causes include AKI, CNI, and TMA. In HSCT patients with nephrotic-range proteinuria, the renal biopsy findings may include MN, MCD, and FSGS. However, MN accounts for a majority of the cases of HSCT-associated glomerular diseases, whereas MCD accounts for most of the remaining cases.[57] Brukamp et al.[57] conducted a meta-analysis based on 46 patients who had HSCT and glomerular disease. Their study revealed a close temporal relationship between the development of nephrotic syndrome shortly after cessation of immunosuppression and the diagnosis of chronic GVHD. Within 9 months after discontinuation of immunosuppressive agents, most patients developed nephrotic syndrome. In a few cases, the temporal relationship was also concomitant with development of chronic GVHD. Because the MN here is secondary, the Anti-PLAR2 antibodies would be negative. Drug-induced causes such as CNI use usually lead to nonnephrotic-range proteinuria from TMA. Renal vein thrombosis is a result of nephrotic syndrome and not a cause of nephrotic syndrome in most cases.

Question 3

A 68-year-old man develops nephrotic-range proteinuria. A kidney biopsy confirms stage 2 membranous nephropathy. His prior history is relevant for hypertension for 5 years and 30 pack-years of tobacco use. He has no weight loss, no cough, or shortness of breath. Which of the following clinical and biopsy findings help distinguish secondary membranous from cancer from primary membranous?

A. Age over 65 and history of smoking are clinical risk factors for secondary membranous nephropathy
B. Absence of circulating anti-PLA2R autoantibodies in serum favors primary membranous nephropathy
C. Presence of IgG4 deposition in the glomeruli favors secondary membranous nephropathy
D. Presence of more than 8 inflammatory cells per glomeruli favors primary membranous nephropathy
E. All of the above

Answer: A

Delineating primary from secondary/cancer associated MN has been a great challenge for nephrologists and nephropathologists. Various studies have elucidated different parameters that help in making this

differentiation.[38–41,127] These parameters could be clinical or historical clues, serological markers, or histopathological findings on the kidney biopsy. Table 55.3 in the chapter summarizes these parameters. Based on that summary in Table 55.3, Choice A is correct.

Question 4

A 70-year-old patient is evaluated for new-onset hematuria. Diagnostic work-up reveals a 5-cm localized mass in the left kidney with imaging patterns consistent with RCC. Further evaluation shows no evidence of metastatic spread or local lymph node involvement. Laboratory work-up reveals an estimated glomerular filtration rate of 46 mL/min/1.73 m^2.

Which of the following would be the best course of therapy?

A. Chemotherapy with a tyrosine kinase–based medication
B. Surveillance with yearly imaging
C. Radical nephrectomy
D. Partial nephrectomy
E. Percutaneous needle biopsy

Answer: D

In the past, radical nephrectomy was considered the treatment of choice for isolated RCC or SRM. However, there is increasing awareness that radical nephrectomy is associated with a higher risk for CKD and its resultant morbidity and mortality. Thus, there has been a shift to partial nephrectomy as the treatment of choice for patients with RCC. This is especially critical in patients with baseline CKD where complete nephrectomy has a risk of leading to ESRD. Tyrosine kinase inhibitors and other chemotherapeutic regimens are reserved for more advanced disease as is radical nephrectomy. Surveillance would risk spread of the cancer over time. Needle biopsy is seldom required as imaging is sufficiently sensitive and specific to make an accurate diagnosis.[65–67]

Question 5

A 65-year-old man presents with the chief complaint of progressive weakness over the past several months. One year ago, he was known to have normal kidney function. He is normotensive and his physical examination is unremarkable. Laboratory studies reveal the following: sodium 135 mmol/L, chloride 105 mmol/L, potassium 3.0 mmol/L, bicarbonate 18 mEq/L, S[Cr] 1.8 mg/dL, urea nitrogen 22 mg/dL, glucose 110 mg/dL, hematocrit 25%, white blood cell count 5600/mm^3, platelets 340,000/mm^3.

Urinalysis shows trace protein, 1+ glucose, normal sediment. 24-h urine protein excretion is 4.8 g. A bone marrow aspirate reveals the diagnosis of multiple myeloma.

Which one of the following is characteristic of the renal abnormality seen in this patient?

A. Evidence of nephrocalcinosis on renal imaging
B. The serum bicarbonate concentration will increase after the administration of oral bicarbonate at 80 mEq/day but then decrease to 18 mmol/L after the therapy is discontinued
C. Bicarbonate therapy will cause serum potassium concentration to decline slightly as a result of a shift into cells
D. The urine pH will be persistently alkaline
E. The urine anion gap will be negative

Answer: B

This patient has multiple myeloma. The finding of AKI, anemia, and trace protein on dipstick, but nephrotic-range protein on laboratory quantification is indicative of this diagnosis. In some patients, light chains, which are freely filtered by the glomerulus, may lead to proximal tubular toxicity (here noted by the presence of glucosuria with a normal serum glucose). Thus, a type II renal tubular acidosis (RTA) may be present, which is typified by a transient increase in serum bicarbonate levels with base therapy, but a rapid return to lower levels once therapy is stopped (indicative of a new set-point for bicarbonate resorption in the tubule). The ability to acidify the urine is maintained, and thus, in the steady state, urine pH may be acidic. The urine anion gap can be variable. Nephrocalcinosis is typical of distal RTA.[128]

Question 6

A 65-year-old patient with stage 4 CKD secondary to diabetes mellitus is diagnosed with locally advanced lung cancer. He has been receiving darbopoietin 100 mcg monthly for anemia. His most recent hemoglobin is 9.9 g/dL, which has been stable for the past 3 months.

With his recent diagnosis of cancer, which of the following changes to his darbopoietin dosing should be made?

A. Darbopoietin dosing should be increased to bring the hemoglobin level to 11 g/dL
B. Darbopoietin dosing should be limited to achieve the lowest possible hemoglobin level to avoid the need for transfusions
C. Darbopoietin dosing should be held until the hemoglobin level is less than 7 g/dL
D. Darbopoietin should not be administered until his malignancy is under control

E. Erythropoietin is the preferred erythropoiesis-stimulating agent in patients with cancer

Answer: B

The most recent guidelines from the American Society of Hematology support limiting erythopoietin dosing to the minimum needed to avoid transfusions. There are no clear, evidence-based hemoglobin targets and thus Answers A and C are incorrect. There is no guidance that suggests avoiding erythropoietin completely in patients with cancer is appropriate. Therefore Answer D is incorrect. Furthermore, there is no evidence favoring one form of erythropoiesis-stimulating agent in the treatment of anemia in a patient with ESRD and malignancy. Therefore Answer E is incorrect.[120]

CHAPTER

56

The Interdisciplinary Clinic for Chronic Kidney Disease

Roberto Pisoni[a], *Carolyn A. Bauer*[b], *Jerry Yee*[c], *Ruth C. Campbell*[a]

[a]Medical University of South Carolina, Division of Nephrology, Charleston, SC, United States; [b]Division of Nephrology, Bronx, NY, United States; [c]Henry Ford Hospital, Division of Nephrology and Hypertension, Detroit, MI, United States

Abstract

The chronic kidney disease (CKD) clinic has emerged as an interdisciplinary care (IDC) model that encompasses patient education, medical management of CKD complications and CKD risk factors, and quality improvement. The CKD clinic team may include physicians, advanced practice providers, nurses, dieticians, pharmacists, and social workers. Team structure and clinic goals should be tailored to local practice needs. Common goals include CKD education, renal replacement therapy (RRT) planning, and treatment of complications of CKD based on national/international guidelines. Data suggest that CKD clinics slow CKD progression, improve CKD and RRT education, and lead to greater rates of home dialysis and permanent access placement. Financing of CKD clinics remains problematic as many insurers do not pay for IDC services. The long-term viability of the CKD clinic model may ultimately depend on demonstrating effectiveness and a reduction in overall patient care costs.

BACKGROUND

Chronic kidney disease (CKD) is a global health problem.[1] Approximately 15% of the US and Canadian populations have CKD.[2,3] The prevalence of CKD has been rising due to increased prevalence of hypertension, obesity, and diabetes mellitus.[4] This is mainly driven by the elderly with significant comorbidities.[5] Individuals with CKD have high morbidity and mortality and increased health care utilization.[6] High poverty rates and low health literacy contribute to the poor outcomes of the CKD population.[7–10] As a result, CKD presents an increasing substantial burden to health services. In 2013, the cost of end-stage renal disease (ESRD) care was $32.8 billion, accounting for more than 7% of US Medicare spending, and was estimated to be over $1 trillion worldwide.[11,12]

The care of individuals with CKD is complex and requires many interactions by nephrologists with patients, their family, other providers, and inpatient services. This occurs despite an increasing physician workload, the pressure to improve outcomes and limit costs, and a shrinking workforce with fewer US nephrology fellowship applicants.[13] These issues have led to a critical evaluation of how CKD care is delivered and what outcomes should be targeted in health care systems. Which individuals would benefit most from intensive management from an interdisciplinary care (IDC) clinic? What should be the CKD goals of care? Slowing CKD progression, decreasing cardiovascular morbidity and mortality, improving perception of quality of life, management of CKD complications, preparation for ESRD care, or all of these? How will this care be delivered in the most cost-effective way and by whom? The IDC clinic has emerged as an alternative to the traditional model of care for individuals with CKD as a way to address many of these pressing issues. In particular, such a clinic may address patient education, quality improvement, management of CKD risk factors and complications, and timely patient preparation for renal replacement therapy (RRT).

DEFINITION OF THE CKD IDC CLINIC

There is no single definition of IDC for CKD. IDC requires that health care providers of different disciplines, including physicians, advanced practice providers

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00056-5

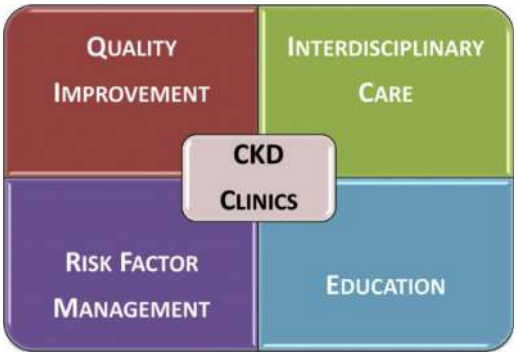


FIGURE 56.1 Interdisciplinary chronic kidney disease clinical aspects of care. Quality improvement, interdisciplinary care, risk factor management, and education of CKD patients require balanced integration.

(APPs: nurse practitioners or physician assistants), nurse specialists, pharmacists, dieticians, and social workers work collaboratively, cohesively, and synergistically and communicate together as a team to provide care for patients. The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines specify that interdisciplinary nephrology care should encompass dietary counseling, education regarding different RRT modalities, transplantation options, vascular access surgery, and ethical, psychological, and social care (Figure 56.1).[14] This approach to CKD care often entails collaboration of health care providers to implement evidence-based, guideline-driven protocols in CKD care within the confines of the patient's (or the patient's health care proxy's) expressed wishes. Financial restraints of the provider(s) and/or patient(s) may limit the ability to offer all of these services to patients. Additionally, not all insurance providers will provide reimbursement for some or all of the disciplines included in IDC-based CKD care in the US. Thus, nephrology practices should identify which aspects of patient care (such as education regarding management of ESRD) or clinical outcomes (such as arteriovenous fistula [AVF] placement) are needed urgently by their patient population and use the available components of IDC to construct an intervention. To do this, the IDC CKD team needs to monitor changes in outcomes for quality improvement processes to maximize patients' benefits.

Based on local needs and resources, IDC clinics often have different staffing models and configurations. Many include APPs who do a large part of the patient education and coordination and follow protocols to achieve guideline benchmarks with the collaboration of a nephrologist. Of APPs associated with nephrology practices in the US, 83% report working in CKD or anemia management clinics.[15] IDC CKD clinic teams may include members similar to the make-up of dialysis units, with dieticians, nurses, and social workers to provide resources and patient support. When patients are deemed likely to progress to ESRD, coordination with transplant surgeons, vascular surgeons, and interventional radiologists is important to ensure timely access placement and a smooth transition to dialytic management of ESRD. Given the increasingly elderly CKD population, geriatricians and palliative care physicians can aid with prognostication, advanced care planning, and symptom management.

Although there is always a focus on patient education and management of comorbidities and complications, how an IDC clinic may achieve these goals may differ. The degree of renal dysfunction required to participate in an IDC clinic may vary. Some IDC clinics standardize the number of visits that a patient will receive from each provider based on CKD stage, others base interventions on individual risk factors and patient preferences. A common IDC CKD clinic structure has the nephrology practice provide interdisciplinary services. Some IDC clinics alternate patients between IDC visits and general nephrology visits. Other IDC clinics may incorporate a nephrology evaluation as part of their services and take referrals directly from primary care physicians (PCPs) instead of accepting patients only from a participating nephrologist.[16] This illustrates the importance of clearly defining the role of the IDC team in relation to both nephrology and primary care.

Different types of nephrology practices and multiple health care delivery models lead to vast differences in IDC in CKD. In the US, these centers range from private practices that include an APP to large integrated managed care consortiums, such as Kaiser Permanente, and to governmental health care agencies, like the Veterans Affairs (VA) System. Although IDC clinics for CKD are prevalent in Canada and Taiwan, the number of patients who receive IDC for CKD in the US is difficult to measure. The US Renal Data System (USRDS) states that of approximately 120,000 patients who progressed to ESRD in 2015, only 8% had dietary care.[2] In addition to IDC clinics started by nephrologists and hospital systems, dialysis providers and start-up companies are contracting with health systems, health plans, nephrologists, and governmental agencies to help manage pre-ESRD patients. These companies employ proprietary risk stratification algorithms, management protocols, technology platforms,

and telephone management to decrease hospitalization and defray health care costs. The VA has started using telehealth to expand their CKD outreach.[17]

TARGET POPULATION OF THE CKD IDC CLINIC

Individuals at the highest risk of progression to ESRD and those who have CKD complications that need specialized management (e.g. anemia, mineral and bone disease, metabolic acidosis, hyperkalemia) are logical populations to target for IDC. The 2012 KDIGO CKD guidelines suggest that patients with progressive CKD be treated in an IDC setting, but no glomerular filtration rate (GFR) cutoff is specified.[14] An accurate identification of this population is necessary. Models are available to estimate the risk of progression to ESRD.[18] An internationally validated risk prediction model of ESRD, called Kidney Failure Risk Equation (KFRE), is available as a web-based calculator and smartphone app.[19–21] Its four-variable version incorporates an individual's age, sex, estimated GFR (eGFR), and urine albumin:creatinine ratio (UACR), whereas the eight-variable equation additionally incorporates serum calcium (S[Ca]), phosphorus, bicarbonate, and albumin (S[Alb]) levels and is incrementally more accurate than the four-variable version. In Ontario, Canada, KFRE is used in the clinical setting to triage nephrology referrals and determine the need of IDC and the time for AVF creation.[22,23] The rate of GFR change over time, the degree of proteinuria, and advanced age are key predictors of fast progression of CKD and may help identify the potential target population for IDC. The 2012 KDIGO guidelines define rapid CKD progression as loss of eGFR >5 mL/min/1.73 m^2 per year.[14] Of more than 36,000 adults with eGFR 30–59 mL/min/1.73 m^2 within a large integrated health care delivery system in northern California, 23% of individuals with diabetes and 15% of those without were recently identified as fast CKD progressors over a 2-year period.[24] Within this population, proteinuria, age >80 years, elevated systolic blood pressure, and heart failure were independent predictors of fast CKD progression regardless of the presence of diabetes. Individuals with these risk factors may warrant more aggressive modification of risk factors and education for RRT. The 2012 KDIGO guidelines recommend referral for access planning when the anticipated risk of starting RRT is >10% within 1 year.[14]

Proteinuria is the strongest modifiable predictor of progression to ESRD in both diabetic and nondiabetic CKD patients.[24,25] Proteinuria is also an independent predictor of cardiovascular disease (CVD) and death.[26–29] Both the relative reduction in proteinuria and the level of achieved proteinuria after initiation of renoprotective treatment are predictors of the subsequent rate of GFR decline over time.[30–32] The degree/category of albuminuria is now included in the KDIGO classification of CKD. The 2012 KDIGO guidelines recommend individuals with UACR >300 mg/g or protein:creatinine ratio >500 mg/g be referred to a nephrologist.[14] A standardized, multimodal intervention targeting urinary protein excretion has been shown to be effective to slow CKD progression in subjects with nondiabetic CKD at high risk of progression to ESRD.[33]

Although elderly patients with CKD are more likely to die than progress to ESRD, they represent the fastest growing group to develop ESRD in several countries. Approximately 25% of incident ESRD individuals were over 75 years of age in 2010.[34] Elderly individuals benefit from starting dialysis with a permanent access.[35] However, there is small survival benefit, and quality of life may actually decrease from starting dialysis in individuals older than age 80 years and with a high burden of comorbidities and/or living in a nursing facility.[36,37] Thus, a thoughtful discussion of RRT modalities, including the option of supportive, nondialytic care, is extremely important. Screening for sensory deficits (e.g. vision, hearing, and reaction), anxiety, depression, and cognitive impairment and involving individuals' family/caregivers is important in this population as these conditions may affect individuals' ability to communicate effectively, retain the information provided, and adhere to treatment recommendations. Individuals with advanced CKD are at high risk of progression to ESRD and have higher rates of CKD complications such as anemia, bone and mineral disease, and CVD that need specialized management. Treating these complications is associated with decreased morbidity and improved quality of life.[14]

GOALS OF THE CKD IDC CLINIC

The ultimate goals of a CKD IDC clinic are to improve morbidity and mortality of patients with kidney disease. The IDC team has the challenging task of using evidence-based guidelines and information from recent studies to decrease the high risk of cardiovascular events and death in the CKD population, decrease the rate of progression to ESRD, treat known complications of CKD, and prepare patients at the highest risk of ESRD for dialysis and when possible renal transplantation (Table 56.1). All of these interventions must be done with the patient's, and often families', understanding and must be consistent with the patient's wishes and values. To accomplish these goals effectively, members of the IDC team must focus on patient education and

TABLE 56.1 Principal Goals of an Interdisciplinary Care Chronic Kidney Disease Clinic

Goal	Comment
Coordination of CKD care	Collaborative engagement/partnership with primary care physicians and specialists
Determination of CKD progression risk and rate	Estimation of GFR decline; proteinuria determination(s)
Mitigation of CKD complications and cardiovascular risk	Blood pressure; mineral and bone disorders; metabolic acidosis; anemia; lipids
CKD education	Multiple component/personnel utilization; MIPPA
Transition to RRT for ESRD	Discussion for prognosis; RRT modality/option planning; transplant and vascular access evaluations

Abbreviations: *CKD*, chronic kidney disease; *ESRD*, end-stage renal disease; *GFR*, glomerular filtration rate; *MIPPA*, Medicare Improvement of Patients and Providers Act; *RRT*, renal replacement therapy.

protocol-driven care based on national and international guidelines, such as the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) and the KDIGO guidelines.[14,38] Treatment protocols should also include findings of large randomized controlled trials (RCTs) that have not yet been integrated into published guidelines to provide the best practices for this high-risk population. To slow progression of kidney disease and improve cardiovascular factors, control of underlying causes of CKD such as diabetes and hypertension needs to be addressed. Complications of CKD including metabolic bone derangements, anemia, electrolyte disturbances, and fluid imbalance must be diagnosed and treated. Given the immunosuppressive nature of advancing CKD and the possible need for kidney transplantation, vaccines to prevent influenza viruses, streptococcal pneumonia (including both the pneumococcal polysaccharide and the 13-valent conjugate pneumococcal vaccinations), herpes zoster, and hepatitis B should be administered in the recommended settings.[39–42]

Patient Education

Despite the awareness of the importance of patient education in improving health outcomes in CKD, almost 80% of newly initiated dialysis patients started hemodialysis (HD) using a catheter.[34,43–47] CKD IDC allows multiple disciplines to facilitate and optimize patient education and has been shown to lead to increased selection of home dialysis modalities, improved permanent access placement, and decreased mortality.[43,45,46] Educational interventions offered for only one day have significant benefits.[43,48] In 2010, under the Medicare Improvement of Patients and Providers Act (MIPPA), Medicare started to reimburse for CKD education provided by a physician, APP, or clinical nurse specialist for Medicare recipients with CKD stage 4 or 5. Up to six sessions of education are reimbursed and can be delivered either as a class or on an individual basis in the outpatient setting.[49] The classes must cover management of comorbidities, prevention of uremic complications, and options for RRT (including HD, peritoneal dialysis [PD], home therapies, access options, and transplantation). A recent survey of US nephrology practices found that 60% offered a CKD education class and that an APP delivered 87% of the classes.[50] The educational materials for these classes were either developed locally, originated from the NKF CKD education series "Your Treatment, Your Choice," or represented a hybrid of local and NKF materials.

An important consideration in CKD education programs is the impact of health literacy. Low health literacy, or how well a patient understands and assimilates information to make decisions regarding his or her health, is common among CKD patients and is associated with increased mortality on dialysis and with lower referral rates for transplantation.[10,51,52] Cognitive impairment is also common in individuals with CKD. A recent study found that 19% of patients with eGFR <20 mL/min/1.73 m^2 had cognitive impairment, which was associated with an increased rate of using a dialysis catheter for dialysis initiation and a lower rate of PD as a first modality.[53] These data support the need to assess patients' understanding of the education that they have been given. An advantage of the NKF "Your Treatment, Your Choice" program is that it provides outcome assessment tools to help determine whether class participants found the information understandable and helpful. IDC may allow for more time and resources to identify barriers to learning.

Cardiovascular Risk Management

Patients with CKD have an extremely high burden of CVD. In addition to delaying and preparing for ESRD, the goal of CKD IDC is to improve patients' cardiovascular health and decrease the incidence of heart attacks, strokes, and congestive heart failure (CHF). The higher risk of death compared with the progression to ESRD becomes even more pronounced in the expanding elderly stage 3 and 4 CKD population, mostly due to CVD.[2,6,54] Traditional risk factors for CVD such as increasing age, hypertension, diabetes, and hyperlipidemia are highly prevalent in the CKD population. In addition, other

nontraditional risk factors for CVD have been identified in patients with CKD, including anemia, fluid overload, vascular calcifications, inflammation, malnutrition, and increased oxidative stress.[55–58] Albuminuria, even when not associated with diabetes, is associated with higher incidence of cardiovascular events.[59,60] Patients frequently have CHF and CKD that need to be comanaged. Treatment with diuretics and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are mainstays of therapy in both conditions. Having CHF and CKD increases a patient's mortality risk and may require earlier dialysis initiation.[61,62] CKD IDC should focus on interventions that modify CVD risk factors. Guideline-driven care for CKD can improve cardiovascular risk, and CKD IDC has been shown to improve mortality both before and after starting dialysis.[44,63–66]

Interventions to decrease cardiovascular events in CKD have had varied results. Smoking is associated with CVD, and observational data suggest that smoking may influence the progression of renal disease. Therefore, smoking cessation should be addressed with each patient.[67,68] Conversely, it is unclear if aspirin therapy confers cardiovascular protection in this high-risk population. A *post hoc* analysis of the large RCT, the Hypertension Optimal Treatment (HOT) study, demonstrated that aspirin decreased mortality and major cardiac events in patients with diastolic hypertension and eGFR <45 mL/min/1.73 m^2.[69] However, a recent meta-analysis including HOT and two other randomized trials did not show any benefit of aspirin in the primary prevention of CVD in the CKD population, and its use was associated with increased bleeding risk.[70] In addition, a meta-analysis evaluating the use of aspirin for secondary prevention in CKD patients with acute coronary syndromes undergoing revascularization procedures revealed only a nonsignificant improvement in cardiovascular outcomes, but an increased bleeding risk.[71] Despite the recommendation of aspirin therapy by the KDIGO 2012 guidelines, more data are likely required to determine the role of aspirin in this population.[14]

Lifestyle modification and lipid lowering can also benefit patients with CKD. Aggressive lipid lowering therapy in pre-ESRD CKD patients has been shown to improve cardiovascular outcomes in RCTs.[72,73] International treatment guidelines now recommend that all pre-ESRD CKD patients over 50 years old be started on a statin, as well as those patients younger than age 50 who are at high risk for coronary artery disease or stroke.[74] In addition to medications, CKD patients should be educated about healthy lifestyle modifications. Dieticians and other members of the IDC team encourage adherence with individualized diets, weight loss when necessary, and appropriate exercise programs.

Hypertension Control

Control of hypertension by CKD IDCs is essential given that it both slows progression of renal disease and decreases the incidence of cardiovascular events.[75–79] New guidelines, including the 2017 American College of Cardiology/American Heart Association and the 2018 European Society of Cardiology/European Society of Hypertension, have altered the blood pressure target to initiate and treat hypertension based on cardiovascular risk.[80,81] These guidelines suggest targets of <130/80 mm Hg in high-risk individuals, which include CKD patients, based on newer studies especially the large randomized Systolic Blood Pressure Intervention Trial (SPRINT). SPRINT excluded patients with diabetes, but 28% of more than 9000 participants had CKD with eGFRs of 20–59 mL/min/1.73 m^2.[82] These newer guidelines are more consistent with the 2012 KDIGO blood pressure guidelines for patients with CKD, which recommended a blood pressure target <130/80 mm Hg for those patients with albuminuria based on renal outcome trials.[83–85] Points of controversy in the guidelines include BP targets in the elderly, those without albuminuria, and those with wide pulse pressures.

Controlling BP in CKD patients takes many visits and interventions, including low salt diet, home BP monitoring, and adherence to medication. A patient-focused, interdisciplinary team providing patient education is recommended to improve hypertension control. CKD IDCs have been shown to improve hypertension control.[86] Management of BP in CKD is particularly difficult because hypertension often worsens as CKD progresses, requires multiple drug combinations, and may be complicated by fluid overload, acute kidney injury, and hyperkalemia. ACEIs or ARBs are used as first-line medications in CKD and are most beneficial in the setting of proteinuria, which is a risk factor both for the development of CVD and advancing CKD.[14] Second-line medications include calcium channel blockers or diuretics followed by beta blockade.[14]

Management of CKD Complications

The CKD IDC team must address complications that arise as CKD progresses. Complications include anemia, metabolic derangements, and metabolic bone disease. Individual dietary counseling is an important part of CKD IDC to decrease complications and engage the patients. Nutritional counseling is paramount as CKD patients are often asked to follow multiple diets including low sugar, low protein, low salt, low potassium, low phosphorus, and fluid restriction, while avoiding malnutrition. CKD clinics educate patients to avoid nephrotoxins, particularly nonsteroidal

antiinflammatory drugs, and ensure that all medications are appropriately dosed based on a patient's eGFR.

Anemia of CKD

As CKD advances, many patients develop anemia of CKD due to ineffective iron use, inflammation, and decreased production of erythropoietin.[87] Previously, CKD clinics were often centered on administration of erythropoiesis-stimulating agents (ESAs) for treatment of anemia. However, the use and insurance coverage of these drugs have greatly decreased because the Trial to Reduce Cardiovascular Events with Aranesp Therapy, the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta trial, and the Correction of Hemoglobin and Outcomes in Renal Insufficiency trial did not demonstrate benefits of hemoglobin normalization and demonstrated potential harm.[88–90] The Food and Drug Administration (FDA) issued a "black box" warning concerning thrombosis and cancer growth associated with these drugs and required that providers distribute a medication guide (risk evaluation and mitigation strategies) to every patient receiving a new prescription.[91] Presently, treatment of anemia with ESAs should be individualized to limit blood transfusions. When CKD programs initiate ESAs, they need to carefully monitor patients monthly to ensure their hemoglobin levels do not rise too rapidly or exceed 11 g/dL. All anemic patients must be screened for iron deficiency, which should be treated with intravenous or oral iron compounds. Supplementing iron may also decrease the amount of ESA necessary.[92] In addition, appropriate evaluations for occult blood loss must be performed before ESA administration.

Metabolic Bone Disease

CKD is often complicated by metabolic bone disease. CKD patients may have deranged circulating calcium levels, elevated circulating phosphate and intact parathyroid hormone levels, and vitamin D deficiency. The KDIGO working group recently published updated mineral and bone disorder guidelines in 2017, which stated that activated vitamin D analogs, such as calcitriol, are no longer routinely recommended to treat hyperparathyroidism but may be considered in severe and progressive cases.[93] Activated vitamin D therapy was associated with hypercalcemia and did not improve cardiovascular outcomes.[94,95] Dieticians and clinicians should encourage low phosphorus diets, adequate 25-hydroxyvitamin D repletion, and avoidance of high doses of calcium-based phosphate binders.

Hyperkalemia and Acidosis

Hyperkalemia and acidosis are complications of CKD that need to be evaluated and treated. Improving acidosis has been shown to decrease progression to ESRD, mitigate bone buffering, and improve nutritional status and lean body mass.[96–98] Hyperkalemia may occur as CKD progresses, which requires dietary management and can hasten the need for RRT. In addition, hyperkalemia limits the use of ACEIs or ARBs. Potassium-binding resins (patiromer and sodium zirconium cyclosilicate) were recently approved by the US FDA and can be used in the setting of chronic ACEI and ARB use.[99–101]

Management of Underlying Disorders

CKD clinic staff must coordinate with primary care providers to ensure that the underlying causes of CKD, such as diabetes and hypertension, are addressed. Diabetes, which is a risk factor for both CVD and CKD, must be controlled by diet and usually by medications. Coordination with the IDC team including the dietician, PCP, and nephrologist is important to control diabetes and prevent hypoglycemia. Comanagement with PCPs and cardiology is also necessary when treating both CKD and CHF, as many therapies impact both disorders. Effective communication with PCPs and other involved physicians is essential to ensure that all providers recognize their specific responsibilities when treating these diseases.

Slowing CKD Progression

The IDC team should address interventions to slow the decline of kidney function. Unfortunately, few interventions delay progression to ESRD. Control of hypertension, especially with ACEIs or ARBs in diabetic and nondiabetic patients with proteinuria, retards progression of CKD and decreases the incidence of cardiovascular events.[75,76,78,79,102–104]

Dietary sodium restriction and diuretic therapy can further increase the efficacy of hypertension and proteinuria reduction by ACEIs or ARBs.[105,106] Other interventions that may slow progression of kidney disease include treatment of metabolic acidosis, avoiding nephrotoxins (e.g. nonsteroidal antiinflammatory drugs and exposure to contrast agents) and volume depletion, quitting smoking, and effective education.[96,107,108] Dieticians and pharmacists in an IDC clinic may work in concert with nephrologists to ensure patient adherence to diet and medications and to determine medications that should be discontinued or whose dose/frequency should be adjusted according to the level of kidney function. A randomized study of individuals with advanced CKD showed that a single educational session with the provision of a printed summary booklet and supportive telephone calls delayed initiation of RRT by approximately 3 months.[43]

Transitioning from CKD to ESRD

IDC should safely and effectively transition individuals with advanced CKD to ESRD with the goal to lower the high morbidity and mortality associated with starting dialysis.[34,109] Ultimately, this should result in reduced costs. The pathways for transitions from CKD to RRT should be well defined, along with the role of the various IDC team members involved. The IDC team should provide patient-centered action plans for initiating dialysis, coordinate listing for kidney transplantation, and define goals of care for individuals who may not desire or benefit from these modalities. Education, in individual and/or group sessions, regarding RRTs is fundamental to this process. Patients and their relatives need to understand the different RRT options (PD, in-center or home HD, and transplantation) to facilitate informed decision-making that best accommodates their desires and circumstances. A discussion of each patient's prognosis and the risks and benefits of each RRT modality should be provided to each individual. The modality of RRT should be established at least 6 months to 1 year before the development of ESRD to allow for timely AVF placement in appropriate patients and to perform the work-up required before transplantation. Individuals who are independent, enjoy travel, are working, and have adequate supply space may opt for PD or home HD. Preparation for dialysis should occur simultaneously with evaluation for transplantation. Individuals must prepare for RRT before the onset of uremia. Patients should be educated to avoid venipuncture, intravenous lines, and BP measurements in the nondominant arm to protect the veins for the potential creation of an AVF and after this is created.

Hemodialysis

Data from the Dialysis Outcomes and Practice Patterns Study show consistent higher mortality rate in the first 120 days after starting HD. However, this mortality rate is significantly higher in the US compared with other countries.[34,109] Risk factors associated with early mortality in HD are older age, hypoalbuminemia, heart failure, use of HD catheter, and lack of predialysis care.[110,111] Individuals beginning HD using a catheter have significantly increased mortality and morbidity compared with those who begin HD using an AVF.[112,113] Pre-ESRD nephrology care and presence of permanent AV access provided most of the 1-year survival advantage shown in patients who started dialysis while receiving care through the Military Health System (MHS) compared with those who initiated dialysis outside the MHS.[114] Pre-ESRD nephrology care for more than 12 months had a comparable survival impact to that of a functioning AVF in this population. Current guidelines recommend consideration of AVF creation when the risk of ESRD is estimated to be greater than 10% within 1 year.[14] Collaborative partnership with a surgeon with high-expertise in AVF and AV graft construction ensures consistent establishment of well-functioning permanent HD accesses in suitable candidates. IDC teams should aim to facilitate the initiation of dialysis in the outpatient setting in appropriate individuals, therefore limiting the need of hospitalization and related high costs. IDC dieticians should work with individuals to prevent, diagnose, and treat malnutrition. Individuals with CHF should be closely monitored and treated for volume overload.

Peritoneal Dialysis

Individuals interested in PD should meet with a PD nurse to receive further education before deciding which RRT modality to pursue. The IDC team should determine whether the patient's living environment has adequate space to perform the mandatory sterile procedures and store supplies. Individuals should also be closely monitored for symptoms, signs, and laboratory studies suggestive of uremia to coordinate the timing of PD catheter placement with an experienced surgeon. Individuals should then be smoothly transitioned into a PD unit to initiate PD training following catheter insertion. Family members should be encouraged to learn about PD and assist the patient.

Kidney Transplantation

Transplantation offers the best survival advantage among the RRT modalities. Transplantation before starting dialysis is associated with improved mortality and allograft survival.[115–117] The IDC team should educate individuals and their families about transplantation, ensure timely referrals for transplant evaluation, and facilitate discussions about living kidney donations between individuals and their families. Individuals should be wait-listed when eGFR <20 mL/min/1.73 m^2 to accrue time on the deceased-donor waiting list before starting dialysis and potentially decrease the duration of dialytic care.

Advanced Care Planning

ESRD in the elderly is associated with a high risk of mortality and decreased functional status and therefore warrants advanced care planning. In the US, 20% of patients who died in the initial 120 days after starting dialysis had discontinued treatment.[109] Predictive tools available to risk stratify a patient's outcomes can aid a clinician's understanding of an individual's prognosis. Clarifying patients' wishes before ESRD may decrease aggressive and costly measures that patients may not want at the end of their lives. If progression to ESRD is likely, the risks and benefits of dialysis and transplantation should be provided to patients to ensure informed

decision-making. In addition, patients should clarify circumstances under which they would want to withdraw from dialysis. Allowing a patient to make these decisions before the onset of an emergency setting benefits the patients' families who will understand their loved ones' wishes before they reach kidney failure. For patients who decide on medical management at stage 5 CKD—the "no dialysis" option—IDC programs should continue to provide services that facilitate the patients' overall wellness and comfort.

CLINICAL OUTCOMES OF THE CKD IDC CLINIC

The prevailing literature suggests that IDC slows CKD progression, decreases hospitalizations, improves mortality rates during transition from CKD to ESRD, and improves AVF placement before initiation of RRT. Snyder and Collins found that a higher number of preventive measures including monitoring of lipids, glucose, and mineral and bone parameters as well as influenza vaccination were associated with a significantly decreased risk of atherosclerotic heart disease in a Medicare CKD cohort.[63] Hemmelgarn et al. showed a 50% decreased mortality risk in a predialysis cohort with IDC compared with a propensity-matched control group that had standard nephrology care.[64] Decreased mortality was also shown in a cohort of patients who had access to IDC in Taiwan.[118] Exposure to IDC decreased mortality rates after dialysis initiation in two other cohort studies.[44,65] Data from Fresenius Medical Care North America, a large dialysis organization, showed that individuals who underwent a predialysis educational program were significantly more likely to choose PD as their RRT, begin HD with an AVF or AV graft, and were less likely to die within the first 90 days following onset of dialysis.[119]

The Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse Practitioners (MASTERPLAN) study, a randomized trial of 788 Dutch patients with CKD stages 3 and 4, showed that the implementation of CKD guidelines by nurse practitioners added to standard nephrology care, after an extended median follow-up of almost 6 years, slowed eGFR decline by 0.45 mL/min/1.73 m^2 per year, and decreased the incidence of the composite endpoint (death, ESRD, and a 50% increase in S[Cr]) by 20% compared with standard nephrology care.[120] The previously published MASTERPLAN trial with median follow-up of 5 years did not show a significant difference in CVD outcomes, but showed that APP supported care significantly decreased CVD risk factors (hypertension, low-density lipoprotein cholesterol, anemia, and proteinuria).[86] The latter trial had several limitations including contamination bias, fewer than expected events likely related to the inclusion of a relatively young and "healthy" CKD population, and being underpowered to demonstrate a significant difference in CVD outcome.

Other trials have shown that CKD education and IDC can slow the progression of CKD to ESRD. A randomized trial demonstrated that a single 90-minute education session along with follow-up phone calls significantly delayed dialysis initiation by approximately 3 months in individuals expected to start dialysis within 6–18 months.[43] English patients with eGFRs <30 mL/min/1.73 m^2 who had access to a nurse, patient education, medication management, and nutrition counseling had a slower eGFR decline over time with the greatest benefit in those patients with rapidly progressive CKD.[121]

Data are conflicting regarding the efficacy of IDC in early CKD and nonprogressive CKD patients. Slower CKD progression was detected in subjects enrolled in IDC compared with historical controls in a large health maintenance organization population.[122] A Canadian RCT found no difference in GFR decline and control of most CKD risk factors by adding a nurse-coordinated model in subjects with slowly progressive CKD.[123] However, nurse-coordinated care was associated with fewer visits to specialists and hospitalization days.

Cohort studies performed in California, Taiwan, and Canada showed that patients exposed to IDC had significantly more AVFs placed and decreased hospitalizations.[48,124,125] A single-center study showed that guideline-driven care by APPs was associated with improved functioning, permanent vascular accesses, and decreased hospitalizations 12 months after dialysis initiation.[126]

ECONOMICS OF CKD IDC CLINICS

CKD IDC have different components and funding sources. IDC is funded by the National Health Service in certain countries such as Canada and Taiwan, whereas many fee-for-service insurance providers only reimburse for physicians or APP visits in the US. This may cause IDC clinics not to be available in many locations. Dieticians are reimbursed by Medicare for stage 4 CKD patients but may not be covered by other US insurance companies. The MIPPA benefits include six education classes, if taught by a physician, an APP, or clinical nurse specialist. A social worker can bill insurance companies only if providing counseling for a DSM-V mental disorder diagnosis. Nursing staff can charge for administration of injectable medications and vaccines. Pharmacist services are not reimbursable in

the US. In addition, enhanced administrative personnel efforts required to coordinate all the providers and educational services are not reimbursable.

Grants, awards, donations, or alternative sources of funding have often been required, which has initially limited CKD IDC clinics to large academic institutions in the US. Data revealing cost savings with implementation of CKD IDC clinics have generated interest by health care organizations that assume responsibility for the quality, cost-effectiveness, and general health care in creating CKD IDC clinics or partnering with other businesses that offer CKD IDC. As mentioned previously, dialysis providers and related companies have developed interdisciplinary models that employ telephone calls and leverage technology to provide care. After such companies enroll a CKD patient, patient profiles may be input into their ESRD facilities as patients progress toward kidney failure. Increased outpatient dialysis starts and greater AVF and PD selection rates can help persuade funders that CKD clinics are cost-effective and sustainable.

In 2007, the average inpatient cost for the first month of dialysis in the US was $9846 per Medicare member and $22,841 per employer group health plan member.[127] This cost could be greatly reduced by increasing outpatient dialysis starts. Increased AVF rates will also lower the expense associated with ESRD. AVFs were associated with approximately $3000 lower vascular access-related expenses compared with HD catheters.[128] IDC may increase the rate of PD as the initial modality for ESRD, which is also cost-effective; according to the USRDS, the total yearly expenditure per patient in 2015 for HD was $89,000 compared with $75,000 for PD.[2] Improved advanced care planning may also defray costs. Discussing patients' wishes and values before ESRD may decrease the number of patients who start dialysis and withdraw within the first 120 days.

Studies have assessed the cost-effectiveness of CKD IDC clinics. IDC clinics show greater pre-ESRD costs compared with conventional nephrology care and likely decrease mortality which would also drive up health care costs. Despite the increased costs of an IDC team, a study in Taiwan reported saving $1200 in patients beginning dialysis.[125] After Taiwan started a nationwide multidisciplinary pay-for-performance initiative in 2006, enrollees were compared with a cohort of patients not enrolled, finding that pre-ESRD patients who attended IDC had lower hospitalization costs but higher outpatient costs.[129] However, once these patients progressed to dialysis, the outpatient, hospitalization, and dialysis costs were less than those of patients who did not receive IDC care.[130] A theoretical model evaluating the cost-effectiveness of US Medicare reimbursement for multidisciplinary care revealed a 0.23 quality of life year (QALY) gain over usual care, with a cost of $51,285 per QALY gained. Although the multidisciplinary care was more costly than standard care, it resulted in a reasonable cost per QALY gained compared with ESRD.[131]

Because financial restraints limit the ability to offer all possible services to all CKD patients, IDC clinics must prioritize the interventions with the best outcomes. Not all patients may benefit to the same degree from IDC. Choosing the patient population most likely to benefit would decrease costs. Progression of CKD may be a slow, unpredictable process, and several years may be needed to demonstrate a financial benefit, particularly if a patient changes health care systems or insurance providers. The additional time spent seeing different providers in IDC and the costs incurred by patients during travel could adversely impact patient engagement. Overcoming some of these barriers may necessitate intensive case management and is potentially costly.

PATIENT SATISFACTION WITH CKD IDC CLINICS

There is lack of data examining patient satisfaction with IDC clinics for CKD. A recent cross-sectional study from Australia, involving adult subjects with CKD, not on dialysis, who attended nurse-led CKD clinics, showed high satisfaction with the quality of care provided in the majority of those who responded to a survey questionnaire.[132] Limited waiting time about access to services, adequate coordination of care, in-depth specialty knowledge, and listening to and understanding individual patient needs were factors contributing to patient satisfaction.

CONCLUSIONS

The CKD clinic has emerged as an IDC model that encompasses patient education, medical management of CKD complications and risk factors, RRT planning, and quality improvement. The CKD IDC clinic team may include physicians, APPs, nurses, dieticians, pharmacists, and social workers. CKD IDC clinics are associated with greater patient preparedness and improved health outcomes during the transition from CKD to ESRD, especially among individuals at increased risk for CKD progression. Different models for IDC in CKD exist. Team structure and clinic goals should be tailored to local practice needs and resources. Funding for IDC services may be challenging as many insurers do not pay for these services despite the potential cost savings

of such clinics. Although CKD IDC appears promising, studies with longer follow-up and higher-risk patients are required to better understand the quality and utility of IDC teams in the management of patients with CKD.

Acknowledgments

The authors express their gratitude to Ms. Sarah Whitehouse for expert proofreading and editing of the manuscript.

References

1. Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney Int* 2011;**80**(12):1258–70.
2. U.S. Renal Data System. *USRDS 2017 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States*. Bethesda: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic, and Hematologic Diseases; 2017.
3. Canadian Institute for Health Information; 2015. www.cihi.ca.
4. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. *J Am Med Assoc* 2007;**298**(17):2038–47.
5. Stevens LA, Li S, Wang C, Huang C, Becker BN, Bomback AS, et al. Prevalence of CKD and comorbid illness in elderly patients in the United States: results from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2010;**55**(3 Suppl. 2):S23–33.
6. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**(13):1296–305.
7. Crews DC, Charles RF, Evans MK, Zonderman AB, Powe NR. Poverty, race, and CKD in a racially and socioeconomically diverse urban population. *Am J Kidney Dis* 2010;**55**(6):992–1000.
8. Devraj R, Gordon EJ. Health literacy and kidney disease: toward a new line of research. *Am J Kidney Dis* 2009;**53**(5):884–9.
9. Crews DC, McClellan WM, Shoham DA, Gao L, Warnock DG, Judd S, et al. Low income and albuminuria among REGARDS (Reasons for Geographic and Racial Differences in Stroke) study participants. *Am J Kidney Dis* 2012;**60**(5):779–86.
10. Cavanaugh KL, Wingard RL, Hakim RM, Eden S, Shintani A, Wallston KA, et al. Low health literacy associates with increased mortality in ESRD. *J Am Soc Nephrol* 2010;**21**(11): 1979–85.
11. U.S. Renal Data System. *USRDS 2016 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States*. Bethesda: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic, and Hematologic Diseases; 2016.
12. Stenvinkel P. Chronic kidney disease: a public health priority and harbinger of premature cardiovascular disease. *J Intern Med* 2010; **268**(5):456–67.
13. Parker MG, Ibrahim T, Shaffer R, Rosner MH, Molitoris BA. The future nephrology workforce: will there be one? *Clin J Am Soc Nephrol* 2011;**6**(6):1501–6.
14. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**(1):1–150.
15. Zuber K, Davis J, Rizk DV. Kidney disease education one year after the Medicare Improvement of Patients and Providers Act: a survey of US nephrology practices. *Am J Kidney Dis* 2012;**59**(6):892–4.
16. Yee JFM, Soman SS. Chronic kidney disease: changing the mean by changing the mien. In: Harrington JT, Newman ED, editors. *Great health care: making it happen*. New York: Springer Science+-Business Media; 2012. p. 143–57.
17. Crowley ST, Belcher J, Choudhury D, Griffin C, Pichler R, Robey B, et al. Targeting access to kidney care via telehealth: the VA experience. *Adv Chron Kidney Dis* 2017;**24**(1):22–30.
18. Tangri N, Kitsios GD, Inker LA, Griffith J, Naimark DM, Walker S, et al. Risk prediction models for patients with chronic kidney disease: a systematic review. *Ann Intern Med* 2013;**158**(8):596–603.
19. Tangri N, Stevens LA, Griffith J, Tighiouart H, Djurdjev O, Naimark D, et al. A predictive model for progression of chronic kidney disease to kidney failure. *J Am Med Assoc* 2011;**305**(15): 1553–9.
20. Tangri NSL, Griffith J, Tighiouart H, Djurdjev O, Naimark D, et al. *Kidney failure risk equation web calculator*. Vancouver: QxMD Software Inc; 2011. Available from: http://www.qxmd.com/calculate-online/nephrology/kidney-failure-risk-equation.
21. Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *J Am Med Assoc* 2016;**315**(2):164–74.
22. Wojciechowski P, Tangri N, Rigatto C, Komenda P. Risk prediction in CKD: the rational alignment of health care resources in CKD 4/5 care. *Adv Chron Kidney Dis* 2016;**23**(4):227–30.
23. Lerner B, Desrochers S, Tangri N. Risk prediction models in CKD. *Semin Nephrol* 2017;**37**(2):144–50.
24. Go AS, Yang J, Tan TC, Cabrera CS, Stefansson BV, Greasley PJ, et al. Contemporary rates and predictors of fast progression of chronic kidney disease in adults with and without diabetes mellitus. *BMC Nephrol* 2018;**19**(1):146.
25. Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G. Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. "Gruppo Italiano di Studi Epidemiologici in Nefrologia" (GISEN). *Kidney Int* 1998; **53**(5):1209–16.
26. Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *J Am Med Assoc* 2001;**286**(4):421–6.
27. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002;**106**(14):1777–82.
28. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation* 2004;**110**(8):921–7.
29. Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, et al. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. *Hypertension* 2005;**45**(2):198–202.
30. Atkins RC, Briganti EM, Lewis JB, Hunsicker LG, Braden G, Champion de Crespigny PJ, et al. Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. *Am J Kidney Dis* 2005;**45**(2): 281–7.
31. Lea J, Greene T, Hebert L, Lipkowitz M, Massry S, Middleton J, et al. The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: results of the African American study of kidney disease and hypertension. *Arch Intern Med* 2005;**165**(8):947–53.
32. Ruggenenti P, Perna A, Remuzzi G, Investigators GG. Retarding progression of chronic renal disease: the neglected issue of residual proteinuria. *Kidney Int* 2003;**63**(6):2254–61.

33. Ruggenenti P, Perticucci E, Cravedi P, Gambara V, Costantini M, Sharma SK, et al. Role of remission clinics in the longitudinal treatment of CKD. *J Am Soc Nephrol* 2008;**19**(6): 1213–24.
34. U.S. Renal Data System. *USRDS 2012 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States*. Bethesda: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic, and Hematologic Diseases; 2012.
35. DeSilva RN, Patibandla BK, Vin Y, Narra A, Chawla V, Brown RS, et al. Fistula first is not always the best strategy for the elderly. *J Am Soc Nephrol* 2013;**24**(8):1297–304.
36. Murtagh FE, Marsh JE, Donohoe P, Ekbal NJ, Sheerin NS, Harris FE. Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. *Nephrol Dial Transplant* 2007;**22**(7):1955–62.
37. Kurella Tamura M, Covinsky KE, Chertow GM, Yaffe K, Landefeld CS, McCulloch CE. Functional status of elderly adults before and after initiation of dialysis. *N Engl J Med* 2009;**361**(16): 1539–47.
38. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis* 2014;**63**(5):713–35.
39. Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2012;**61**(40):816–9.
40. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis* 2014;**58**(3):e44–100.
41. Langan SM, Thomas SL, Smeeth L, Margolis DJ, Nitsch D. Zoster vaccination is associated with a reduction of zoster in elderly patients with chronic kidney disease. *Nephrol Dial Transplant* 2016; **31**(12):2095–8.
42. Dinits-Pensy M, Forrest GN, Cross AS, Hise MK. The use of vaccines in adult patients with renal disease. *Am J Kidney Dis* 2005; **46**(6):997–1011.
43. Devins GM, Mendelssohn DC, Barre PE, Taub K, Binik YM. Predialysis psychoeducational intervention extends survival in CKD: a 20-year follow-up. *Am J Kidney Dis* 2005;**46**(6):1088–98.
44. Goldstein M, Yassa T, Dacouris N, McFarlane P. Multidisciplinary predialysis care and morbidity and mortality of patients on dialysis. *Am J Kidney Dis* 2004;**44**(4):706–14.
45. Stehman-Breen CO, Sherrard DJ, Gillen D, Caps M. Determinants of type and timing of initial permanent hemodialysis vascular access. *Kidney Int* 2000;**57**(2):639–45.
46. Buck J, Baker R, Cannaby AM, Nicholson S, Peters J, Warwick G. Why do patients known to renal services still undergo urgent dialysis initiation? A cross-sectional survey. *Nephrol Dial Transplant* 2007;**22**(11):3240–5.
47. Cavanaugh KL, Wingard RL, Hakim RM, Elasy TA, Ikizler TA. Patient dialysis knowledge is associated with permanent arteriovenous access use in chronic hemodialysis. *Clin J Am Soc Nephrol* 2009;**4**(5):950–6.
48. Levin A, Lewis M, Mortiboy P, Faber S, Hare I, Porter EC, et al. Multidisciplinary predialysis programs: quantification and limitations of their impact on patient outcomes in two Canadian settings. *Am J Kidney Dis* 1997;**29**(4):533–40.
49. Young HN, Chan MR, Yevzlin AS, Becker BN. The rationale, implementation, and effect of the Medicare CKD education benefit. *Am J Kidney Dis* 2011;**57**(3):381–6.
50. Davis JS, Zuber K. Implementing patient education in the CKD clinic. *Adv Chron Kidney Dis* 2013;**20**(4):320–5.
51. Fraser SD, Roderick PJ, Casey M, Taal MW, Yuen HM, Nutbeam D. Prevalence and associations of limited health literacy in chronic kidney disease: a systematic review. *Nephrol Dial Transplant* 2013;**28**(1):129–37.
52. Grubbs V, Gregorich SE, Perez-Stable EJ, Hsu CY. Health literacy and access to kidney transplantation. *Clin J Am Soc Nephrol* 2009; **4**(1):195–200.
53. Harhay MN, Xie D, Zhang X, Hsu CY, Vittinghoff E, Go AS, et al. Cognitive impairment in non-dialysis-dependent CKD and the transition to dialysis: findings from the chronic renal insufficiency cohort (CRIC) study. *Am J Kidney Dis* 2018;**72**(4):499–508.
54. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004;**164**(6):659–63.
55. Jurkovitz CT, Abramson JL, Vaccarino LV, Weintraub WS, McClellan WM. Association of high serum creatinine and anemia increases the risk of coronary events: results from the prospective community-based atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol* 2003;**14**(11):2919–25.
56. Vlagopoulos PT, Tighiouart H, Weiner DE, Griffith J, Pettitt D, Salem DN, et al. Anemia as a risk factor for cardiovascular disease and all-cause mortality in diabetes: the impact of chronic kidney disease. *J Am Soc Nephrol* 2005;**16**(11):3403–10.
57. Gosmanova EO, Le NA. Cardiovascular complications in CKD patients: role of oxidative stress. *Cardiol Res Pract* 2011;**2011**:156326.
58. Muntner P, Hamm LL, Kusek JW, Chen J, Whelton PK, He J. The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. *Ann Intern Med* 2004;**140**(1):9–17.
59. van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2011;**79**(12):1341–52.
60. Chronic Kidney Disease Prognosis C, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; **375**(9731):2073–81.
61. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004; **109**(8):1004–9.
62. Crews DC, Scialla JJ, Liu J, Guo H, Bandeen-Roche K, Ephraim PL, et al. Predialysis health, dialysis timing, and outcomes among older United States adults. *J Am Soc Nephrol* 2014;**25**(2):370–9.
63. Snyder JJ, Collins AJ. Association of preventive health care with atherosclerotic heart disease and mortality in CKD. *J Am Soc Nephrol* 2009;**20**(7):1614–22.
64. Hemmelgarn BR, Manns BJ, Zhang J, Tonelli M, Klarenbach S, Walsh M, et al. Association between multidisciplinary care and survival for elderly patients with chronic kidney disease. *J Am Soc Nephrol* 2007;**18**(3):993–9.
65. Curtis BM, Ravani P, Malberti F, Kennett F, Taylor PA, Djurdjev O, et al. The short- and long-term impact of multi-disciplinary clinics in addition to standard nephrology care on patient outcomes. *Nephrol Dial Transplant* 2005;**20**(1):147–54.
66. Ravani P, Marinangeli G, Tancredi M, Malberti F. Multidisciplinary chronic kidney disease management improves survival on dialysis. *J Nephrol* 2003;**16**(6):870–7.
67. Hallan SI, Orth SR. Smoking is a risk factor in the progression to kidney failure. *Kidney Int* 2011;**80**(5):516–23.
68. Orth SR, Hallan SI. Smoking: a risk factor for progression of chronic kidney disease and for cardiovascular morbidity and

mortality in renal patients–absence of evidence or evidence of absence? *Clin J Am Soc Nephrol* 2008;**3**(1):226–36.
69. Jardine MJ, Ninomiya T, Perkovic V, Cass A, Turnbull F, Gallagher MP, et al. Aspirin is beneficial in hypertensive patients with chronic kidney disease: a post-hoc subgroup analysis of a randomized controlled trial. *J Am Coll Cardiol* 2010;**56**(12):956–65.
70. Major RW, Oozeerally I, Dawson S, Riddleston H, Gray LJ, Brunskill NJ. Aspirin and cardiovascular primary prevention in non-endstage chronic kidney disease: a meta-analysis. *Atherosclerosis* 2016;**251**:177–82.
71. Palmer SC, Di Micco L, Razavian M, Craig JC, Perkovic V, Pellegrini F, et al. Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2012;**156**(6):445–59.
72. Tonelli M, Isles C, Curhan GC, Tonkin A, Pfeffer MA, Shepherd J, et al. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation* 2004;**110**(12):1557–63.
73. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**(9784):2181–92.
74. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int Suppl* 2013;**3**(3):259–305.
75. Ruggenenti P, Perna A, Gherardi G, Gaspari F, Benini R, Remuzzi G. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril Efficacy in Nephropathy. *Lancet* 1998;**352**(9136):1252–6.
76. Wright Jr JT, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *J Am Med Assoc* 2002;**288**(19):2421–31.
77. Agodoa LY, Appel L, Bakris GL, Beck G, Bourgoignie J, Briggs JP, et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *J Am Med Assoc* 2001;**285**(21):2719–28.
78. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**(12):851–60.
79. Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006;**354**(2):131–40.
80. Whelton PK, Carey RM, Aronow WS, Casey Jr DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;**71**(19):e127–248.
81. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;**39**(33):3021–104.
82. Group SR, Wright Jr JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**(22):2103–16.
83. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl* 2012;**2**(2):337–414.
84. Appel LJ, Wright Jr JT, Greene T, Agodoa LY, Astor BC, Bakris GL, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010;**363**(10):918–29.
85. Peterson JC, Adler S, Burkart JM, Greene T, Hebert LA, Hunsicker LG, et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann Intern Med* 1995;**123**(10):754–62.
86. van Zuilen AD, Bots ML, Dulger A, van der Tweel I, van Buren M, Ten Dam MA, et al. Multifactorial intervention with nurse practitioners does not change cardiovascular outcomes in patients with chronic kidney disease. *Kidney Int* 2012;**82**(6):710–7.
87. Babitt JL, Lin HY. Mechanisms of anemia in CKD. *J Am Soc Nephrol* 2012;**23**(10):1631–4.
88. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;**355**(20):2085–98.
89. Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006;**355**(20):2071–84.
90. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;**361**(21):2019–32.
91. https://www.fda.gov/downloads/Drugs/DrugSafety/ucm088591.pdf.
92. Besarab A, Amin N, Ahsan M, Vogel SE, Zazuwa G, Frinak S, et al. Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients. *J Am Soc Nephrol* 2000;**11**(3):530–8.
93. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). *Kidney Int Suppl* 2017;**7**(7):1–59.
94. Wang AY, Fang F, Chan J, Wen YY, Qing S, Chan IH, et al. Effect of paricalcitol on left ventricular mass and function in CKD–the OPERA trial. *J Am Soc Nephrol* 2014;**25**(1):175–86.
95. Thadhani R, Appelbaum E, Pritchett Y, Chang Y, Wenger J, Tamez H, et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. *J Am Med Assoc* 2012;**307**(7):674–84.
96. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol* 2009;**20**(9):2075–84.
97. Mathur RP, Dash SC, Gupta N, Prakash S, Saxena S, Bhowmik D. Effects of correction of metabolic acidosis on blood urea and bone metabolism in patients with mild to moderate chronic kidney disease: a prospective randomized single blind controlled trial. *Ren Fail* 2006;**28**(1):1–5.
98. Abramowitz MK, Melamed ML, Bauer C, Raff AC, Hostetter TH. Effects of oral sodium bicarbonate in patients with CKD. *Clin J Am Soc Nephrol* 2013;**8**(5):714–20.
99. Bakris GL, Pitt B, Weir MR, Freeman MW, Mayo MR, Garza D, et al. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. *J Am Med Assoc* 2015;**314**(2):151–61.
100. Kosiborod M, Rasmussen HS, Lavin P, Qunibi WY, Spinowitz B, Packham D, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *J Am Med Assoc* 2014;**312**(21):2223–33.
101. Packham DK, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G, et al. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med* 2015;**372**(3):222–31.

102. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**(12):861–9.
103. Solomon SD, Rice MM, Jablonski AK, Jose P, Domanski M, Sabatine M, et al. Renal function and effectiveness of angiotensin-converting enzyme inhibitor therapy in patients with chronic stable coronary disease in the Prevention of Events with ACE inhibition (PEACE) trial. *Circulation* 2006;**114**(1):26–31.
104. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol* 2017;**28**(9):2812–23.
105. Esnault VL, Ekhlas A, Delcroix C, Moutel MG, Nguyen JM. Diuretic and enhanced sodium restriction results in improved antiproteinuric response to RAS blocking agents. *J Am Soc Nephrol* 2005;**16**(2):474–81.
106. Vogt L, Waanders F, Boomsma F, de Zeeuw D, Navis G. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. *J Am Soc Nephrol* 2008;**19**(5):999–1007.
107. Gadola L, Noboa O, Marquez MN, Rodriguez MJ, Nin N, Boggia J, et al. Calcium citrate ameliorates the progression of chronic renal injury. *Kidney Int* 2004;**65**(4):1224–30.
108. Susantitaphong P, Sewaralthahab K, Balk EM, Jaber BL, Madias NE. Short- and long-term effects of alkali therapy in chronic kidney disease: a systematic review. *Am J Nephrol* 2012; **35**(6):540–7.
109. Robinson BM, Zhang J, Morgenstern H, Bradbury BD, Ng LJ, McCullough KP, et al. Worldwide, mortality risk is high soon after initiation of hemodialysis. *Kidney Int* 2014;**85**(1):158–65.
110. Bradbury BD, Fissell RB, Albert JM, Anthony MS, Critchlow CW, Pisoni RL, et al. Predictors of early mortality among incident US hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol* 2007;**2**(1):89–99.
111. McQuillan R, Trpeski L, Fenton S, Lok CE. Modifiable risk factors for early mortality on hemodialysis. *Int J Nephrol* 2012;**2012**:435736.
112. Astor BC, Eustace JA, Powe NR, Klag MJ, Fink NE, Coresh J, et al. Type of vascular access and survival among incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study. *J Am Soc Nephrol* 2005;**16**(5):1449–55.
113. Xue JL, Dahl D, Ebben JP, Collins AJ. The association of initial hemodialysis access type with mortality outcomes in elderly Medicare ESRD patients. *Am J Kidney Dis* 2003;**42**(5):1013–9.
114. Nee R, Fisher E, Yuan CM, Agodoa LY, Abbott KC. Pre-end-stage renal disease care and early survival among incident dialysis patients in the US Military health system. *Am J Nephrol* 2017;**45**(6): 464–72.
115. Liem YS, Weimar W. Early living-donor kidney transplantation: a review of the associated survival benefit. *Transplantation* 2009; **87**(3):317–8.
116. Meier-Kriesche HU, Kaplan B. Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: a paired donor kidney analysis. *Transplantation* 2002;**74**(10):1377–81.
117. Mange KC, Joffe MM, Feldman HI. Effect of the use or nonuse of long-term dialysis on the subsequent survival of renal transplants from living donors. *N Engl J Med* 2001;**344**(10):726–31.
118. Wu IW, Wang SY, Hsu KH, Lee CC, Sun CY, Tsai CJ, et al. Multidisciplinary predialysis education decreases the incidence of dialysis and reduces mortality–a controlled cohort study based on the NKF/DOQI guidelines. *Nephrol Dial Transplant* 2009;**24**(11): 3426–33.
119. Lacson Jr E, Wang W, DeVries C, Leste K, Hakim RM, Lazarus M, et al. Effects of a nationwide predialysis educational program on modality choice, vascular access, and patient outcomes. *Am J Kidney Dis* 2011;**58**(2):235–42.
120. Peeters MJ, van Zuilen AD, van den Brand JA, Bots ML, van Buren M, Ten Dam MA, et al. Nurse practitioner care improves renal outcome in patients with CKD. *J Am Soc Nephrol* 2014; **25**(2):390–8.
121. Richards N, Harris K, Whitfield M, O'Donoghue D, Lewis R, Mansell M, et al. Primary care-based disease management of chronic kidney disease (CKD), based on estimated glomerular filtration rate (eGFR) reporting, improves patient outcomes. *Nephrol Dial Transplant* 2008;**23**(2):549–55.
122. Bayliss EA, Bhardwaja B, Ross C, Beck A, Lanese DM. Multidisciplinary team care may slow the rate of decline in renal function. *Clin J Am Soc Nephrol* 2011;**6**(4):704–10.
123. Barrett BJ, Garg AX, Goeree R, Levin A, Molzahn A, Rigatto C, et al. A nurse-coordinated model of care versus usual care for stage 3/4 chronic kidney disease in the community: a randomized controlled trial. *Clin J Am Soc Nephrol* 2011;**6**(6):1241–7.
124. Yeoh HH, Tiquia HS, Abcar AC, Rasgon SA, Idroos ML, Daneshvari SF. Impact of predialysis care on clinical outcomes. *Hemodial Int* 2003;**7**(4):338–41.
125. Wei SY, Chang YY, Mau LW, Lin MY, Chiu HC, Tsai JC, et al. Chronic kidney disease care program improves quality of pre-end-stage renal disease care and reduces medical costs. *Nephrology* 2010;**15**(1):108–15.
126. Lee W, Campoy S, Smits G, Vu Tran Z, Chonchol M. Effectiveness of a chronic kidney disease clinic in achieving K/DOQI guideline targets at initiation of dialysis–a single-centre experience. *Nephrol Dial Transplant* 2007;**22**(3):833–8.
127. U.S. Renal Data System. *USRDS 2010 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States*. Bethesda: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic, and Hematologic Diseases; 2010.
128. Lee H, Manns B, Taub K, Ghali WA, Dean S, Johnson D, et al. Cost analysis of ongoing care of patients with end-stage renal disease: the impact of dialysis modality and dialysis access. *Am J Kidney Dis* 2002;**40**(3):611–22.
129. Lin MY, Cheng LJ, Chiu YW, Hsieh HM, Wu PH, Lin YT, et al. Effect of national pre-ESRD care program on expenditures and mortality in incident dialysis patients: a population-based study. *PLoS One* 2018;**13**(6):e0198387.
130. Hsieh HM, Lin MY, Chiu YW, Wu PH, Cheng LJ, Jian FS, et al. Economic evaluation of a pre-ESRD pay-for-performance programme in advanced chronic kidney disease patients. *Nephrol Dial Transplant* 2017;**32**(7):1184–94.
131. Lin E, Chertow GM, Yan B, Malcolm E, Goldhaber-Fiebert JD. Cost-effectiveness of multidisciplinary care in mild to moderate chronic kidney disease in the United States: a modeling study. *PLoS Med* 2018;**15**(3):e1002532.
132. Coleman S, Havas K, Ersham S, Stone C, Taylor B, et al. Patient satisfaction with nurse-led chronic kidney disease clinics: a multicenter evaluation. *J Ren Care* 2017;**43**(1):11–20.
133. Rahman M, Pressel S, Davis BR, Nwachuku C, Wright Jr JT, Whelton PK, et al. Cardiovascular outcomes in high-risk hypertensive patients stratified by baseline glomerular filtration rate. *Ann Intern Med* 2006;**144**(3):172–80.
134. Devins GM, Mendelssohn DC, Barre PE, Binik YM. Predialysis psychoeducational intervention and coping styles influence time to dialysis in chronic kidney disease. *Am J Kidney Dis* 2003; **42**(4):693–703.
135. Bayliss EA, Bhardwaja B, Ross C, Beck A, Lanese DM. Interdisciplinary team care may slow the rate of decline in renal function. *Clin J Am Soc Nephrol* 2011;**6**(4):704–10.
136. U.S. Food and Drug Administration. *FDA Drug Safety Communication: modified dosing recommendations to improve the safe use of erythropoiesis-stimulating agents (ESAs) in chronic kidney disease*. Silver Spring (MD): U.S. Food and Drug Administration; 2011. Available from: http://www.fda.gov/drugs/drugsafety/ucm259639.htm.

QUESTIONS AND ANSWERS

Question 1

A 48-year-old man with a medical history of obesity, hypertension, diabetes, and hyperlipidemia presents to an IDC CKD clinic. He is a current smoker and drinks four glasses of wine per day. His laboratory results are significant for an eGFR 29 mL/min/1.73 m^2, urinary protein-to-creatinine 2 g/g, an LDL-C 130 mL/dL, and hemoglobin 9.1 mg/dL.

Which one of the following agents may increase cardiovascular risk in this patient?

A. Angiotensin-converting enzyme inhibitor
B. Aspirin
C. ESA
D. 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor

Answer: C

Aspirin, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, smoking cessation, and blood pressure control may reduce cardiovascular risk in CKD patients. ESAs have been associated with a small increase in the risk of stroke.[69,73,90,133]

Question 2

A 78-year-old man with a history of hypertension, diabetes, and hyperlipidemia presents to an IDC CKD clinic for evaluation. His laboratory results are significant for an eGFR of 16 mL/min/1.73 m^2, UACR 30 mg/g, S[Ca] 8.9 mg/dL, S[Alb] 4.5 g/dL, serum phosphorus 4.6 mg/dL, and venous total carbon dioxide 20 mmol/L.

Which one of the following statements regarding this patient's CKD care is correct?

A. Education for this patient could delay the start of dialysis
B. The patient's nephrologist should have referred him to an IDC CKD clinic when his eGFR was greater than 30 mL/min/1.73 m^2
C. An IDC CKD clinic is required to have a social worker and pharmacist on staff
D. The patient no longer needs to see his primary physician now that he has enrolled in the CKD clinic.

Answer: A

Patient education has been shown to delay the start of dialysis by approximately 3 months.

A randomized study in advanced CKD found a 3-month delay to the start of dialysis in patients who received a single education intervention with nurse follow-up. There is conflicting evidence regarding the efficacy of CKD clinics in early CKD. In a large health maintenance organization cohort, IDC care was found to retard CKD progression. However, in a randomized trial of Canadian patients with slowly progressive early CKD, the CKD program did not improve outcomes. IDC clinics have different staffing models. Economic constraints often limit the ability of an IDC program to hire ancillary providers who cannot bill in a fee-for-service model. The IDC does not replace the need for primary care. The IDC teams needs to coordinate care with the primary care provider to ensure understanding of each provider's role.[123,134,135]

Question 3

A 64-year-old woman presents to an IDC CKD clinic with an eGFR of 20 mL/min/1.73 m^2 and a hemoglobin of 9.1 g/dL.

Which one of the following statements regarding the use of ESAs in CKD is correct?

A. ESAs should be used to delay the progression of CKD
B. ESAs should be used to normalize the patient's hemoglobin
C. ESAs should be used to prevent stroke
D. ESAs should be used to avoid blood transfusions

Answer: D

The FDA recommends that ESAs be used in CKD to avoid blood transfusions to mitigate risk for allosensitization of potential kidney allograft recipients. Normalization of hemoglobin did not improve outcomes and was associated in some studies with increased risk. ESAs did not retard the progression of CKD.[88,90,136]

Question 4

A 71-year-old woman with CKD due to diabetic nephropathy presents to her nephrologist for a routine visit. Her laboratory testing reveals an eGFR 32 mL/min/1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula), UACR 40 mg/g, S[Ca] 9 mg/dL, S[Alb] 4 g/dL, serum phosphorus 4.5 mg/dL, and serum bicarbonate concentration 21 mmol/L. Her eGFR has been stable from her last visit 6 months ago.

Which one of the following statements describing her 2-year risk of progression to ESRD is correct?

A. 3%
B. 5%
C. 7%
D. 21%

Answer: A

Using the ESRD calculator developed by Tangri et al., the estimated risk of progression to ESRD requiring dialysis or transplantation is 3%. The equation is also available as a smartphone app.[19,20]

Question 5

A 49-year-old man with type 2 diabetes presents to his nephrologist for routine follow-up. He had a renal biopsy 2 years ago for nephrotic range proteinuria that showed focal segmental glomerulosclerosis. His laboratory results show an eGFR of 35 mL/min/1.73 m^2 by the CKD-EPI equation, UACR 2800 mg/g, S[Ca] 8.7 mg/dL, S[Alb] 2.8 g/dL, serum phosphorus 4.0 mg/dL, and serum bicarbonate 22 mmol/L. His eGFR 1 year ago was 41 mL/min/1.73 m^2 and 55 mL/min/1.73 m^2 at the time of the biopsy.

Using the 2012 KDIGO guidelines, which one of the following statements best describes the rate of loss of GFR?

A. Slow progression
B. Nonprogression
C. Rapid progression
D. Regressive progression

Answer: C

Rapid progression, per 2012 KDIGO guidelines, is defined as a sustained decline in eGFR of >5 mL/min/1.73 m^2 per year. The ability to identify patients with rapid progression allows for earlier referral to CKD and RRT education, rather than simply identifying CKD stage.[14]

Question 6

A nephrology practice would like to start an Interdisciplinary Chronic Kidney Disease Clinic that focuses on education and has decided to use NKF materials: "Your Treatment, Your Choice." The practice is involved in the process of writing a business plan to support the personnel who will be involved in the education.

Which one of the following statements regarding the MIPPA benefit for CKD education is correct?

A. Patients with eGFRs >30 mL/min/1.73 m^2 are eligible for the CKD education benefit
B. Patients with an albumin:creatinine ratio >2000 mg/g are eligible for the CKD education benefit
C. Eligible patients may receive up to 10 sessions of CKD education
D. CKD education must be delivered by a physician, APP (nurse practitioner/physician assistant), or clinical nurse specialist

Answer: D

The MIPPA establishes Medicare coverage for six educational sessions for Medicare beneficiaries with stage 4 CKD (precursor to kidney failure, defined as an eGFR of 15–29 mL/min/1.73 m^2). Educational sessions must cover management of CKD (management of comorbid conditions, reducing progression to ESRD and prevention of complications) and RRT options. Both individual and group sessions are eligible for coverage. Each session should be 1 hour, with at least 31 documented minutes of time for billing purposes. The educational sessions must be delivered by a physician, APP (nurse practitioner/physician assistant), or clinical nurse specialist.[49]

CHAPTER

57

Slowing Progression of Chronic Kidney Disease

Paul Drawz[a], *Thomas H. Hostetter*[b], *Mark E. Rosenberg*[a]

[a]Division of Renal Diseases and Hypertension, University of Minnesota Medical School, Minneapolis, MN, United States; [b]Department of Medicine, University of North Carolina, Chapel Hill, NC, United States

Abstract

Early identification of chronic kidney disease (CKD) provides an opportunity to implement therapies to improve kidney function and slow progression. This chapter will first review the epidemiology of progression to define the normal and CKD-related rate of decline in kidney function and discuss the competing risks between death and development of end-stage renal disease. Common pathophysiologic mechanisms underlie the progression of most kidney diseases, including glomerular capillary hypertension, renal fibrosis induced by renal inflammation, podocyte loss, proteinuria, and activation of systems such as the renin–angiotensin–aldosterone system and intrarenal activation of developmental and injury pathways. These pathophysiologic factors present potential targets for therapy. The importance of controlling blood pressure will be discussed along with the target blood pressure in CKD patients. Therapy directed at inhibiting the renin–angiotensin–aldosterone system remains the mainstay of treatment with single agent inhibition of this system being as good as dual blockade with fewer adverse effects. Other therapies include glycemic control, correction of metabolic acidosis, and dietary protein restriction. Emerging therapies targeting endothelin, uric acid, kidney fibrosis, oxidant stress, and kidney augmentation hold promise for the future.

INTRODUCTION

The increasing incidence and prevalence of chronic kidney disease (CKD) places significant health burdens on patients and costs on our already stressed healthcare system. Screening programs and the reporting of estimated glomerular filtration rate (eGFR) are leading to earlier identification of CKD, allowing a focus on what can be done to slow progression of CKD once it is identified. Progression of kidney disease is defined as a loss of GFR over time and includes the need to initiate renal replacement therapy (RRT). Common mechanisms underlie progression of kidney disease and form the basis for therapeutic interventions. Established and emerging therapies should be rational, based on solid evidence and easily and inexpensively applied widely to diverse populations.

EPIDEMIOLOGIC ISSUES

Rates of Progression

Once the diagnosis of CKD is established, it is important to monitor GFR and magnitude of proteinuria to assess evidence of progression. The frequency of measurement of these parameters will depend on the severity and course of CKD, following the general principle that more frequent monitoring is needed as kidney disease progresses. Progression of CKD is variable depending on the population being studied, the underlying disease, the adequacy of therapy, the presence of risk factors, and other unknown factors. To provide perspective on CKD progression it is important to note the decline in kidney function in various populations. The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the evaluation and management of CKD reviewed the available longitudinal population studies and showed a decline in kidney function of 0.3–1.0 mL/min/1.73 m^2/year in those without proteinuria or comorbidity.[1] Rates were two to three times higher in those with proteinuria and/or significant comorbidity.

In patients with established CKD, more rapid rates of progression were present. For example, in the Modification of Diet in Renal Disease (MDRD) study the rate of progression ranged from 2.3 to 4.5 mL/min/year.[2] In a study of 4231 patients with a GFR less than 60 mL/min/1.73 m^2, the mean decline in GFR was 2.65 mL/min/1.73 m^2/year.[3] Based on these data, KDIGO defines rapid progression as a sustained decline in eGFR of more than 5 mL/min/1.73 m^2/year. This population of

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00057-7

rapid progressors should be the target of more aggressive intervention, as they are at higher risk for the development of end-stage renal disease (ESRD) and cardiovascular complications.

Predicting Risk of Progression

An important tool to aid clinicians in their approach to progression is risk prediction formulas that estimate the likelihood of developing ESRD. Tangri and colleagues, in a cohort of patients with stage 3–5 CKD, developed a four-variable risk equation.[4–7] The formula is based on age, sex, eGFR, and albumin:creatinine ratio. It is available online (https://qxmd.com/calculate/calculator_308/kidney-failure-risk-equation-4-variable). This formula was able to predict ESRD at 2 and 5 years and can be used by clinicians to target therapies to those at highest risk for progression.

Competing Risk of Cardiovascular Disease

Not all patients with CKD progress to ESRD. More patients will die before they reach ESRD, predominantly of CVD. These competing risks between ESRD and CVD depend on the population of patients studied, with the general finding that older patients with milder CKD are more likely to die of CVD, whereas younger patients with more severe CKD are more likely to progress to ESRD.[8–11] Emphasis should be placed on both reducing cardiovascular risk and slowing progression of CKD.

PATHOPHYSIOLOGIC MECHANISMS OF PROGRESSION

Common mechanisms underlie the progression of most kidney diseases. These mechanisms initially involve adaptive changes to loss of nephrons that eventually have maladaptive consequences. Clinical manifestations of progression common to most renal diseases are decreased GFR, hypertension, and proteinuria. Common pathologic findings are glomerulosclerosis, tubulointerstitial fibrosis, inflammation, tubular atrophy, and capillary loss. These common mechanisms provide important targets for therapeutic intervention. A number of excellent reviews on pathophysiology of CKD are available.[12–14]

Glomerular Hyperfiltration

The best described common mechanism of progression, and the one that changed the paradigmatic way we approach CKD, is that of glomerular hyperfiltration.[15–18] Reductions in nephron number cause increased filtration rate in residual nephrons—the greater the degree of nephron loss, the greater the compensatory increase in the function of the residual units. After these seemingly adaptive increases in function, pathologic changes appear, resulting in the development of glomerular sclerosis. Not only does graded reduction in renal mass lead to graded increases in injury of the residual nephrons, but renal ablation also hastens injury in other experimental renal diseases. For example, diabetic animals have greater degrees of glomerular sclerosis if they undergo unilateral nephrectomy.[19] In addition, concurrent dietary manipulations that modify renal hemodynamics also alter the degree to which any given level of reduction of renal mass provokes subsequent glomerulosclerosis. In particular, dietary protein restriction lessens renal injury with reductions in renal mass in experimental models. Because higher dietary protein elevates whole-kidney glomerular and single-nephron filtration rate, its combination with compensatory hyperfiltration exaggerates and its restriction lessens disease.[20]

There appears to be a critical amount of renal mass that has to be lost before hyperfiltration leads to adverse consequences. Unilateral nephrectomy, such as occurs in kidney donors, is not usually enough to lead to significant progressive kidney disease.[21] On the other hand, some have suggested that loss of renal mass, perhaps at susceptible periods of development or in susceptible individuals, may be associated with subsequent injury. For example, unilateral renal agenesis is a relatively rare congenital condition, but it has been associated with proteinuria and sclerosis of the single kidney as patients age.[22] Conceivably in this circumstance, the solitary kidney has subtle developmental defects that render it susceptible to injury. Likewise, progressive damage to the remaining kidney after removal of a contralateral diseased kidney may reflect unrecognized bilateral diseases.[23] However, with greater loss of renal mass, injury may be seen in humans. One study of subtotal nephrectomy for aggressive renal cancer suggested sclerotic injury develops in the spared but hypertrophied glomeruli.[24] Perhaps as in animal studies, some variations occur among different groups of people and susceptibility to loss of renal mass may be more pronounced in some individuals.

If increased single-nephron filtration causes subsequent injury, the question arises regarding what determinant of filtration is responsible for the damage. Filtration is governed by the imbalance of hydrostatic and oncotic pressures across the glomerular capillary wall. The increase in glomerular capillary pressure seems to be preeminent among the determinants of increased single-nephron filtration after renal mass reduction in aggravating progressive sclerotic changes.[15] In most disease models, the capillary

hypertension can be attributed to decreases in afferent vascular resistance within the kidney. In most cases this is accompanied by arterial hypertension, with resultant excess transmission of the arterial pressure to the glomerulus. The efferent vascular resistance often is maintained at a level close to normal. One can envision this latter phenomenon as also contributing to the maintenance of glomerular pressure because postglomerular resistance fails to decrease in parallel with the preglomerular resistance.

The remarkable efficacy of drugs that reduce angiotensin II (AII) levels or action in models with glomerular hypertension and in clinical studies support this view based on the following considerations. This response to angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) suggests that AII may in some fashion maintain increased glomerular pressures. As one of its prime actions, AII preferentially constricts the efferent arteriole. On this basis, AII often has been invoked as maintaining efferent tone in the face of afferent vasodilation, the latter mediated by less well-defined vasodilators. Prostaglandin species and nitric oxide may disproportionately play roles in this portion of the renal circulation. Glomerular hypertension results and is especially severe if arterial hypertension conspires with these intrarenal adjustments.

The potential for glomerular capillary pressures to induce progressive sclerotic injury seems clear. This link raises the question of how increased glomerular pressure is translated into cellular pathology. Following renal mass reduction, renal hypertrophy occurs including enlargement of glomeruli. Increased glomerular tension, as predicted by the Laplace law, may represent a final common pathway by which compensatory growth and/or glomerular hypertension result in glomerular injury.[25] Greater wall tension on glomerular capillaries would occur in larger glomeruli leading to more injury.[25] Elevated glomerular pressure may also lead to podocyte damage and increased protein leakage across the glomerular basement membrane, an initiating factor in the development of glomerular sclerosis.[26] Mechanical stress, as could occur with glomerular hypertension, can also lead to adverse effects on glomerular endothelial and mesangial cells.[27–29]

Measurement of SNGFR in Humans and Its Implications

Denic and colleagues reported estimates of single nephron glomerular filtration rate (SNGFR) in humans.[30] The subjects were living kidney donors, and SNGFR was calculated by dividing total GFR (iothalamate clearance) by nephron number derived by CT scan and kidney biopsy. The resulting value of 80 nL/min was higher but consistent with animal measurements derived from direct sampling of glomerular ultrafiltrate.[15] As discussed above, glomerular hyperfiltration occurs in models of diabetes and following reduction of renal mass. The increased glomerular pressures and flows that drive hyperfiltration play a role in progression of kidney diseases. In the Denic study, an elevated SNGFR was associated with risk factors for progression including obesity, a family history of ESRD, and more glomerulosclerosis, suggesting compensation in remaining nephrons to maintain total GFR. Measurement of SNGFR provides a unique window into the inner workings of the kidney and in many ways confirms the experimental models of kidney disease progression. Although far from a routine clinical test, the level of SNGFR may be an important determinant of renal reserve, dictating the aggressiveness of therapy to slow progression of kidney diseases.

In a follow-up study these investigators demonstrated the number of nonsclerotic glomeruli decreased with aging and to a greater extent than the decrease seen in cortical volume (Figure 57.1).[31] This age-related loss of nephrons was associated with older age, shorter height, family history of ESRD, higher serum uric acid levels, and lower measured GFR and was not always reflected by the degree of glomerulosclerosis seen on kidney biopsy, suggesting resorption of sclerotic glomeruli.

Renal Fibrosis

The extent of tubulointerstitial disease is a major risk factor and predictor of progression in all forms of kidney disease.[32,33] Progression of CKD is better correlated with the degree of interstitial fibrosis than with glomerular damage.[34] However, controversy exists regarding whether the driver for progression associated with tubulointerstitial fibrosis is the interstitial fibrotic process that subsequently destroys healthy nephrons, or whether fibrosis occurs as a consequence of tubular injury as part of healing.[35] Explanations for how a glomerular disease can lead to scarring in the interstitium have been elegantly reviewed.[32,36] Inflammation plays an important role in leading to tubulointerstitial fibrosis mediated by a variety of cytokines, chemokines, and growth factors, including monocyte chemoattractant protein-1, nuclear factor κB (NF-κB), transforming growth factor β (TGF-β), platelet-derived growth factor (PDGF), interleukin-10 (IL-10), and others.[37]

Loss of Podocytes

Loss of podocytes is commonly seen in progressive kidney disease, and plays a role in accelerating progression.[38] Damage to podocytes leads to disruption of the glomerular filtration barrier and to loss of separation between the glomerular tuft and Bowman's capsule.[22] The

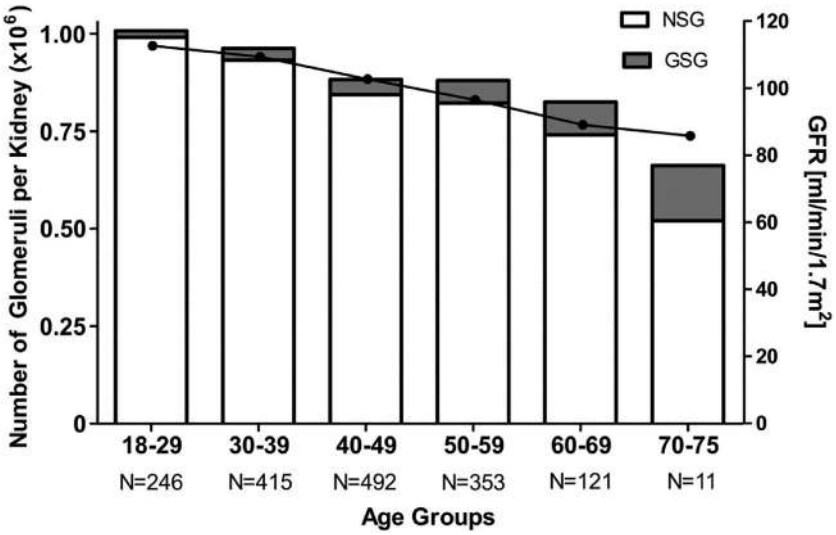


FIGURE 57.1 Nephron number (left axis) and glomerular filtration rate (GFR) (right axis) in different age groups of kidney donors demonstrating a decrease in both measurements with aging. *GSG*, globally sclerotic glomeruli; *NSG*, nonsclerotic glomeruli. *Reproduced from Reference 31 with permission from American Society of Nephrology.*

consequence is focal glomerulosclerosis, or if inflammation is involved, a proliferative crescenteric process that can lead to obliteration of glomeruli or obstruction of the glomerular tubular junction and loss of filtration. An important role for podocyte injury as a pathogenic factor is supported by experimental models of podocyte-specific injury and the identification of podocyte-specific genes as a cause for genetic forms of focal segmental glomerulosclerosis (FSGS).[14,39] Parietal epithelial cells lining Bowman's space have been recognized as playing a role in progression of kidney disease and as a potential therapeutic target.

The Notch signaling pathway plays a critical role in kidney development, after which its activity is decreased.[40] Reactivation of Notch signaling in glomerular cells occurs in such disorders as FSGS, diabetic nephropathy, HIV-associated nephropathy (HIVAN) and lupus nephritis, where it may play a pathogenic role in progression of kidney disease. Supporting evidence for such a role comes from experimental models demonstrating sustained activation of Notch signaling in podocytes results in podocyte dedifferentiation, detachment, and apoptosis, leading to albuminuria, glomerulosclerosis and death secondary to renal failure.[41,42] Inhibition of Notch signaling improves the course of experimental diabetic nephropathy, suggesting Notch signaling is a potential therapeutic target in human disease.[43,44]

Renin–Angiotensin–Aldosterone System

The renin–angiotensin–aldosterone system (RAAS) plays an important pathophysiologic role in the progression of CKD.[26,45–47] Mechanisms for these adverse effects include glomerular hypertension secondary to preferential maintenance of efferent arteriolar tone, promotion of glomerulosclerosis and systemic and glomerular hypertension. AII can also have direct effects of increasing mesangial cell proliferation and matrix expansion. Profibrotic actions mediated by AII include increases in fibrotic growth factors such as basic-fibroblast growth factor, TGF-β, PDGF, and plasminogen activator inhibitor-1.[48–52] Activation of the transcription factor NF-κB, enhanced expression of cell adhesion molecules, stimulation of proinflammatory cytokines, monocyte activation, and generation of reactive oxygen species are other ways in which AII can contribute to renal damage.[10,26,28,29,52–55] Aldosterone, in addition to AII, may contribute to damage both by raising vascular pressures and by activating profibrotic pathways.[56–58]

Proteinuria

Proteinuria is a risk factor for the development of ESRD in the general population and a powerful predictor of renal outcomes in CKD patients.[59–61] Reduction of proteinuria in clinical trials is associated with improved renal outcomes.[62–64] The fact that proteinuria is a prognostic factor in most kidney diseases has given rise to the hypothesis that proteinuria may be a direct pathogenic factor involved in transferring glomerular injury to the tubulointerstitium.[62] Potential mechanisms include damage by toxic molecules in proteinuric tubular fluid, excessive reabsorption, and degradation of proteins by tubular cells leading to spillage of lysosomal enzymes into the cytoplasm with intracellular toxic effects on tubular cells, and production of profibrotic and proinflammatory molecules produced by tubular cells as a consequence of the proteinuria.

There is no uniform consensus regarding the "proteinuria hypothesis," because not all studies have found deleterious effects of filtered proteins on tubular cells.[28] Furthermore, tubulointerstitial damage is not a feature of minimal change disease, in which heavy proteinuria is found.[26] A counterargument is that the selectivity of the proteinuria is also an important factor, and that when the proteinuria is highly selective as in minimal change disease, there is less damage to tubules and interstitium.

THERAPY TO SLOW PROGRESSION OF CKD

The diagnosis of CKD and assessment of the tempo of progression set the stage for implementing therapies directed at slowing progression and preventing the development of ESRD. Established therapies exist to slow progression of CKD and emerging therapies are being tested for effectiveness in CKD patients (Table 57.1).

Blood Pressure Control

CKD and hypertension are interrelated. CKD is associated with a number of physiologic alterations that lead to elevated blood pressure including sodium retention, increased sympathetic tone, and endothelial dysfunction. The majority of patients with CKD have hypertension, and its prevalence is over 90% among patients with moderate to severe CKD.[65] On the other hand, hypertension may be a cause of and accelerate progression of CKD.[66,67] Given this tight relationship between CKD and hypertension, and early prepost studies that demonstrated a potential slowing of progression of CKD associated with administration of antihypertensive medications, it has long been presumed that blood pressure control is critical to slowing the progression of CKD.[68] In fact, the KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease claimed that "lowering blood pressure in CKD patients reduces the rate of CKD progression."[69] Unfortunately, although observational studies demonstrate that lower-achieved blood pressures are associated with slower decline in renal function, the assumption that lower blood pressure targets slow progression of CKD is not supported by evidence from multiple randomized controlled trials (RCTs).

TABLE 57.1 Interventions to Slow Progression of Chronic Kidney Disease (CKD)

ESTABLISHED THERAPIES
Hypertension control
Renin–angiotensin–aldosterone system blockade
Dietary protein restriction
Correction of metabolic acidosis
Glycemic control
Comprehensive CKD clinics
EMERGING THERAPIES
Endothelin antagonists—avosentan, atrasentan
Anti-inflammatory agents—bardoxolone, pentoxifylline
Antifibrotic agents—pirfenidone, TGF-β antibodies
Specific glucose-lowering agents (SGLT2 inhibitors, GLP-1 analogues)
Cellular therapies

Blood Pressure Target to Slow Progression of CKD

A number of studies have evaluated the effect of standard vs. intense blood pressure targets on progression of CKD. All failed to demonstrate slowing of progression of CKD with the more intense blood pressure targets (Table 57.2). Among the 840 participants in the MDRD study, there was no difference in decline in GFR over 2.2 years of follow-up between the usual blood pressure target (mean arterial pressure [MAP] 107 mm Hg [approximately 140/90 mm Hg]) and the low blood pressure target (MAP target 92 mm Hg [approximately 125/75 mm Hg]) groups.[2] In the African American Study of Kidney Disease and Hypertension (AASK) trial, 1094 African Americans with CKD but without diabetes were randomized to a usual blood pressure target (MAP 102–107 mm Hg) and a low blood pressure target (MAP 92 mm Hg).[73] As in MDRD, there was no difference in GFR decline between groups and the occurrence of a 50% decline in GFR, ESRD, death, or a composite of the three was similar in both groups. Similar lack of reduction in CKD progression was observed in three smaller trials comparing standard and low blood pressure targets (REIN-2, Lewis et al., and Toto et al.) (Table 57.2).[70–72] Although the primary results of these trials do not indicate a benefit of lowering blood pressure, secondary analyses have revealed potential benefits in certain subgroups, such as in participants with proteinuria.

In secondary analyses of the MDRD study, there was a benefit of the low blood pressure target in the minority of participants with significant proteinuria (>3 g/day) (Figure 57.2).[2] Additionally, in long-term passive follow-up, the low blood pressure target was associated with a reduction in the development of ESRD in the entire cohort.[76] Similarly, in the long-term follow-up of the AASK cohort, the intense blood pressure target was associated with a reduction in a composite outcome of doubling of serum creatinine concentration (S[Cr]), ESRD, or death among the minority (33%) of

TABLE 57.2 Outcomes of Trials Evaluating the Effect of a Low Blood Pressure Target on Progression of Renal Disease

Study/Patients	N	Low BP Target (mm Hg)	Standard BP Target (mm Hg)	Outcome	Secondary Analyses
Nondiabetic, hypertensive, CKD[70]	77	DBP 65–80	DBP 85–95	GFR slope (mL/min/1.73 m^2/yr) −0.31 vs −0.050 p > 0.25	NR
Type 1 diabetic nephropathy[71]	129	MAP 92	MAP 100–107	Change in iGFR (mL/min/1.73 m^2) 62–54 vs 64–58 p = 0.62	Median proteinuria 535 vs. 1723 mg/24 h p = 0.02
REIN-2 non-DM proteinuria[72]	335	DBP <90	<130/80	ESRD HR 1.00 (95% CI 0.61–1.64) p = 0.99	No difference in urinary protein excretion
MDRD (Study 1) GFR[2] 25–55 mL/min/1.73 m^2	585	MAP <92	MAP 107	GFR slope (mL/min/3 yrs) 10.7 vs. 12.3 p = 0.18	**1.** Benefit of low BP target in patients with significant proteinuria **2.** Decreased risk of kidney failure in low BP target arm in long-term follow-up HR 0.68 (95% CI 0.57–0.82)
MDRD (Study 2) GFR[2] 13–24 mL/min/1.73 m^2	255	MAP <92	MAP 107	GFR slope (mL/min/yr) 3.7 vs. 4.2 p = 0.28	
AASK—nondiabetic AA with CKD[73]	1094	MAP <92	MAP 102–107	GFR slope (mL/min/1.73 m^2/yr) −2.21 vs. −1.95 p = 0.24	Long-term follow-up **1.** No difference in doubling of S [Cr], ESRD, or death overall **2.** Decreased risk of composite among patients with a UPCR>0.22 (HR 0.73)
SPRINT—nondiabetic with CKD[74]	2646	SBP <120	SBP <140	Decrease in eGFR of ≥50% or ESRD HR 0.90 (95% CI 0.44–1.83)	

AA, African American; *BP*, blood pressure; *CKD*, chronic kidney disease; *DBP*: diastolic blood pressure; *GFR*: glomerular filtration rate; *HR*: hazard ratio; *iGFR*, iothalomate GFR; *MAP*, mean arterial pressure; *NR*: not reported; *UPCR*, urine protein:creatinine ratio.

Adapted from Reference 75, with kind permission from Springer Science and Business Media.

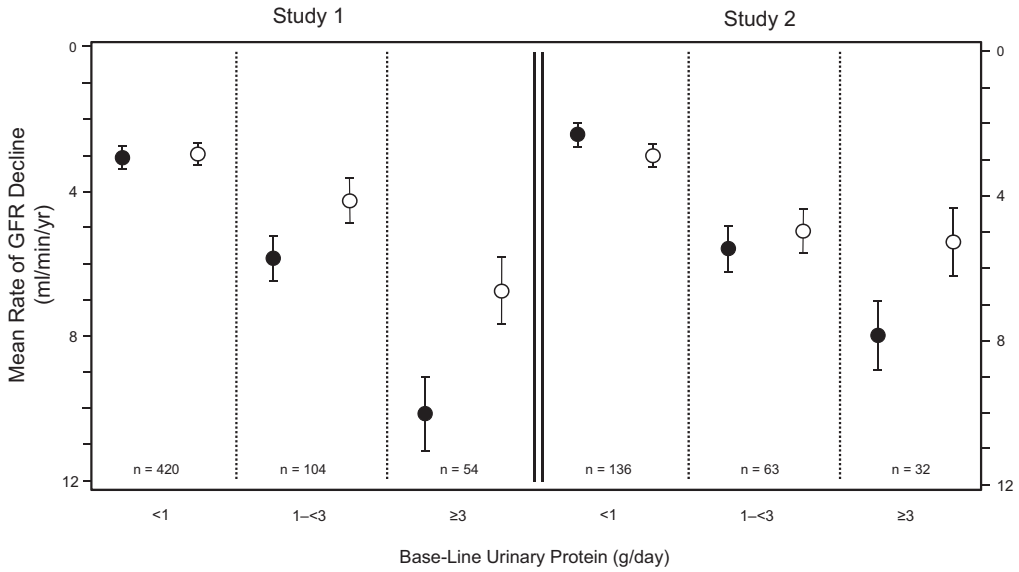


FIGURE 57.2 Renal function decline in the Modification of Diet in Renal Disease study by baseline urine protein. The *open circles* are the low blood pressure target arm (mean arterial pressure [MAP] 92 mm Hg) and the *closed circles* are the usual blood pressure target arm (MAP 107 mm Hg). *Reproduced from Reference 2 with permission from Massachusetts Medical Society, © 1994.*

participants with proteinuria (urine protein:creatinine ratio [UPCR] >0.22 g/g). In combined analyses of individual-level data from both MDRD and AASK that included posttrial follow-up, intense blood pressure lowering was associated with reduced risk for ESRD (HR 0.88, 95% CI 0.78−1.00) and all-cause mortality (HR 0.87, 95% CI 0.76−0.99).[77] The results of these secondary analyses have led some experts to recommend lower blood pressure targets in CKD patients with proteinuria.

The more recent results from the Systolic Blood Pressure Intervention Trial (SPRINT) are consistent with prior studies. SPRINT randomized 9361 participants, of whom 2646 had CKD at baseline, to an intense blood pressure target (systolic BP <120 mm Hg) or a standard blood pressure target (<140 mm Hg). After a median follow-up of 3.3 years, the study was terminated early due to a significant reduction in the primary cardiovascular composite outcome in the intensive treatment group.[78] There was no significant effect modification by baseline CKD status. Among those with CKD, the intensive treatment was associated with a reduction in the primary cardiovascular outcome and all-cause mortality. The prespecified kidney outcome was a composite of ≥50% decrease in eGFR from baseline or ESRD. Although the number of events was low, there was no difference in the kidney outcome between the intensive and standard groups (HR 0.90, 95% CI 0.44−1.83) (Figure 57.3).[74] These results have been incorporated in the recent clinical practice guideline from the American Heart Association/American College of Cardiology that recommends a blood pressure target of ≤130/80 mm Hg.[79] Although the appropriate blood pressure goal to reduce progression of CKD is unknown, a target blood pressure of ≤130/80 mm Hg is reasonable given the benefits with regard to CVD risk reduction.

Other Methods of Measuring Blood Pressure

The previous discussion of BP targets as they relate to slowing progression of CKD is predicated on measurement of BP in the clinic. Methods for measuring BP outside the clinic have been available for over 30 years.[80] Measurement of BP outside the clinic may provide a more accurate and independent assessment of the risk of CVD and mortality associated with hypertension.[75] Patients with elevated BP outside the clinic, with either normal clinic BP (masked hypertension) or elevated clinic BP (sustained hypertension), are at increased risk for adverse clinical events, regardless of their clinic BP.[81] In patients with CKD, blood pressures measured at home and with ambulatory blood pressure monitoring (ABPM) are stronger and independent predictors of ESRD.[71,72] An advantage of ABPM is the ability to measure BP throughout the day and night. Nighttime BP and the relative decline in BP from day to night, otherwise known as dipping status, are independent predictors of cardiovascular events and all-cause mortality.[82]

Despite the potentially stronger relationship between home and ambulatory blood pressure and adverse outcomes, further research is needed to determine whether modifying antihypertensive treatment based on home and ambulatory blood pressure reduces adverse clinical events.

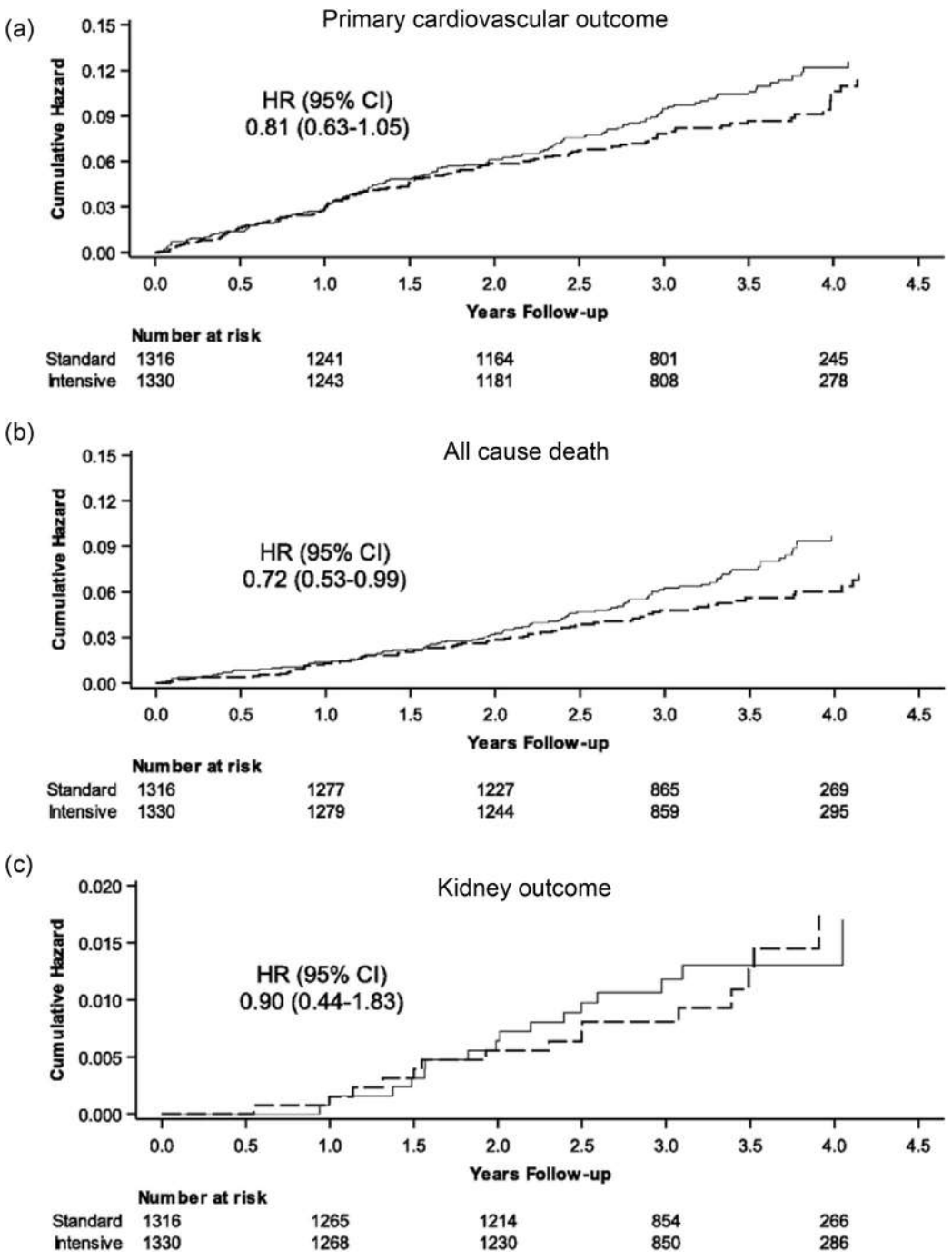


FIGURE 57.3 Outcomes in Systolic Blood Pressure Intervention Trial participants with CKD. Dashed lines are the intensive group (SBP<120 mm Hg) and solid lines are the standard group (SBP <140 mm Hg). (a) Primary cardiovascular outcome (composite of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure, and death from cardiovascular cause). (b) All cause death outcome. (c) Kidney outcome (composite of a ≥50% decrease in estimated glomerular filtration rate (eGFR) from baseline or the development of end-stage renal disease. Significant differences favoring the intensive group are demonstrated in panels a and b, but no difference was seen in the renal outcome shown in panel c. *Reproduced from Reference 74 with permission from American Society of Nephrology.*

Finally, it is now feasible to measure central aortic blood pressure in the clinic.[83] Newer devices allow measurement of 24-hr ambulatory central blood pressure.[84] Whether central blood pressure is a better predictor of progression of renal disease than peripheral blood pressure is unknown, but central blood pressure may be important in patients with CKD, given the relationship between renal function and aortic stiffness.[85] There are no randomized trials to guide clinicians regarding the use of clinic BP targets as opposed to ambulatory/

newer BP targets in patients with CKD. Despite this, the new AHA/ACC guidelines and the US Preventive Services Task Force recommend obtaining BP measurements outside the clinic in the diagnosis of hypertension, and to guide therapy for those on antihypertensive medications.[86–88] Further research is needed to define the clinical utility of blood pressures measured outside the clinic.

Inhibition of the Renin–Angiotensin–Aldosterone System

RAAS inhibition remains the major strategy for slowing progression of CKD. The system can be inhibited at multiple steps, with a number of different drugs that include ACEIs, ARBs, renin inhibitors, and aldosterone antagonists. Animal studies, initially in the remnant kidney model, demonstrated a beneficial effect of ACEIs on limiting kidney injury.[89] Subsequent animal studies demonstrated a preferential effect of ACEIs over other antihypertensives that achieved similar reductions in systemic blood pressure in arresting progressive kidney disease.[90,91] The beneficial effects are related in part to efferent arteriolar vasodilation and subsequent decrease in glomerular hypertension, effects mediated by inhibiting the preferential role of AII on this vessel, but also through ACEI increasing bradykinin levels.[92] These and other studies laid the foundation for the first clinical studies demonstrating ACEI can slow the progression of diabetic kidney disease in humans.

Evidence has mounted over the years that RAAS inhibition has preferential effects on reducing proteinuria and slowing progression of CKD compared to other agents. The magnitude of these beneficial effects of RAAS blockade is estimated to be about a 20% risk reduction. A beneficial effect has been demonstrated in both diabetic and nondiabetic kidney disease, in early and late-stage CKD, and with ACEIs and ARBs.[93–99] In diabetics, most studies have demonstrated RAAS blockade slows progression from normoalbuminuria to microalbuminuria, from microalbuminuria to overt diabetic nephropathy, as well as the progression of established diabetic nephropathy.[94,96,100–102] However, in a trial in normotensive, normoalbuminuric type 1 diabetic patients, with normal GFR, early treatment with ARBs or ACEIs did not slow nephropathy progression, assessed as either the fraction of glomerular volume occupied by mesangium or the incidence of microalbuminuria.[103]

Inhibition of renin is another means of interrupting the RAAS. Addition of a renin inhibitor to an ARB reduced proteinuria in patients with diabetic nephropathy.[104–106] However, add-on therapy with a renin inhibitor was associated with adverse effects.

Dual Blockade of the RAAS

On the basis of preclinical studies, and the reasoning that single agents directed at inhibiting the RAAS do not completely block the system, studies combining drugs to inhibit the RAAS pathway at more than one site have been performed. The most common combination has been an ACEI plus an ARB. Initial animal and clinical studies demonstrated a beneficial effect of dual therapy on the surrogate endpoint of proteinuria. Also, meta-analysis demonstrated a greater reduction in proteinuria with combination therapy but did not examine GFR endpoints.[107] The field was misled by the COOPERATE study that demonstrated a dramatic beneficial effect of dual blockade on long-term renal outcomes, but the study was subsequently retracted due to inconsistencies in the data.[108] Enthusiasm for dual therapy was subsequently reduced by the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial.[109] In this study 25,620 subjects with established atherosclerotic vascular disease or diabetes with end-organ damage were randomized to receive the ACEI ramapril, ARB telmisartan, or both drugs. Combination therapy was associated with a higher occurrence of the composite primary renal outcome of dialysis, doubling of S[Cr] and death. Interestingly there was dissociation between a greater reduction in proteinuria with combination therapy but worse renal outcomes.

The ALTITUDE trial studied the effects of adding the renin inhibitor aliskiren to ACEI or ARB therapy.[106] This study was terminated early secondary to adverse outcomes including hyperkalemia, hypotension, and stroke. The Veterans Administration multicenter trial in type 2 diabetic patients with nephropathy, examining the effects of combining losartan and lisinopril compared with losartan alone (NEPHRON-D), was stopped because of a higher incidence of acute kidney injury (AKI) and hyperkalemia in the combination group.[110]

In a systematic review and meta-analysis of dual blockade compared with monotherapy, RCTs stratified for patients with and without heart failure were analyzed.[111] This analysis was not directed at patients with CKD. Dual blockade did not improve all cause or cardiovascular mortality but was associated with a reduction in hospitalizations for heart failure compared to monotherapy. However, dual therapy was associated with a higher incidence of hypotension, hyperkalemia, acute renal failure, and withdrawal of treatment because of adverse events. A meta-analysis examining the safety of combined vs. single RAAS blockade in CKD patients demonstrated a greater reduction in proteinuria and GFR, without any benefit on the outcomes of doubling of S[Cr], hospitalization, or

mortality.[112] Similar to other studies, combination therapy was associated with a higher risk of hyperkalemia and hypotension. Based on these studies, dual blockade of RAAS is not recommended.

Despite these studies, the issue of dual blockade remains an active one. An ongoing trial, Preventing ESRD in Overt Nephropathy of Type 2 Diabetes (VALID), is comparing the effects of dual inhibition of the renin–angiotensin system on ESRD and cardiovascular events in type 2 diabetic patients with overt nephropathy (S[Cr] between 1.8 and 3.2 mg/dL and spot morning urine albumin:creatinine ratio (UACR) >1000 mg/g [ClinicalTrials.gov: NCT00494715]). Patients will be treated for 3 years to comparable BP levels with the ACEI benazepril, the ARB valsartan, or combination therapy using halved dosages of the ACEI and ARB together.[113]

Aldosterone Antagonism

Aldosterone antagonists have beneficial effects in many different animal models of kidney disease, whether used alone or when combined with other RAAS inhibitors.[114,115] In human disease, both nonselective antagonists such as spironolactone, and selective antagonists such as eplerenone, have been studied. Most studies have only examined the surrogate endpoint of proteinuria and have demonstrated that aldosterone antagonists reduce proteinuria compared to ACEIs or ARBs alone.[116] These studies were small, with short-term follow-up, and have not addressed the effects of aldosterone antagonism on progression of CKD. Some studies have examined the effects of aldosterone antagonists on GFR but have not shown a change in end of study GFR. A beneficial effect on reducing blood pressure has been demonstrated in many studies. Adverse effects of aldosterone antagonism, including gynecomastia and especially hyperkalemia, limit the attractiveness of this approach. These risks coupled with the lack of conclusive evidence for efficacy argue against using aldosterone blockade to slow progression of CKD at this time.

Trials are ongoing examining the effects of finerenone, a nonsteroidal mineralcorticoid receptor antagonist that is more selective than spironolactone and has greater receptor affinity than eplerenone. The Mineralcorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy resulted in a dose-dependent reduction of proteinuria after 90 days of treatment with finerenone in diabetic patients with albuminuria (mostly on an ACEI or ARB).[117] Hyperkalemia developed in 1.8% of patients compared to none in the placebo group.

Other Therapeutic Considerations

Dietary Protein Restriction

In most experimental renal diseases, increased protein intake is associated with progressive decline in GFR, increases in proteinuria, and worse glomerulosclerosis.[20,118] Unfortunately, the concept of restricting protein intake to slow progression of CKD has not easily translated to the clinic.[119,120] In the MDRD study, the largest RCT, no reduction in progression of CKD was observed with dietary protein restriction.[2] However, a Cochrane review of 10 randomized trials including 2000 nondiabetic participants found that low-protein diets reduced the incidence of a composite of death or ESRD.[121] Additionally, there appeared to be a dose–response effect of dietary protein restriction in CKD patients.[121] A significant benefit was observed when a very low–protein diet (0.3–0.6 g/kg/day) was compared to a higher-protein diet (RR 0.63, 95% CI 0.48–0.83). There was only marginal benefit when a low-protein diet (0.6 g/kg/day) was compared to a higher-protein diet (RR 0.76, 95% CI 0.54–1.05). No analysis was performed evaluating the impact of low-protein diet on development of ESRD. Despite the findings from this review, the negative results from MDRD and the difficulty in counseling patients to follow low-protein diets has led to the infrequent prescription of low-protein diets for patients with CKD. Avoidance of high-protein diet is recommended for all patients with CKD in the absence of malnutrition. With the appropriate monitoring and nutritionist support, it is reasonable to counsel patients with CKD to target a protein intake of 0.6 g/kg/day.

Bicarbonate Supplementation

Moderate and severe CKD is associated with metabolic acidosis *via* multiple mechanisms, including decreased ammoniagenesis, reduced excretion of protons, and hyperkalemia. Low S[HCO_3] is associated with increased risk for progression of CKD and even loss of kidney function in the general population.[122,123] Two RCTs have evaluated whether treating metabolic acidosis reduces progression of CKD. One hundred and thirty-four patients with a creatinine clearance of 15–30 mL/min/1.73 m^2 and a S[HCO_3] < 20 and >16 mmol/L were randomized to $NaHCO_3$ 600 mg three times a day vs. placebo. After 2 years, treatment with $NaHCO_3$ slowed decline in creatinine clearance and was associated with a decrease in the rate of developing ESRD (6.5% vs. 33%, $p < 0.001$).[124] A second study of 120 patients with hypertensive CKD with a GFR between 60 and 90 mL/min/1.73 m^2 and a UACR between 200 and 2000 mg/g randomized participants to $NaHCO_3$, NaCl (both 0.5 mEq/kg/day), and placebo

and followed them for 5 years. Treatment with $NaHCO_3$ slowed decline in GFR compared to NaCl and placebo, and also was associated with decreased UACR during follow-up.[125] The beneficial effect of bicarbonate supplementation on progression of CKD may be mediated through decreases in activation of complement by ammonia and by endothelin and aldosterone, and may also extend to improvement in physical functioning.[126,127]

To address the sodium load associated with alkali therapy, the effect of TRC101, a sodium-free acid binder, was examined in 135 CKD patients with a mean eGFR of 35 mL/min/1.73 m^2. Therapy was demonstrated to increase serum bicarbonate levels safely.[128]

In summary, bicarbonate supplementation is recommended to slow progression of CKD in patients with low bicarbonate levels, but the benefits of bicarbonate supplementation may extend to those with bicarbonate levels in the normal range. Further study is needed to determine the degree of effectiveness of bicarbonate supplementation.

Allopurinol

Uric acid levels are elevated in patients with renal dysfunction, and hyperuricemia is associated with endothelial dysfunction, activation of the RAAS, and hypertension.[129] A number of small, short-term clinical trials have suggested that lowering uric acid benefits patients with CKD. In one such study, 113 patients with eGFR <60 mL/min/1.73 m^2 were randomized to allopurinol 100 mg/day vs. usual therapy. After 24 months, those in the allopurinol group had a significant reduction in S[UA], an increase in eGFR, and a reduction in risk for cardiovascular events compared to the usual care group.[130] In long-term observational follow-up, treatment with allopurinol was again associated with reduced risk for a composite of starting dialysis, doubling of S[Cr], or ≥50% decline in eGFR (HR 0.32, 95% CI 0.15–0.69).[131] Allopurinol has been associated with reduction in risk for progression of CKD and, in a study of type 2 diabetic patients with urine protein excretion >500 mg/day, significant reduction of proteinuria.[132] A meta-analysis of 11 studies including 753 participants found that urate-lowering therapy was associated with slowing of progression of CKD.[133] Follow-up was 12 months or less in all but one of the studies included in the meta-analysis. The benefits of allopurinol may extend beyond its reduction in uric acid levels, through other properties including antiinflammatory and antioxidant effects, and reduction in reactive oxygen species.[134] In a study of febuxostat, a nonpurine-selective inhibitor of xanthine oxidase, in 443 patients with stage 3 CKD and asymptomatic hyperuricemia treated for 108 weeks, the decline in eGFR was not different compared to a placebo-treated group.[135] Until results are available from larger, long-term RCTs, lowering uric acid to reduce progression of CKD cannot be recommended, especially considering the relatively high incidence of serious allergic reactions with allopurinol.

Glycemic Control

Intensive Glucose Control

Diabetes mellitus is a major cause of CKD and ESRD. Elevated blood glucose and hemoglobin A1c are associated with progression of CKD. In patients with both type 1 and type 2 diabetes, intensive blood glucose control reduced the incidence of abnormal albuminuria and its progressive increase.[136–141] Intense therapy likely reduces progression of CKD in patients with type 1 diabetes as demonstrated in long-term follow-up of the Diabetes Control and Complications Trial (DCCT).[142] However, the results of intensive glucose control on the decline in GFR, or development of ESRD, have been mixed.[138,141,143] A meta-analysis of seven trials including 28,065 participants with type 2 diabetes revealed that while intensive glucose control reduced albuminuria, there was no improvement in the rate of doubling of S[Cr] or development of ESRD.[144] Most of the studies mentioned above excluded participants with elevated S[Cr] at baseline. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial (ADVANCE) study, intensive glucose control in type 2 diabetics reduced the occurrence of new or worsening nephropathy and ESRD with the caveat that there were a small number of ESRD events.[140] In a 6-year posttrial follow-up of ADVANCE, ADVANCE Observational (Advance-ON), the reduction in ESRD persisted.[145,146] Of importance, there was no increased risk of cardiovascular events or death. Based on these data, it is reasonable to target a hemoglobin A1c of approximately 7% in patients with CKD and diabetes.

Specific Glucose-Lowering Drugs

An emerging area is the investigation of whether some glucose-lowering drugs have beneficial effects on diabetic nephropathy and cardiovascular outcomes above and beyond their effects on glucose control. This area will be reviewed below.

Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

These drugs inhibit sodium and glucose transport in the S1 segment of the proximal tubule and consequently increase glucose and sodium excretion. In addition to effects on glycemic control, SGLT2 inhibitors lower BP, weight, and albuminuria and are associated with a decline in GFR.[147] In the first of these studies, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME

trial), the effect of empagliflozin was examined in 7020 adults with type 2 diabetes mellitus and established CVD with an eGFR of at least 30 mL/min/1.73 m^2.[148] Empagliflozin treatment over a median follow-up of 3.1 years reduced the risk of cardiovascular events, defined as a composite of first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The risk of the prespecified renal outcome of incident or worsening nephropathy (progression to macroalbuminuria, doubling of S[Cr] accompanied by an eGFR $\leq$45 mL/min/1.73 m^2, initiation of RRT, or death from renal disease) and incident albuminuria was also reduced by empagliflozin (Figure 57.4).[150] Interestingly, treatment with empagliflozin was associated with a decrease in eGFR that was reversible after stopping the study drug.

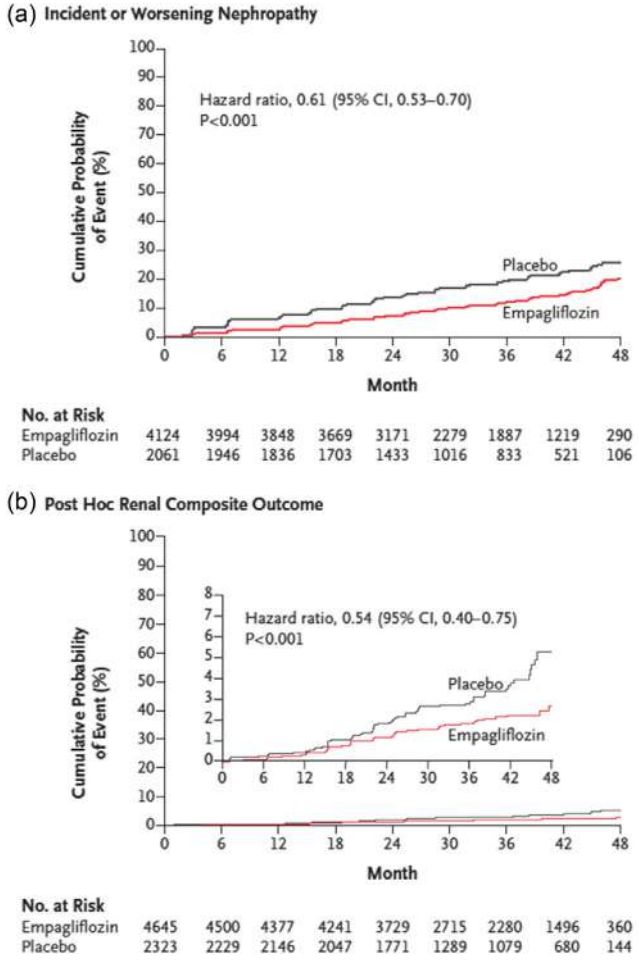


FIGURE 57.4 Empagliflozin and progression of kidney disease in type 2 diabetes. Kaplan–Meier analysis of (a). incident or worsening nephropathy (defined as progression to macroalbuminuria, a doubling of S[Cr] accompanied by an eGFR $\leq$45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease). (b) *Post hoc* renal composite outcome in which progression to macroalbuminuria was excluded from the composite renal outcome. The inset in panel b expands the y axis. *Reproduced from Reference 149 with permission from Massachusetts Medical Society, © 1994.*

In the CANVAS Program, the SGLT2 inhibitor canagliflozin was studied in 10,142 type 2 diabetic subjects at high risk for CVD. Canagliflozin decreased the primary cardiovascular endpoint of death from cardiovascular cause, nonfatal myocardial infarction, or nonfatal stroke.[151] The renal outcomes were not statistically significant based on the "prespecified hypothesis testing sequence," with a possible benefit in progression of albuminuria and the composite of sustained 40% reduction in eGFR, the need for RRT, or death from renal causes. There was an unexplained increased risk for amputation in the canagliflozin group.

The use of SGLT2 inhibitors is not recommended when the eGFR is <30 mL/min/1.73 m^2. To assess the safety and efficacy of SGLT2 inhibitors in patients with more severe CKD, the results of 11 phase 3 randomized placebo-controlled trials in type 2 diabetic patients treated for an average of 102 weeks with dapagliflozin, another SGLT2 inhibitor, were analyzed. These patients had stages 3b and 4 CKD (eGFR of 15–45 mL/min/1.73 m^2).[152] In this analysis dapagliflozin did not improve glycemic control but decreased albuminuria, BP, and body weight. Interestingly, serum phosphate concentration levels increased, but there were no other serious adverse effects.

These results demonstrating renal protective effects of SGLT2 inhibitors are promising, but before they are widely used as renal protective agents studies are needed examining long-term kidney outcomes. In this regard the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation trial (CREDENCE; ClinicalTrials.gov number NCT02065791) provides important information about renal outcomes.[147] This was a trial in 4400 patients with type 2 diabetes and UACR >300 to $\leq$5000 mg/g and eGFR $\geq$30 to <90 mL/min/1.73 m^2 adding canagliflozin to standard care consisting of maximum labeled or tolerated dose of ACEI or ARB. The primary endpoint was a composite of time to dialysis or kidney transplantation, doubling of S[Cr], and renal or CV death. The relative risk of the primary outcome was 30% lower in the canaglifozin group than in the placebo group. The canaglifozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke. There were no differences in the rates of amputation or fracture. This exciting study provides strong data for a renal protective effect of canaglifozin.

The potential mechanism of the beneficial effects of SGLT2 inhibitors may be through decreasing hyperfiltration. By reducing proximal reabsorption of sodium, distal sodium delivery is increased, activating tubular glomerular feedback leading to afferent arteriolar vasoconstriction and a reduction in hyperfiltration. This is a

class effect and is reversible after stopping the drug. If true then these drugs may also be effective in nondiabetic kidney disease, a hypothesis that is being tested in the Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With CKD (DAPA CKD) in which half the patients are diabetic and half are nondiabetic. The primary outcome is a composite of ≥50% sustained decline in eGFR, ESRD, or CV or kidney death (ClinicalTrials.gov NCT03036150).[147]

Dipeptidyl Peptidase Inhibitor Linagliptin

Linagliptin inhibits the breakdown of incretin hormones, which leads to increased glucose-dependent insulin secretion, inhibition of glucagon secretion, and improved glucose control. Pooled data from 13 phase 2 or 3 trials of the dipeptidyl peptidase inhibitor (DPP-4) linagliptin in type 2 diabetics showed intervention reduced the risk of kidney disease events by 16% compared to placebo.[153] The ongoing Cardiovascular safety and Renal Microvascular outcomE study with LINAgliptin in type 2 diabetics at high cardiovascular risk (CARMELINA) study is a randomized, double-blind, placebo-controlled trial with a cardiovascular primary outcome and a renal secondary outcome (ClinicalTrials.gov Identifier: NCT01897532).

Glucagon-like Peptide-1 Analogues

Another class of glucose-lowering medications is the human glucagon-like peptide-1 (GLP-1) analogues that act by stimulating insulin release. Cardiovascular and renal protective effects have been demonstrated with these agents. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial in type 2 diabetic patients with high cardiovascular risk demonstrated improved cardiovascular outcomes and lower mortality in patients treated with liraglutide.[154] The effects of liraglutide on renal outcomes were a prespecified secondary outcome comprised of new onset of persistent macroalbuminuria, persistent doubling of S[Cr], the need for RRT, or death due to renal cause.[155] Over a median follow-up of 3.84 years, liraglutide decreased the composite renal outcome, with the result driven primarily by a decrease in new onset of persistent macroalbuminuria. The beneficial effect was not related to glucose control, BP reduction, or a reduction in body weight, but it is likely multifactorial, acting through antiinflammatory and antioxidant mechanisms.[156–158]

In the Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN 6), treatment once weekly with the GLP-1 receptor analogue semaglutide reduced the incidence of the primary cardiovascular outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in 3297 patients with type 2 diabetes.[159] The prespecified secondary renal outcome of rates of new or worsening nephropathy was lower with semaglutide compared to placebo.

Emerging Therapies

Endothelin Antagonists

Endothelins are vasoconstricting peptides. Endothelin-1 (ET-1) is the major isoform in the human kidney. ET-1 has a number of potentially adverse effects on the kidney in animal models, including vasoconstriction, glomerular hypertension, proteinuria, and interstitial fibrosis. Preclinical studies have demonstrated that ET-1 antagonism reduces proteinuria and improves GFR.[160,161] However, a multicenter randomized trial of the endothelin antagonist avosentan compared with placebo was terminated after 4 months due to excess cardiovascular events in the avosentan group.[162] There was less proteinuria with avosentan but no difference in time to doubling of S[Cr], ESRD, or death. Atrasentan is another endothelin antagonist that is more selective for the endothelin A receptor. Patients with type 2 diabetes on maximal doses of ACEI or ARB, eGFR 30–75 mL/min/1.73 m^2, and UACR 300–3500 mg/g were randomly assigned to placebo or to 0.75 or 1.25 mg of atrasentan for 12 weeks.[163]

Atrasentan significantly reduced albuminuria, although there was a large variability between patients. Edema as a side effect was most common with the highest 1.25 mg dose.

These results led to a Phase 3 trial examining the effects of atrasentan on renal outcomes in diabetic patients is the Study Of diabetic Nephropathy with AtRasentan (SONAR); NCT01858532).[164] This double-blind, placebo–controlled trial in patients with stage 2–4 CKD and macroalbuminuria used an enrichment design randomizing patients with a ≥30% decrease in urinary albumin excretion at 6 weeks with no substantial fluid retention during the enrichment period. The primary endpoint was a composite of sustained doubling of S[Cr] or ESRD. 2648 patients were randomly assigned to atrasentan 0.75 mg orally per day or placebo with median follow-up of 2.2 years. Atrasentan significantly reduced the risk of renal events with no differences seen in hospital admission for heart failure or death.

Antiinflammatory Agents

Inflammation and oxidant stress can accelerate the progression of CKD. Bardoxolone methyl is a synthetic oleanane triterpenoid that activates NRF2, a transcription factor that controls expression of antioxidant, antiinflammatory, and cytoprotective genes.[165] In a phase 2 RCT

involving 227 adults with type 2 diabetes and moderate to severe CKD, bardoxolone improved eGFR at 24 and 52 weeks, but albuminuria was increased with higher doses of bardoxolone (BEAM Study).[166] A phase 3 trial evaluating the effect of bardoxolone on clinical endpoints in 2185 patients with type 2 diabetes and an eGFR between 15 and 30 mL/min/1.73 m^2 was stopped due to excess cardiovascular events, mainly heart failure, in the bardoxolone arm (BEACON Study).[167] In a *post hoc* analysis of this study, a bardoxolone-associated increase in eGFR was sustainable for 1 year and was associated with improved renal outcomes.[168]

This class of inflammatory modulating drugs presents an intriguing therapeutic option that is being tested in the CARDINAL Program, a phase 2/3 trial designed to assess the safety, tolerability, and efficacy of bardoxolone in Alport syndrome.[169,170]

Pentoxifylline is a nonspecific phosphodiesterase inhibitor originally approved for the treatment of peripheral vascular disease. It also has antiinflammatory and antifibrotic properties.[171] There have been several meta-analyses demonstrating mixed results of pentoxifylline on proteinuria.[172–175] In a randomized open-label trial in patients with type 2 diabetes mellitus and stage 3–4 CKD, treatment with pentoxifylline for 2 years in addition to RAAS inhibitors reduced the rate of decline in eGFR and lowered albuminuria compared to a control group.[176] More definitive long-term trials looking at hard renal endpoints are needed before pentoxifylline can be considered standard therapy for preventing progression of diabetic kidney disease.

Antifibrotic Therapies

Pirfenidone is a synthetic molecule that has been demonstrated to have antifibrotic properties in both cell culture and mouse models of diabetic kidney disease.[177] Trials in humans have been promising as well. In an open-label trial involving 18 patients with FSGS treated with pirfenidone for a median of 13 months, treatment was associated with a 25% improvement in the slope of change in GFR.[178] In a RCT including 52 participants with diabetic nephropathy, eGFR increased in participants assigned to pirfenidone 1200 mg/day, whereas a decline in GFR was noted in participants assigned to placebo ($p = 0.026$ vs. pirfenidone at 1200 mg/day).[179] The dropout rate was high in a third arm of the trial in which participants were assigned to pirfenidone 2400 mg/day.

Sulodexide, another antifibrotic agent, showed promise in early studies, but larger, more recent trials have failed to demonstrate a beneficial effect in patients with diabetic nephropathy.[180–183] Larger RCTs are needed to evaluate whether pirfenidone will be beneficial in slowing the progression of CKD.

Cellular Therapy and Kidney Augmentation

A number of factors are driving the use of cellular therapy and kidney augmentation to treat CKD. These include the availability of and initial success in using mesenchymal stem cells (MSCs) in nonrenal conditions and in treating AKI and kidney transplant patients.[184,185] Also, the growing gap between patients on the kidney transplant wait list and the availability of kidneys has generated interest in alternative approaches to renal replacement. A beneficial effect of MSC infusion has been demonstrated in animal models of kidney disease such as glomerulonephritis, Alport syndrome, FSGS, lupus nephritis, diabetic nephropathy, and the remnant kidney model.[186] In the glomerulonephritis model, maldifferentiation of intraglomerular MSCs into adipocytes occurred and was accompanied by glomerular sclerosis.[187] MSCs have been infused into patients with CKD, although the data from such studies are difficult to interpret. Umbilical cord-derived MSCs have been used for patients with lupus nephritis but had no additional effect compared to standard therapy.[188]

Implantable bioartificial kidney devices have been envisioned in which renal tubular cells are part of the device and are linked to a glomerular membrane.[189,190] The goal of these approaches is to restore the metabolic, immune, and transport functions of the kidney. Kidney cells are also critical components of a bioengineered kidney designed by injecting endothelial and neonatal kidney cells into a decellularized kidney scaffold.[191] Such a device has demonstrated *in vitro* and *in vivo* function. A kidney-on-a-chip model has been developed to allow kidney cells to be cultured in three-dimensional channels using a microfluidic device.[192] This model has been used to examine nephrotoxicity, kidney stones, kidney fibrosis, and disease modeling and may help facilitate the development of whole organs to be used for renal replacement. Work continues in this rapidly developing area with enormous potential for the treatment of CKD but also with many barriers to success.[193]

CONCLUSION

Slowing progression of kidney disease is a critical goal for CKD patients. Given the limited evidence for slowing progression of CKD with intensive BP control (systolic BP <120 mm Hg) vs. standard control (SBP <140 mm Hg), current recommendations to target BP <130/80 mm Hg are based on beneficial reductions in cardiovascular events and all-cause mortality. RAAS blockade can slow progression of CKD and is the most widely studied and used treatment. Single agent inhibition of the RAAS should be used, as dual blockade is not

more efficacious and is associated with a higher incidence of adverse events. A few other interventions may also slow progression of CKD, including glucose control with a specific beneficial effect of SGLT2 inhibitors and GLP-1 analogues. Bicarbonate supplementation should be considered in the treatment of patients with CKD, as there may be beneficial effects on outcomes. Low-protein diets may be effective in nondiabetic kidney disease. Lowering uric acid may reduce progression, although the evidence is not robust. Future therapies directed at endothelin, fibrosis, oxidant stress, and inflammation are being studied with the hope that our therapeutic armamentarium will increase in the future.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:1−150.
2. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 1994; **330**(13):877−84.
3. Levin A, Djurdjev O, Beaulieu M, Er L. Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. *Am J Kidney Dis* 2008;**52**(4): 661−71.
4. Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *J Am Med Assoc* 2016;**315**(2):164−74.
5. Tangri N, Inker LA, Hiebert B, Wong J, Naimark D, Kent D, et al. A dynamic predictive model for progression of CKD. *Am J Kidney Dis* 2017;**69**(4):514−20.
6. Tangri N, Rigatto C. Longitudinal studies 5: development of risk prediction models for patients with chronic disease. *Methods Mol Biol* 2015;**1281**:145−56.
7. Hingwala J, Wojciechowski P, Hiebert B, Bueti J, Rigatto C, Komenda P, et al. Risk-based triage for nephrology referrals using the kidney failure risk equation. *Can J Kidney Health Dis* 2017;**4**: 2054358117722782.
8. Foley RN, Murray AM, Li S, Herzog CA, McBean AM, Eggers PW, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 2005;**16**(2):489−95.
9. Forsblom C, Harjutsalo V, Thorn LM, Waden J, Tolonen N, Saraheimo M, et al. Competing-risk analysis of ESRD and death among patients with type 1 diabetes and macroalbuminuria. *J Am Soc Nephrol* 2011;**22**(3):537−44.
10. De Nicola L, Minutolo R, Chiodini P, Borrelli S, Zoccali C, Postorino M, et al. The effect of increasing age on the prognosis of non-dialysis patients with chronic kidney disease receiving stable nephrology care. *Kidney Int* 2012;**82**(4):482−8.
11. Menon V, Wang X, Sarnak MJ, Hunsicker LH, Madero M, Beck GJ, et al. Long-term outcomes in nondiabetic chronic kidney disease. *Kidney Int* 2008;**73**(11):1310−5.
12. Schnaper HW. Remnant nephron physiology and the progression of chronic kidney disease. *Pediatr Nephrol* 2014;**29**(2):193−202.
13. Fogo AB. Mechanisms of progression of chronic kidney disease. *Pediatr Nephrol* 2007;**22**(12):2011−22.
14. Noone D, Licht C. Chronic kidney disease: a new look at pathogenetic mechanisms and treatment options. *Pediatr Nephrol* 2014; **29**(5):779−92.
15. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol* 1981;**241**(1): F85−93.
16. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N Engl J Med* 1982;**307**(11):652−9.
17. Hostetter TH, Troy JL, Brenner BM. Glomerular hemodynamics in experimental diabetes mellitus. *Kidney Int* 1981;**19**(3):410−5.
18. Hostetter TH. Hyperfiltration and glomerulosclerosis. *Semin Nephrol* 2003;**23**(2):194−9.
19. Steffes MW, Mauer SM. Diabetes and nephropathy: progression, regression, and the effect of therapy. *Compr Ther* 1978;**4**(6):59−62.
20. Hostetter TH, Meyer TW, Rennke HG, Brenner BM. Chronic effects of dietary protein in the rat with intact and reduced renal mass. *Kidney Int* 1986;**30**(4):509−17.
21. Ibrahim HN, Foley R, Tan L, Rogers T, Bailey RF, Guo H, et al. Long-term consequences of kidney donation. *N Engl J Med* 2009; **360**(5):459−69.
22. Kiprov DD, Colvin RB, McCluskey RT. Focal and segmental glomerulosclerosis and porteinuria associated with unilateral renal agenesis. *Lab Invest* 1982;**46**(3):275−81.
23. Zucchelli P, Cagnoli L, Casanova S, Donini U, Pasquali S. Focal glomerulosclerosis in patients with unilateral nephrectomy. *Kidney Int* 1983;**24**(5):649−55.
24. Novick AC, Gephardt G, Guz B, Steinmuller D, Tubbs RR. Long-term follow-up after partial removal of a solitary kidney. *N Engl J Med* 1991;**325**(15):1058−62.
25. Daniels BS, Hostetter TH. Adverse effects of growth in the glomerular microcirculation. *Am J Physiol* 1990;**258**(5 Pt 2): F1409−16.
26. Kriz W, LeHir M. Pathways to nephron loss starting from glomerular diseases-insights from animal models. *Kidney Int* 2005;**67**(2): 404−19.
27. Becker BN, Yasuda T, Kondo S, Vaikunth S, Homma T, Harris RC. Mechanical stretch/relaxation stimulates a cellular renin-angiotensin system in cultured rat mesangial cells. *Exp Nephrol* 1998;**6**(1):57−66.
28. Riser BL, Cortes P, Zhao X, Bernstein J, Dumler F, Narins RG. Intraglomerular pressure and mesangial stretching stimulate extracellular matrix formation in the rat. *J Clin Investig* 1992; **90**(5):1932−43.
29. Durvasula RV, Petermann AT, Hiromura K, Blonski M, Pippin J, Mundel P, et al. Activation of a local tissue angiotensin system in podocytes by mechanical strain. *Kidney Int* 2004;**65**(1): 30−9.
30. Denic A, Mathew J, Lerman LO, Lieske JC, Larson JJ, Alexander MP, et al. Single-nephron glomerular filtration rate in healthy adults. *N Engl J Med* 2017;**376**(24):2349−57.
31. Denic A, Lieske JC, Chakkera HA, Poggio ED, Alexander MP, Singh P, et al. The substantial loss of nephrons in healthy human kidneys with aging. *J Am Soc Nephrol* 2017;**28**(1):313−20.
32. Nath KA. Tubulointerstitial changes as a major determinant in the progression of renal damage. *Am J Kidney Dis* 1992;**20**(1):1−17.
33. Leaf IA, Duffield JS. What can target kidney fibrosis? *Nephrol Dial Transplant* 2017;**32**(Suppl. l_1):i89−97.
34. D'Amico G, Ferrario F, Rastaldi MP. Tubulointerstitial damage in glomerular diseases: its role in the progression of renal damage. *Am J Kidney Dis* 1995;**26**(1):124−32.
35. Kaissling B, Lehir M, Kriz W. Renal epithelial injury and fibrosis. *Biochim Biophys Acta* 2013;**1832**(7):931−9.

36. Meyer TW. Tubular injury in glomerular disease. *Kidney Int* 2003; **63**(2):774–87.
37. Lv W, Booz GW, Wang Y, Fan F, Roman RJ. Inflammation and renal fibrosis: recent developments on key signalling molecules as potential therapeutic targets. *Eur J Pharmacol* 2018;**820**:65–76.
38. Shankland SJ. The podocyte's response to injury: role in proteinuria and glomerulosclerosis. *Kidney Int* 2006;**69**(12):2131–47.
39. Wharram BL, Goyal M, Wiggins JE, Sanden SK, Hussain S, Filipiak WE, et al. Podocyte depletion causes glomerulosclerosis: diphtheria toxin-induced podocyte depletion in rats expressing human diphtheria toxin receptor transgene. *J Am Soc Nephrol* 2005;**16**(10):2941–52.
40. Kato H, Susztak K. Repair problems in podocytes: Wnt, Notch, and glomerulosclerosis. *Semin Nephrol* 2012;**32**(4):350–6.
41. Niranjan T, Murea M, Susztak K. The pathogenic role of Notch activation in podocytes. *Nephron Exp Nephrol* 2009;**111**(4):e73–9.
42. Waters AM, Wu MY, Onay T, Scutaru J, Liu J, Lobe CG, et al. Ectopic Notch activation in developing podocytes causes glomerulosclerosis. *J Am Soc Nephrol* 2008;**19**(6):1139–57.
43. Ahn SH, Susztak K. Getting a Notch closer to understanding diabetic kidney disease. *Diabetes* 2010;**59**(8):1865–7.
44. Lin CL, Wang FS, Hsu YC, Chen CN, Tseng MJ, Saleem MA, et al. Modulation of Notch-1 signaling alleviates vascular endothelial growth factor-mediated diabetic nephropathy. *Diabetes* 2010; **59**(8):1915–25.
45. Rosenberg ME, Smith LJ, Correa-Rotter R, Hostetter TH. The paradox of the renin-angiotensin system in chronic renal disease. *Kidney Int* 1994;**45**(2):403–10.
46. Ruggenenti P, Cravedi P, Remuzzi G. Mechanisms and treatment of CKD. *J Am Soc Nephrol* 2012;**23**(12):1917–28.
47. Zhang F, Liu H, Liu D, Liu Y, Li H, Tan X, et al. Effects of RAAS inhibitors in patients with kidney disease. *Curr Hypertens Rep* 2017;**19**(9):72.
48. Oikawa T, Freeman M, Lo W, Vaughan DE, Fogo A. Modulation of plasminogen activator inhibitor-1 in vivo: a new mechanism for the anti-fibrotic effect of renin-angiotensin inhibition. *Kidney Int* 1997;**51**(1):164–72.
49. Ketteler M, Noble NA, Border WA. Transforming growth factor-beta and angiotensin II: the missing link from glomerular hyperfiltration to glomerulosclerosis? *Annu Rev Physiol* 1995;**57**:279–95.
50. Floege J, Alpers CE, Burns MW, Pritzl P, Gordon K, Couser WG, et al. Glomerular cells, extracellular matrix accumulation, and the development of glomerulosclerosis in the remnant kidney model. *Lab Invest* 1992;**66**(4):485–97.
51. Floege J, Burns MW, Alpers CE, Yoshimura A, Pritzl P, Gordon K, et al. Glomerular cell proliferation and PDGF expression precede glomerulosclerosis in the remnant kidney model. *Kidney Int* 1992; **41**(2):297–309.
52. Ruster C, Wolf G. Angiotensin II as a morphogenic cytokine stimulating renal fibrogenesis. *J Am Soc Nephrol* 2011;**22**(7):1189–99.
53. Gomez-Garre D, Largo R, Tejera N, Fortes J, Manzarbeitia F, Egido J. Activation of NF-kappaB in tubular epithelial cells of rats with intense proteinuria: role of angiotensin II and endothelin-1. *Hypertension* 2001;**37**(4):1171–8.
54. Wolf G. Role of reactive oxygen species in angiotensin II-mediated renal growth, differentiation, and apoptosis. *Antioxidants Redox Signal* 2005;**7**(9–10):1337–45.
55. LeBleu VS, Taduri G, O'Connell J, Teng Y, Cooke VG, Woda C, et al. Origin and function of myofibroblasts in kidney fibrosis. *Nat Med* 2013;**19**(8):1047–53.
56. Brown NJ. Contribution of aldosterone to cardiovascular and renal inflammation and fibrosis. *Nat Rev Nephrol* 2013;**9**(8):459–69.
57. Greene EL, Kren S, Hostetter TH. Role of aldosterone in the remnant kidney model in the rat. *J Clin Investig* 1996;**98**(4):1063–8.
58. Ibrahim HN, Rosenberg ME, Greene EL, Kren S, Hostetter TH. Aldosterone is a major factor in the progression of renal disease. *Kidney Int Suppl* 1997;**63**:S115–9.
59. Eddy AA. Proteinuria and interstitial injury. *Nephrol Dial Transplant* 2004;**19**(2):277–81.
60. Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med* 2009;**169**(4):342–50.
61. Peralta CA, Shlipak MG, Judd S, Cushman M, McClellan W, Zakai NA, et al. Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. *J Am Med Assoc* 2011;**305**(15):1545–52.
62. Cravedi P, Remuzzi G. Pathophysiology of proteinuria and its value as an outcome measure in chronic kidney disease. *Br J Clin Pharmacol* 2013;**76**(4):516–23.
63. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, Marcantoni C, et al. Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. *Kidney Int* 2001; **60**(3):1131–40.
64. Heerspink HJ, Kropelin TF, Hoekman J, de Zeeuw D. Reducing albuminuria as surrogate endpoint C. Drug-induced reduction in albuminuria is associated with subsequent renoprotection: a meta-analysis. *J Am Soc Nephrol* 2015;**26**(8):2055–64.
65. Lash JP, Go AS, Appel LJ, He J, Ojo A, Rahman M, et al. Chronic Renal Insufficiency Cohort (CRIC) Study: baseline characteristics and associations with kidney function. *Clin J Am Soc Nephrol* 2009; **4**(8):1302–11.
66. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, et al. Blood pressure and end-stage renal disease in men. *N Engl J Med* 1996;**334**(1):13–8.
67. Bakris GL, Weir MR, Shanifar S, Zhang Z, Douglas J, van Dijk DJ, et al. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. *Arch Intern Med* 2003; **163**(13):1555–65.
68. Parving HH, Andersen AR, Smidt UM, Svendsen PA. Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. *Lancet* 1983;**1**(8335): 1175–9.
69. Wheeler DC, Becker GJ. Summary of KDIGO guideline. What do we really know about management of blood pressure in patients with chronic kidney disease? *Kidney Int* 2013;**83**(3): 377–83.
70. Toto RD, Mitchell HC, Smith RD, Lee HC, McIntire D, Pettinger WA. "Strict" blood pressure control and progression of renal disease in hypertensive nephrosclerosis. *Kidney Int* 1995; **48**(3):851–9.
71. Lewis JB, Berl T, Bain RP, Rohde RD, Lewis EJ. Effect of intensive blood pressure control on the course of type 1 diabetic nephropathy. Collaborative Study Group. *Am J Kidney Dis* 1999;**34**(5): 809–17.
72. Ruggenenti P, Perna A, Loriga G, Ganeva M, Ene-Iordache B, Turturro M, et al. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005;**365**(9463): 939–46.
73. Wright Jr JT, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *J Am Med Assoc* 2002;**288**(19): 2421–31.
74. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol* 2017;**28**(9):2812–23.

75. Mehta R, Drawz PE. Is nocturnal blood pressure reduction the secret to reducing the rate of progression of hypertensive chronic kidney disease? *Curr Hypertens Rep* 2011;**13**(5):378–85.
76. Sarnak MJ, Greene T, Wang X, Beck G, Kusek JW, Collins AJ, et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. *Ann Intern Med* 2005;**142**(5):342–51.
77. Ku E, Gassman J, Appel LJ, Smogorzewski M, Sarnak MJ, Glidden DV, et al. BP control and long-term risk of ESRD and mortality. *J Am Soc Nephrol* 2017;**28**(2):671–7.
78. Group SR, Wright Jr JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**(22): 2103–16.
79. Whelton PK, Carey RM, Aronow WS, Casey Jr DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;**71**(19):2199–269.
80. Drawz PE, Abdalla M, Rahman M. Blood pressure measurement: clinic, home, ambulatory, and beyond. *Am J Kidney Dis* 2012;**60**(3): 449–62.
81. Niiranen TJ, Hanninen MR, Johansson J, Reunanen A, Jula AM. Home-measured blood pressure is a stronger predictor of cardiovascular risk than office blood pressure: the Finn-Home study. *Hypertension* 2010;**55**(6):1346–51.
82. Agarwal R, Andersen MJ. Prognostic importance of ambulatory blood pressure recordings in patients with chronic kidney disease. *Kidney Int* 2006;**69**(7):1175–80.
83. Hansen TW, Li Y, Boggia J, Thijs L, Richart T, Staessen JA. Predictive role of the nighttime blood pressure. *Hypertension* 2011;**57**(1): 3–10.
84. Townsend RR, Chirinos JA, Parsa A, Weir MA, Sozio SM, Lash JP, et al. Central pulse pressure in chronic kidney disease: a chronic renal insufficiency cohort ancillary study. *Hypertension* 2010; **56**(3):518–24.
85. Williams B, Lacy PS, Baschiera F, Brunel P, Dusing R. Novel description of the 24-hour circadian rhythms of brachial versus central aortic blood pressure and the impact of blood pressure treatment in a randomized controlled clinical trial: the Ambulatory Central Aortic Pressure (AmCAP) Study. *Hypertension* 2013; **61**(6):1168–76.
86. Carey RM, Muntner P, Bosworth HB, Whelton PK. Prevention and control of hypertension: JACC health promotion series. *J Am Coll Cardiol* 2018;**72**(11):1278–93.
87. Siu AL, Force USPST. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2015;**163**(10):778–86.
88. Whelton PK, Carey RM, Aronow WS, Casey Jr DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;**71**(19):e127–248.
89. Townsend RR, Wimmer NJ, Chirinos JA, Parsa A, Weir M, Perumal K, et al. Aortic PWV in chronic kidney disease: a CRIC ancillary study. *Am J Hypertens* 2010;**23**(3):282–9.
90. Anderson S, Meyer TW, Rennke HG, Brenner BM. Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. *J Clin Investig* 1985;**76**(2):612–9.
91. Anderson S, Rennke HG, Brenner BM. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Investig* 1986;**77**(6):1993–2000.
92. Kakinuma Y, Kawamura T, Bills T, Yoshioka T, Ichikawa I, Fogo A. Blood pressure-independent effect of angiotensin inhibition on vascular lesions of chronic renal failure. *Kidney Int* 1992;**42**(1): 46–55.
93. Kon V, Fogo A, Ichikawa I. Bradykinin causes selective efferent arteriolar dilation during angiotensin I converting enzyme inhibition. *Kidney Int* 1993;**44**(3):545–50.
94. Lewis SD, Ng AS, Baldwin JJ, Fusetani N, Naylor AM, Shafer JA. Inhibition of thrombin and other trypsin-like serine proteinases by cyclotheonamide A. *Thromb Res* 1993;**70**(2):173–90.
95. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**(12):851–60.
96. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet* 1997;**349**(9069):1857–63.
97. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**(12):861–9.
98. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* 2003;**139**(4): 244–52.
99. Casas JP, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet* 2005;**366**(9502):2026–33.
100. Hou FF, Zhang X, Zhang GH, Xie D, Chen PY, Zhang WR, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med* 2006;**354**(2):131–40.
101. Ravid M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. *Arch Intern Med* 1996;**156**(3):286–9.
102. Captopril reduces the risk of nephropathy in IDDM patients with microalbuminuria. The Microalbuminuria Captopril Study Group. *Diabetologia* 1996;**39**(5):587–93.
103. Bjorck S, Mulec H, Johnsen SA, Norden G, Aurell M. Renal protective effect of enalapril in diabetic nephropathy. *BMJ* 1992; **304**(6823):339–43.
104. Mauer M, Zinman B, Gardiner R, Suissa S, Sinaiko A, Strand T, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* 2009;**361**(1):40–51.
105. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK, Investigators AS. Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med* 2008;**358**(23):2433–46.
106. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012;**367**(23):2204–13.
107. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008;**148**(1):30–48.
108. Retraction. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *Ann Intern Med* 2009;**151**(12):897.
109. Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, et al. Renal outcomes with telmisartan, ramipril, or

both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008;**372**(9638):547–53.
110. Fried LF, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth W, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;**369**(20): 1892–903.
111. Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials. *BMJ* 2013;**346**:f360.
112. Susantitaphong P, Sewaralthahab K, Balk EM, Eiam-ong S, Madias NE, Jaber BL. Efficacy and safety of combined vs. single renin-angiotensin-aldosterone system blockade in chronic kidney disease: a meta-analysis. *Am J Hypertens* 2013;**26**(3):424–41.
113. Gentile G, Remuzzi G, Ruggenenti P. Dual renin-angiotensin system blockade for nephroprotection: still under scrutiny. *Nephron* 2015;**129**(1):39–41.
114. Epstein M. Aldosterone blockade: an emerging strategy for abrogating progressive renal disease. *Am J Med* 2006;**119**(11):912–9.
115. Ponda MP, Hostetter TH. Aldosterone antagonism in chronic kidney disease. *Clin J Am Soc Nephrol* 2006;**1**(4):668–77.
116. Shavit L, Lifschitz MD, Epstein M. Aldosterone blockade and the mineralocorticoid receptor in the management of chronic kidney disease: current concepts and emerging treatment paradigms. *Kidney Int* 2012;**81**(10):955–68.
117. Bakris GL, Agarwal R, Chan JC, Cooper ME, Gansevoort RT, Haller H, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *J Am Med Assoc* 2015;**314**(9):884–94.
118. Nath KA, Kren SM, Hostetter TH. Dietary protein restriction in established renal injury in the rat. Selective role of glomerular capillary pressure in progressive glomerular dysfunction. *J Clin Investig* 1986;**78**(5):1199–205.
119. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. *N Engl J Med* 2017;**377**(18):1765–76.
120. Koppe L, Fouque D. The role for protein restriction in addition to renin-angiotensin-aldosterone system inhibitors in the management of CKD. *Am J Kidney Dis* 2018;**73**(2):248–57.
121. Fouque D, Laville M. Low protein diets for chronic kidney disease in non diabetic adults. *Cochrane Database Syst Rev* 2009;(3): CD001892.
122. Dobre M, Yang W, Chen J, Drawz P, Hamm LL, Horwitz E, et al. Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: a report from the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis* 2013;**62**(4):670–8.
123. Shah SN, Abramowitz M, Hostetter TH, Melamed ML. Serum bicarbonate levels and the progression of kidney disease: a cohort study. *Am J Kidney Dis* 2009;**54**(2):270–7.
124. Mahajan A, Simoni J, Sheather SJ, Broglio KR, Rajab MH, Wesson DE. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. *Kidney Int* 2010;**78**(3):303–9.
125. Goraya N, Simoni J, Jo C, Wesson DE. Dietary acid reduction with fruits and vegetables or bicarbonate attenuates kidney injury in patients with a moderately reduced glomerular filtration rate due to hypertensive nephropathy. *Kidney Int* 2012;**81**(1): 86–93.
126. Wesson DE, Simoni J, Broglio K, Sheather S. Acid retention accompanies reduced GFR in humans and increases plasma levels of endothelin and aldosterone. *Am J Physiol Renal Physiol* 2011; **300**(4):F830–7.
127. Abramowitz MK, Melamed ML, Bauer C, Raff AC, Hostetter TH. Effects of oral sodium bicarbonate in patients with CKD. *Clin J Am Soc Nephrol* 2013;**8**(5):714–20.
128. Bushinsky DA, Hostetter T, Klaerner G, Stasiv Y, Lockey C, McNulty S, et al. Randomized, controlled trial of TRC101 to increase serum bicarbonate in patients with CKD. *Clin J Am Soc Nephrol* 2018;**13**(1):26–35.
129. Johnson RJ, Nakagawa T, Jalal D, Sanchez-Lozada LG, Kang DH, Ritz E. Uric acid and chronic kidney disease: which is chasing which? *Nephrol Dial Transplant* 2013;**28**(9):2221–8.
130. Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincon A, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *Clin J Am Soc Nephrol* 2010;**5**(8):1388–93.
131. Goicoechea M, Garcia de Vinuesa S, Verdalles U, Verde E, Macias N, Santos A, et al. Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial. *Am J Kidney Dis* 2015;**65**(4):543–9.
132. Momeni A, Shahidi S, Seirafian S, Taheri S, Kheiri S. Effect of allopurinol in decreasing proteinuria in type 2 diabetic patients. *Iran J Kidney Dis* 2010;**4**(2):128–32.
133. Wang H, Wei Y, Kong X, Xu D. Effects of urate-lowering therapy in hyperuricemia on slowing the progression of renal function: a meta-analysis. *J Ren Nutr* 2013;**23**(5):389–96.
134. George J, Struthers AD. The role of urate and xanthine oxidase inhibitors in cardiovascular disease. *Cardiovasc Ther* 2008;**26**(1): 59–64.
135. Kimura K, Hosoya T, Uchida S, Inaba M, Makino H, Maruyama S, et al. Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: a randomized trial. *Am J Kidney Dis* 2018;**72**(6):798–810.
136. Effect of intensive therapy on the development and progression of diabetic nephropathy in the diabetes control and complications trial. The diabetes control and complications (DCCT) research group. *Kidney Int* 1995;**47**(6):1703–20.
137. Group AC, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;**358**(24):2560–72.
138. Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010;**376**(9739):419–30.
139. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;**352**(9131):837–53.
140. Perkovic V, Heerspink HL, Chalmers J, Woodward M, Jun M, Li Q, et al. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. *Kidney Int* 2013;**83**(3):517–23.
141. MacIsaac RJ, Jerums G, Ekinci EI. Glycemic control as primary prevention for diabetic kidney disease. *Adv Chron Kidney Dis* 2018;**25**(2):141–8.
142. Group DER, de Boer IH, Sun W, Cleary PA, Lachin JM, Molitch ME, et al. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med* 2011;**365**(25): 2366–76.
143. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;**360**(2):129–39.
144. Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. *Arch Intern Med* 2012;**172**(10):761–9.
145. Zoungas S, Chalmers J, Neal B, Billot L, Li Q, Hirakawa Y, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med* 2014;**371**(15):1392–406.
146. Wong MG, Perkovic V, Chalmers J, Woodward M, Li Q, Cooper ME, et al. Long-term benefits of intensive glucose control for preventing end-stage kidney disease: ADVANCE-ON. *Diabetes Care* 2016;**39**(5):694–700.

147. Perkovic V, Jardine MJ, Neal B, et al. CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 2019;**380**(24):2295–306.
148. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**(22):2117–28.
149. Wanner C, Inzucchi SE, Zinman B. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;**375**(18): 1801–2.
150. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;**375**(4):323–34.
151. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**(7):644–57.
152. Dekkers CCJ, Wheeler DC, Sjostrom CD, Stefansson BV, Cain V, Heerspink HJL. Effects of the sodium-glucose co-transporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and Stages 3b-4 chronic kidney disease. *Nephrol Dial Transplant* 2018;**33**(7): 1280.
153. Cooper ME, Perkovic V, McGill JB, Groop PH, Wanner C, Rosenstock J, et al. Kidney disease end points in a pooled analysis of individual patient-level data from a large clinical trials program of the dipeptidyl peptidase 4 inhibitor linagliptin in type 2 diabetes. *Am J Kidney Dis* 2015;**66**(3):441–9.
154. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;**375**(4):311–22.
155. Mann JFE, Orsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med* 2017;**377**(9):839–48.
156. Fujita H, Morii T, Fujishima H, Sato T, Shimizu T, Hosoba M, et al. The protective roles of GLP-1R signaling in diabetic nephropathy: possible mechanism and therapeutic potential. *Kidney Int* 2014; **85**(3):579–89.
157. Kodera R, Shikata K, Kataoka HU, Takatsuka T, Miyamoto S, Sasaki M, et al. Glucagon-like peptide-1 receptor agonist ameliorates renal injury through its anti-inflammatory action without lowering blood glucose level in a rat model of type 1 diabetes. *Diabetologia* 2011;**54**(4):965–78.
158. von Scholten BJ, Persson F, Rosenlund S, Hovind P, Faber J, Hansen TW, et al. The effect of liraglutide on renal function: a randomized clinical trial. *Diabetes Obes Metab* 2017;**19**(2):239–47.
159. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;**375**(19):1834–44.
160. Brochu E, Lacasse S, Moreau C, Lebel M, Kingma I, Grose JH, et al. Endothelin ET(A) receptor blockade prevents the progression of renal failure and hypertension in uraemic rats. *Nephrol Dial Transplant* 1999;**14**(8):1881–8.
161. Wolf SC, Brehm BR, Gaschler F, Brehm S, Klaussner M, Smykowski J, et al. Protective effects of endothelin antagonists in chronic renal failure. *Nephrol Dial Transplant* 1999;**14**(Suppl. 4):29–30.
162. Mann JF, Green D, Jamerson K, Ruilope LM, Kuranoff SJ, Littke T, et al. Avosentan for overt diabetic nephropathy. *J Am Soc Nephrol* 2010;**21**(3):527–35.
163. de Zeeuw D, Coll B, Andress D, Brennan JJ, Tang H, Houser M, et al. The endothelin antagonist atrasentan lowers residual albuminuria in patients with type 2 diabetic nephropathy. *J Am Soc Nephrol* 2014;**25**(5):1083–93.
164. Heerspink HL, Parving HH, Andress DL, et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. *Lancet* 2019;**393**(10184):1937–47.
165. Abboud HE. Synthetic oleanane triterpenoids: magic bullets or not? *Kidney Int* 2013;**83**(5):785–7.
166. Pergola PE, Krauth M, Huff JW, Ferguson DA, Ruiz S, Meyer CJ, et al. Effect of bardoxolone methyl on kidney function in patients with T2D and Stage 3b-4 CKD. *Am J Nephrol* 2011;**33**(5): 469–76.
167. de Zeeuw D, Akizawa T, Audhya P, Bakris GL, Chin M, Christ-Schmidt H, et al. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med* 2013;**369**(26): 2492–503.
168. Chin MP, Bakris GL, Block GA, Chertow GM, Goldsberry A, Inker LA, et al. Bardoxolone methyl improves kidney function in patients with chronic kidney disease stage 4 and type 2 diabetes: post-hoc analyses from bardoxolone methyl evaluation in patients with chronic kidney disease and type 2 diabetes study. *Am J Nephrol* 2018;**47**(1):40–7.
169. Baigent C, Lennon R. Should we increase GFR with bardoxolone in Alport syndrome? *J Am Soc Nephrol* 2018;**29**(2):357–9.
170. Toto RD. Bardoxolone-the phoenix? *J Am Soc Nephrol* 2018;**29**(2): 360–1.
171. Lin SL, Chen RH, Chen YM, Chiang WC, Lai CF, Wu KD, et al. Pentoxifylline attenuates tubulointerstitial fibrosis by blocking Smad3/4-activated transcription and profibrogenic effects of connective tissue growth factor. *J Am Soc Nephrol* 2005;**16**(9):2702–13.
172. McCormick BB, Sydor A, Akbari A, Fergusson D, Doucette S, Knoll G. The effect of pentoxifylline on proteinuria in diabetic kidney disease: a meta-analysis. *Am J Kidney Dis* 2008;**52**(3): 454–63.
173. Leporini C, Pisano A, Russo E, DA G, de Sarro G, Coppolino G, et al. Effect of pentoxifylline on renal outcomes in chronic kidney disease patients: a systematic review and meta-analysis. *Pharmacol Res* 2016;**107**:315–32.
174. Jiang X, Zhou S, Yao J, Kong X, Cui M. Effect of pentoxifylline in proteinuric chronic kidney disease: a systematic review and meta-analysis. *J Nephrol* 2016;**29**(5):653–62.
175. Liu D, Wang LN, Li HX, Huang P, Qu LB, Chen FY. Pentoxifylline plus ACEIs/ARBs for proteinuria and kidney function in chronic kidney disease: a meta-analysis. *J Int Med Res* 2017;**45**(2):383–98.
176. Navarro-Gonzalez JF, Mora-Fernandez C, Muros de Fuentes M, Chahin J, Mendez ML, Gallego E, et al. Effect of pentoxifylline on renal function and urinary albumin excretion in patients with diabetic kidney disease: the PREDIAN trial. *J Am Soc Nephrol* 2015;**26**(1):220–9.
177. RamachandraRao SP, Zhu Y, Ravasi T, McGowan TA, Toh I, Dunn SR, et al. Pirfenidone is renoprotective in diabetic kidney disease. *J Am Soc Nephrol* 2009;**20**(8):1765–75.
178. Cho ME, Smith DC, Branton MH, Penzak SR, Kopp JB. Pirfenidone slows renal function decline in patients with focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol* 2007;**2**(5):906–13.
179. Sharma K, Ix JH, Mathew AV, Cho M, Pflueger A, Dunn SR, et al. Pirfenidone for diabetic nephropathy. *J Am Soc Nephrol* 2011;**22**(6): 1144–51.
180. Ceol M, Nerlich A, Baggio B, Anglani F, Sauer U, Schleicher E, et al. Increased glomerular alpha 1 (IV) collagen expression and deposition in long-term diabetic rats is prevented by chronic glycosaminoglycan treatment. *Lab Invest* 1996;**74**(2):484–95.
181. Gambaro G, Kinalska I, Oksa A, Pont'uch P, Hertlova M, Olsovsky J, et al. Oral sulodexide reduces albuminuria in microalbuminuric and macroalbuminuric type 1 and type 2 diabetic patients: the Di.N.A.S. randomized trial. *J Am Soc Nephrol* 2002;**13**(6): 1615–25.
182. Lewis EJ, Lewis JB, Greene T, Hunsicker LG, Berl T, Pohl MA, et al. Sulodexide for kidney protection in type 2 diabetes patients with microalbuminuria: a randomized controlled trial. *Am J Kidney Dis* 2011;**58**(5):729–36.

183. Packham DK, Wolfe R, Reutens AT, Berl T, Heerspink HL, Rohde R, et al. Sulodexide fails to demonstrate renoprotection in overt type 2 diabetic nephropathy. *J Am Soc Nephrol* 2012; **23**(1):123–30.
184. Salem HK, Thiemermann C. Mesenchymal stromal cells: current understanding and clinical status. *Stem Cell* 2010;**28**(3):585–96.
185. Cantaluppi V, Biancone L, Quercia A, Deregibus MC, Segoloni G, Camussi G. Rationale of mesenchymal stem cell therapy in kidney injury. *Am J Kidney Dis* 2013;**61**(2):300–9.
186. Caldas HC, Hayashi AP, Abbud-Filho M. Repairing the chronic damaged kidney: the role of regenerative medicine. *Transplant Proc* 2011;**43**(10):3573–6.
187. Kunter U, Rong S, Boor P, Eitner F, Muller-Newen G, Djuric Z, et al. Mesenchymal stem cells prevent progressive experimental renal failure but maldifferentiate into glomerular adipocytes. *J Am Soc Nephrol* 2007;**18**(6):1754–64.
188. Deng D, Zhang P, Guo Y, Lim TO. A randomised double-blind, placebo-controlled trial of allogeneic umbilical cord-derived mesenchymal stem cell for lupus nephritis. *Ann Rheum Dis* 2017;**76**(8):1436–9.
189. Fissell WH, Roy S, Davenport A. Achieving more frequent and longer dialysis for the majority: wearable dialysis and implantable artificial kidney devices. *Kidney Int* 2013;**84**(2): 256–64.
190. Humes HD, Buffington D, Westover AJ, Roy S, Fissell WH. The bioartificial kidney: current status and future promise. *Pediatr Nephrol* 2014;**29**(3):343–51.
191. Song JJ, Guyette JP, Gilpin SE, Gonzalez G, Vacanti JP, Ott HC. Regeneration and experimental orthotopic transplantation of a bioengineered kidney. *Nat Med* 2013;**19**(5):646–51.
192. Lee J, Kim K, Kim S. Kidney on chips. *Methods Cell Biol* 2018;**146**: 85–104.
193. Kim S, Fissell WH, Humes DH, Roy S. Current strategies and challenges in engineering a bioartificial kidney. *Front Biosci* 2015;**7**:215–28.
194. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**(9784):2181–92.

QUESTIONS AND ANSWERS

Question 1

A 55-year-old man is referred to the nephrology clinic for management of CKD. He has a history of hypertension, gout, and an 8-year history of type 2 diabetes complicated by retinopathy. He is currently taking amlodipine 10 mg daily, hydrochlorothiazide 25 mg daily, and glipizide 5 mg daily. His review of systems is completely negative. On examination, his blood pressure is 150/85 mm Hg, which is similar to recent values at his primary care provider's office. S[Cr] is 2 mg/dL (eGFR 36 mL/min/1.73 m^2), HCO3 is 22 mmol/L, Vitamin D 20 nmol/L, UACR is 85 mg/g, and HbA1c is 8.5%.

Which ONE of the following is most likely to slow progression of his CKD?

A. Cholesterol lowering with simvastatin 40 mg daily
B. ACE inhibition with lisinopril 40 mg daily
C. Correction of acidosis with sodium bicarbonate 650 mg TID
D. Dietary protein restriction
E. Vitamin D supplementation

Answer: B

RAAS blockade (Choice B) reduces progression of proteinuria in diabetic nephropathy and slows progression of CKD. Although treatment with a statin (Choice A) may reduce the incidence of CVD in patients with CKD, the SHARP study failed to demonstrate a benefit of cholesterol lowering with regard to progression of CKD.[194] Treatment with sodium bicarbonate (Choice C) has slowed progression of CKD in two small studies, but larger studies are needed to confirm these beneficial effects.[124,125] In the largest study to date, MDRD, dietary protein restriction did not affect rate of decline in renal function (Choice D).[2] There have been no studies demonstrating that vitamin D supplementation (Choice E) slows progression of CKD.

Question 2

A 60-year-old woman is referred to the nephrology clinic for management of hypertension and CKD. She has a 15-year history of hypertension and S[Cr] is 2.1 mg/dL (eGFR 25 mL/min/1.73 m^2). She is taking lisinopril 40 mg daily and hydrochlorothiazide 25 mg daily. Her review of systems is completely negative. On examination, her blood pressure is 155/78 mm Hg, which is similar to recent values at her primary care provider's office. Her UACR is 200 mg/g.

Which ONE of the following is correct regarding treatment of her hypertension?

A. The most appropriate BP target for her is <140/90 mm Hg, which will reduce her risk of CVD
B. The most appropriate BP target for her is <140/90 mm Hg, which will reduce her risk of CVD and slow progression of her CKD
C. The most appropriate BP target for her is <130/80 mm Hg, which will reduce her risk of CVD
D. The most appropriate BP target for her is <130/80 mm Hg, which will reduce her risk of CVD and slow progression of her CKD
E. The most appropriate BP target for her is <125/75 mm Hg, which will reduce her risk of CVD and slow progression of her CKD

Answer: C

Targeting a BP of 130/80 mm Hg will reduce her risk of CVD (Choice C). Although the most appropriate target is not clear, the most recent guidelines from the American Heart Association/American College of Cardiology recommend a blood pressure target of ≤130/80 mm Hg for CKD patients.[88] A number of clinical trials, including MDRD, AASK, and SPRINT, have failed to demonstrate a benefit of lower BP targets with regard to slowing progression of CKD, especially among patients with lower levels of proteinuria (Choices B, D, and E).[2,73,74]

Question 3

A 45-year-old man is seen in follow-up in the nephrology clinic for management of CKD. He has stage 3 CKD with an eGFR of 40 mL/min/1.73 m^2 secondary to FSGS. He also has a past medical history significant for hypertension and dyslipidemia. He is doing well and takes lisinopril 40 mg daily, chlorthalidone 25 mg daily, and simvastatin 40 mg daily. On examination, his blood pressure is 128/78 mm Hg. Cardiac examination reveals a regular rate and rhythm with no S3 or S4, lungs are clear to auscultation, and extremities are without edema. His UPCR is 350 mg/g, which has been stable for the past 2 years. After attending a recent research conference, you consider treatment with pentoxifylline, a novel new agent with potential to slow progression of CKD.

Which of the following is the mechanism of action of pentoxifylline?

A. It is an ET-1 antagonist that reduces proteinuria and improves GFR
B. It is a selective inhibitor of protein kinase C-β
C. It reduces uric acid by inhibiting the enzyme xanthine oxidase
D. It has antiinflammatory and antifibrotic properties
E. It inhibits the renin−angiotensin aldosterone system

Answer: D

Pentoxifylline has both antiinflammatory and antifibrotic properties (Choice D) and, in small pilot studies, has reduced proteinuria and slowed progression of CKD. A larger randomized trial to evaluate the role of pentoxifylline in the care of patients with CKD is underway. Examples of ET-1 antagonists include avosentan and atrasentan (Choice A). Selective inhibitors of protein kinase C-β (Choice B), such as ruboxistaurin, have been shown to reduce albuminuria and stabilize eGFR in patients with diabetic nephropathy. Allopurinol reduces uric acid by inhibiting the enzyme xanthine oxidase (Choice C) and may lower blood pressure and slow progression of CKD but larger RCTs are needed to evaluate its use in CKD patients.

Question 4

A 57-yr-old woman has progressive decrease in GFR from biopsy proven focal and segmental glomerular sclerosis. Her current S[Cr] is 3.7 mg/dL and eGFR using the abbreviated MDRD equation is 16 mL/min/1.73 m^2. A UPCR is 4560 mg/g. Other medical problems include hypertension, currently treated with furosemide 40 mg orally twice daily and lisinopril 40 mg once daily. Her BP is 140/85 mm Hg.

Which ONE of the following statements is correct?

A. She should be referred for mesenchymal stem cell (MSC) infusion therapy to reduce her risks for progression to ESRD
B. The renin inhibitor aliskiren should be added to her antihypertensive regimen to reduce the risks of progression to ESRD
C. Vitamin D should be added because of its benefits in slowing progression of CKD
D. Addition of a dihydropyridine calcium channel blocker should be avoided because of the risk of accelerating the progression of her renal disease
E. Management in a multidisciplinary CKD clinic is associated with better adherence to CKD guidelines and improved outcomes once patients initiate dialysis

Answer: E

This patient has Stage 4 CKD secondary to focal and segmental glomerular sclerosis. Significant proteinuria is present and the blood pressure is poorly controlled. There is evidence supporting Answer E, that the way we deliver care to CKD patients can affect health outcomes. Specifically multidisciplinary CKD clinics are associated with better adherence to CKD guidelines, a higher incidence of fistula use at initiation of dialysis, more outpatient dialysis starts (vs. emergency inpatient starts), and improved outcomes once patients initiate dialysis.[1] MSC infusion has been used following kidney transplantation with mixed results and is being studied in the setting of AKI.[184,186] There is no evidence that such MSC therapy alters the course of CKD; therefore, Answer A is incorrect. There is no evidence that vitamin D alters the progression of CKD making Answer C incorrect. The ALTITUDE trial studied the effects of adding the renin inhibitor aliskiren to ACEI or ARB therapy.[106] This study was terminated early secondary to adverse outcomes including hyperkalemia, hypotension, and stroke in the dual therapy arm. Calcium channel blockers should not be the drugs of first choice in the setting of CKD. However when used in combination with an ACEI or ARB, dihydropyridine calcium channel blockers can effectively lower blood pressure and do not limit the antiproteinuric effects of the ACEI or ARB. There is no evidence that calcium channel blockers accelerate the progression of CKD, making Answer D incorrect.

Question 5

A 54-yr-old man presented with edema and hypertension (BP 150/100 mm Hg). He was found to have S[Cr] 2.8 mg/dL and a urinary protein excretion of 6 g/24 h. A renal biopsy showed membranous glomerulonephritis. He was started on the ACE inhibitor lisinopril, 20 mg/day, and a loop diuretic. One week later his BP was 125/75 mm Hg, his urinary protein excretion decreased to 3 g/24 h, but S[Cr] had increased to 3.2 mg/dL.

Which ONE of the following statements regarding his management would be MOST appropriate?

A. Replace the ACE inhibitor with a beta blocker and evaluate for renal artery stenosis
B. Discontinue the loop diuretic
C. Continue the current antihypertensive regimen and recheck S[Cr] in 1 week
D. Replace the ACE inhibitor with an AII receptor blocker
E. Add steroids and cyclophosphamide to his current drug regimen to treat his glomerular disease

Answer: C

In this patient with CKD secondary to membranous glomerulonephritis treatment with an ACE inhibitor brought his blood pressure into the target range and significantly reduced proteinuria, but was associated with an increase in S[Cr] from 2.8 to 3.2. This increase in S[Cr] is expected, due to the effects of the ACE inhibitor on dilating the efferent arteriole.[18] A decline in GFR has been observed in most clinical studies of ACE inhibitor or ARB treatment. As long as this decrease is less than 30% then treatment can be continued. Therefore, the best response is to continue the current antihypertensive drugs and recheck S[Cr] in one week. There is no evidence that using an ARB instead of an ACE

inhibitor would be more beneficial. Substituting the ACE inhibitor for other treatment would mean a loss of the potential renal protective effects of the ACE inhibitor. The 13% increase in S[Cr] is not enough to launch an evaluation for renal artery stenosis. There are no data demonstrating that discontinuing the loop diuretic or adding cytotoxic therapy would beneficial.

Question 6

A 63-yr-old man has CKD from IgA nephropathy. Two years ago he was hypertensive, S[Cr] was 2.1 mg/dL, estimated GFR by the MDRD equation was 34 mL/min/1.73 m^2, and UPCR was 2000 mg/g. Treatment was started with an ACEI. Over the past two years S[Cr] has increased to 3.4 mg/dL, estimated GFR has decreased to 20 mL/min/1.73 m^2, and UPCR is 2600 mg/g despite maximal dosing of his ACE inhibitor. His current BP is 125/80 mm Hg.

Which ONE of the following changes in his management would be BEST?

A. Switch to a different ACE inhibitor because the current one is ineffective
B. Discontinue the ACE inhibitor and start a dihydropyridine calcium channel blocker
C. Add an ARB to his current medications
D. Intensify BP control by starting a beta blocker
E. Continue current treatment and begin to prepare the patient for renal replacement therapy

Answer: E

This patient with CKD secondary to IgA nephropathy has had progression of his renal failure with estimated GFR decreasing from 34 to 20 mL/min/1.73 m^2 despite maximal dosing of his ACE inhibitor and optimal control of blood pressure. There is no evidence that switching to a different ACE inhibitor will be more effective so Answer A is incorrect. The cornerstone of therapy for this patient is inhibition of AII; therefore, stopping the ACE inhibitor and starting a calcium channel blocker is not indicated, making Answer B incorrect. Addition of an ARB to his current medications has not been demonstrated to improve renal outcomes and is associated with more adverse effects.[107,109] Therefore, dual therapy with ACEI and ARB is not recommended and Answer C is incorrect. There is no evidence that further lowering his blood pressure below 125/80 mm Hg will be beneficial, making Answer D incorrect. The correct course of action is to continue his current therapy and begin the process of preparing the patient for renal replacement therapy. This should involve education about options, assessment of his candidacy and potential donors for transplantation, and planning vascular access if there are no donors or he is not a candidate for transplantation. Therefore, Answer E is correct.

CHAPTER

58

Approach to the Patient with Non-nephrotic Proteinuria

Renu Regunathan-Shenk, Ehsan Nobakht, Scott D. Cohen

Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States

Abstract

This chapter reviews the approach to the patient with non-nephrotic proteinuria. The definition and prevalence of proteinuria are considered. Proteinuria is important because it has implications for progression of chronic kidney disease (CKD) and increased cardiovascular risk. The type of proteinuria may provide important diagnostic clues to the etiology of CKD. Evaluation includes review of the urine sediment, serological evaluation, and renal biopsy if appropriate. Lifestyle modification and antagonism of the renin–angiotensin–aldosterone system form the cornerstone of conservative management for all patients with proteinuric kidney disease. Immunosuppressive therapy may be indicated, depending on the etiology of the patient's renal disease. Additional specific therapies to reduce proteinuria and slow progression of CKD are eagerly awaited.

INTRODUCTION

Proteinuria has been a classic sign of kidney disease since the premodern era. Hippocrates (460–370 BCE) first described the relationship between "foamy urine" and renal disease. Avicenna (Ibn Sina) (980–1037), the Persian physician, also addressed this relationship.[1,2] In 1832, Dr. Richard Bright explained the association of proteinuria and kidney disease.[3] Today, proteinuria is defined as excretion of more than 150 mg of proteinuria within 24 hours. There are different types of protein which may be excreted in the urine of healthy individuals, including albumin, immunoglobulins, and Tamm–Horsfall mucoprotein, which is the most abundant urinary protein in individuals with normal renal function.[4] Albuminuria is the hallmark of glomerular damage and a consequence of impaired glomerular filtration function. A graded association between albuminuria and adverse outcomes regardless of cause of kidney disease and glomerular filtration rate (GFR) categories has been established.[5]

DEFINITION OF PROTEINURIA

There are different types of proteinuria which may indicate the site of damage along the nephron.[6] Albuminuria is a marker of injury to the glomerular filtration barrier, while urinary excretion of predominantly low molecular weight proteins (such as beta-2 microglobulin and alpha-1 macroglobulin) may be viewed as potential evidence of tubular damage or overflow proteinuria, but low molecular weight proteinuria can also be seen in glomerular disease.[7,8] Proteinuria greater than 3.5 g/day or nephrotic range proteinuria with or without nephrotic syndrome suggests underlying glomerulopathy, such as focal segmental glomerulosclerosis (FSGS), membranous nephropathy, minimal change disease, diabetic nephropathy, or amyloidosis.

Non-nephrotic proteinuria has a distinct differential diagnosis. Non-nephrotic proteinuria may be associated with glomerular diseases, however, the differential diagnosis expands to include each renal compartment, including diseases of the renal vasculature and tubulointerstitium.

Proteinuria is classically categorized into glomerular, tubular, and overflow etiologies.[9] The structure of the glomerular basement membrane (GBM) allows the passage of small amounts of protein each day through diffusion and convection. This protein is then largely reabsorbed in the proximal convoluted tubule.[10] Tamm–Horsfall protein is secreted into the tubule in the thick ascending limb of Henle's loop.[11]

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00058-9

The glomerular filtration barrier consists of three layers.[12] The first layer is the endothelial fenestrae, which are in direct contact with the blood.[12] The fenestrations are pores that measure less than 100 nm in diameter and are coated with a negatively charged glycocalyx which serves as both a size and charge barrier to passage of negatively charged molecules greater than 100 nm, including albumin.[12] The second layer is the GBM, made up of type IV collagen and laminin, along with negatively charged proteoglycans, including heparin sulfates.[12] The third or outermost layer is composed of the visceral epithelial cells or podocytes, with their interdigitating foot processes, linked by slit diaphragms which create pore sizes up to 7 nm in diameter.[12] The filtration barrier favors the passage of small (up to 35 nm) and uncharged or cationic molecules.[12]

Albumin is a 70 kD molecule with a diameter of 6 nm and anionic charge. Albumin is filtered by the glomerulus and is mostly reabsorbed by the proximal tubule by receptor-mediated endocytosis.[11,13] Under normal circumstances up to 20–30 mg of albumin is excreted each day.[11,13] Defects in the glomerular filtration barrier (glomerular proteinuria) or tubular reabsorption of filtered protein (tubular proteinuria) or an excessive overload of filtered proteins (overflow proteinuria) that overwhelms tubular reabsorptive capabilities can lead to pathologic levels of proteinuria.

Glomerular proteinuria mostly comprises albumin and occurs because of defects in the size and charge selective barrier.[9,13] This can occur from a variety of glomerular diseases that may result from inflammation, deposition, scarring, or genetic conditions that affect integral membrane proteins, including nephrin and podocin. The majority of the albumin that is filtered across the glomerulus is reabsorbed in the proximal tubule, such that only 4–7 mg of albuminuria is typically found in the urine of individuals with normal renal function.[9,13] Albuminuria above 30 mg/day and less than 300 mg/day (previously termed microalbuminuria) is now considered "moderate albuminuria" in the most recent KDIGO chronic kidney disease (CKD) staging guidelines.[14] Increasing levels of albuminuria are a marker of endothelial injury and are associated with increased risk of cardiovascular disease (CVD). Albuminuria over 300 mg/day is called "severely increased albuminuria" (previously termed macroalbuminuria) and is the level at which standard urine dipsticks are able to detect proteinuria.[14]

Tubular proteinuria is made up of low molecular weight proteins <25 kD, including beta-2 microglobulin, retinol-binding protein, immunoglobulin light chains, and breakdown products of albumin.[8,15] These proteins are generally freely filtered across the glomerular filtration barrier and undergo tubular reabsorption. Tubular proteinuria can be increased in both tubulointerstitial and glomerular diseases. Urine dipsticks detect albumin and are not sensitive for the detection of tubular proteins which are typically excreted in low levels.

Overflow proteinuria occurs with overproduction of proteins, including immunoglobulin light chains in multiple myeloma, myoglobin in the setting of rhabdomyolysis, lysozyme with acute myelomonocytic leukemia, and free hemoglobinuria with intravascular hemolysis that overwhelms the ability of haptoglobin to bind the hemoglobin.[16] The capacity of the proximal tubule to reabsorb the large quantities of proteinuria is often exceeded in these states, leading to nephrotoxic acute renal tubular injury.

PREVALENCE OF PROTEINURIA

Healthy adults excrete less than 150 mg of protein into their urine daily; approximately 20% of this is albumin and the remainder includes Tamm–Horsfall protein, immunoglobulin fragments, and low molecular weight proteins.[17,18] Previous studies estimate the prevalence of microalbuminuria or moderately increased albuminuria (urinary albumin:creatinine ratio [UACR] 30–300 mg/g) to be between 5.1% and 8.2% in the general population. The prevalence of severely increased albuminuria, previously known as macroalbuminuria, is estimated in the general population to be less than 2%.[19,20] However, many conditions are associated with increased risk of developing albuminuria, such as type 1 and type 2 diabetes,[21–23] obesity,[24] hypertension,[25] urologic disease,[26] and renal malignancy.[27]

SIGNIFICANCE

Proteinuria is a significant predictor of CKD progression, development of end-stage renal disease (ESRD), and is associated with cardiovascular mortality. Albuminuria is associated with worse prognosis at every stage of CKD.[20] According to the 2018 Center for Disease Control National Vital Statistic Report, proteinuric kidney disease (including nephritis, nephrotic syndrome, and nephrosis) was the ninth leading cause of death in 2015 and 2016.[28] Several trials have demonstrated the association of proteinuria with estimated GFR (eGFR) decline. In a subgroup analysis of the Modification of Diet in Renal Disease study, patients with greater than 3 g of proteinuria had an eGFR decline of 5.7–6.6 mL/min/year.[29,30] In the African American Study of Kidney Disease and Hypertension (AASK) trial, the median time to ESRD in patients with eGFR of 30 mL/min/min/1.73 m^2 varied by nearly 5 years for patients with lower vs. higher levels of proteinuria.[31] Conversely, reduction of proteinuria by angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin

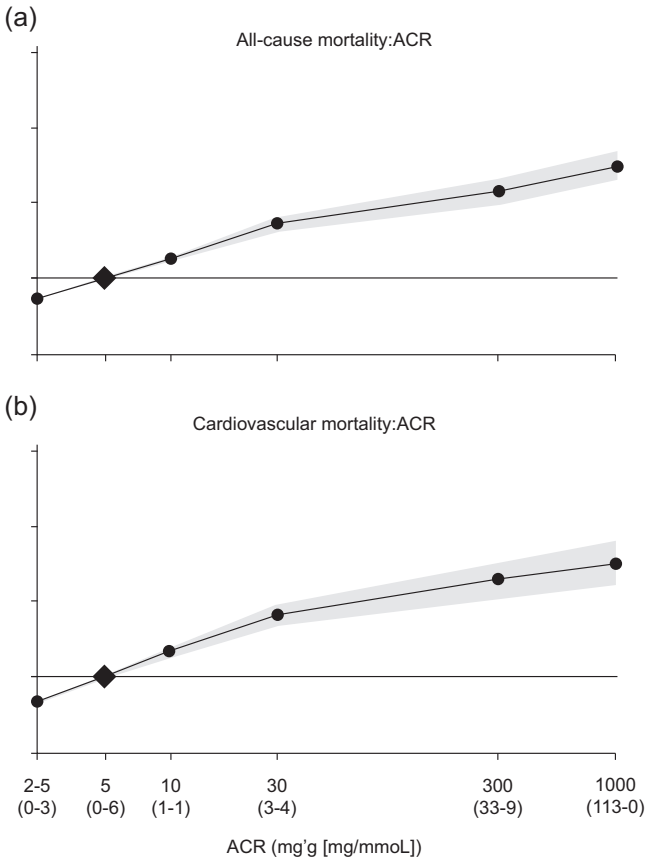


FIGURE 58.1 Relationship of albuminuria with mortality. Hazard ratios and 95% CIs (*shaded areas*) according to albumin:creatinine ratio (ACR) (a, b) adjusted for each other, age, sex, ethnic origin, history of cardiovascular disease, systolic blood pressure, diabetes, smoking, and total cholesterol. The reference (*diamond*) was ACR 5 mg/g (0·6 mg/mmol). Circles represent statistically significant and triangles represent not significant. ACR plotted in mg/g. To convert ACR in mg/g into mg/mmol multiply by 0·113. Approximate conversions to mg/mmol are shown in parentheses. *Reprinted with permission from reference 33 (Elsevier).*

receptor blockers (ARBs) was associated with reduction of the risk of both developing ESRD and with decline of GFR. In the Ramipril Efficacy in Nephropathy (REIN) trial, patients with 3 g or more of proteinuria were randomized to treatment with ramipril or a placebo plus conventional antihypertensives to achieve a goal diastolic BP less than 90 mm Hg.[32] At the end of the follow-up period, the mean absolute GFR was 12 mL/min higher in the ramipril group than the placebo group.[32]

Proteinuria is also significantly associated with CVD morbidity. In a meta-analysis of the CKD Prognosis Consortium, investigators demonstrated that UACR had a linear relationship to all cause and CVD mortality (Figure 58.1).[33] Similarly, a meta-analysis of 10 cohorts including 266,975 patients demonstrated that albuminuria and eGFR were multiplicatively associated with all-cause mortality and CVD mortality, independent of each other and of CVD risk factors.[34] Because of the important relationship between albuminuria and all cause and CVD mortality, as well as risk of CKD progression to ESRD, the KDIGO classification of CKD was updated to include albuminuria as well (Figure 58.2).

DIAGNOSTIC APPROACH TO NON-NEPHROTIC RANGE PROTEINURIA IN PATIENTS WITHOUT DIABETES

The approach to non-nephrotic range proteinuria in patients without diabetes is summarized in six steps (Table 58.1 and Figure 58.3).

History and Physical Examination

A comprehensive history and physical examination should be done with emphasis on signs and symptoms of primary and secondary renal disorders. Comorbidities such as hypertension, diabetes, inflammatory conditions, malignancies, and chronic infections may suggest etiologies of proteinuria. Family history of kidney disease may be positive in hereditary kidney disorders such as hereditary nephritis. A variety of renal diseases are caused or associated with medications. Therefore, a careful review of current and prior medications is essential. Patients may not report use of over-the-counter medications, supplements, or herbal medicines. Further questioning the patient about all medications and supplements and duration of therapy is useful. Physical examination should include blood pressure measurement and a thorough cardiopulmonary examination, as well as attention to skin lesions, which may be seen in some systemic disorders with renal involvement. Edema is an important finding, however, it is more likely in patients with nephrotic range proteinuria.

Obtaining a detailed history of comorbidities based on self-reported history and objective features can provide helpful information for the diagnostic approach. For example, duration of hypertension may not be clearly known for some patients. Objective features such as hypertensive retinopathy and left ventricular hypertrophy noted on ECG or echocardiogram may suggest chronic long-standing hypertension as a potential cause of kidney disease, in contrast to a recent onset of hypertension, which may be a consequence of acute or chronic kidney diseases. Absence of signs and symptoms of microvascular complications of diabetes, such as diabetic retinopathy and neuropathy, may indicate etiologies of proteinuria other than diabetic kidney

Percentage of US Population by eGFR and Albuminuria Category: KDIGO 2012 and NHANES 1999-2006				Persistent albuminuria categories Description and range			
				A1	A2	A3	
				Normal to mildly increased <30 mg/g <3 mg/mmol	Moderately increased 30-300 mg/g 3-30 mg/mmol	Severely increased >300 mg/g >30mg/mmol	
GFR categories (ml/min/ 1.73m²) Description and range	G1	Normal or high	≥90	55.6	1.9	0.4	57.9
	G2	Mildly decreased	60-89	32.9	2.2	0.3	35.4
	G3a	Mildly to moderately decreased	45-59	3.6	0.8	0.2	4.6
	G3b	Moderately to severely decreased	30-44	1.0	0.4	0.2	1.6
	G4	severely decreased	15-29	0.2	0.1	0.1	0.4
	G5	Kidney failure	<15	0.0	0.0	0.1	0.1
				93.2	5.4	1.3	100.0

FIGURE 58.2 Prevalence of chronic kidney disease (CKD) in the US by glomerular filtration rate (GFR) and albuminuria.

TABLE 58.1 Approach to the Nondiabetic Patient with Non-nephrotic Proteinuria

1. Comprehensive history and physical examination
2. Urine studies
3. Serological workup
4. Kidney imaging
5. Renal biopsy
6. Genetic studies

disease. Non-nephrotic range proteinuria in a diabetic patient is not necessarily due to diabetic kidney disease, and other etiologies should be considered as well. Review of past recorded diagnoses and all comorbidities with attention to the onset and duration of the disorders can provide useful diagnostic clues. Questioning about the accuracy of past documented and "labeled" diagnoses may be necessary, and sometimes can change the entire diagnostic approach.

Urine Studies

The first step in the diagnostic approach to proteinuria is to confirm the result by performing a quantitative test for proteinuria on a random urine sample, followed by an additional test on an early morning urine sample excluding the possibility of orthostatic proteinuria. Orthostatic proteinuria and other benign functional causes of proteinuria are more likely with low grade levels of proteinuria (especially less than 1 g/day) and in younger individuals. The presence of hypertension, decreased GFR, microscopic hematuria, and cellular casts excludes benign functional causes of proteinuria and, therefore, obviates the need for an early morning urine sample to rule out orthostatic proteinuria. Obtaining the prior records of urine studies is helpful to understand the acuity of the process. Benign functional causes of proteinuria are mainly transient. Such transient proteinuria may be associated with fever, exercise, or urinary tract infection.[35–37] Transient proteinuria has been found in 11% of the school-age population, aged 8–15 years. In the absence of other signs of kidney disease, such as hematuria, isolated proteinuria (up to 1 g in 24 hours) may not warrant additional evaluation (such as renal biopsy).[38]

URINE DIPSTICK

Urine dipstick analysis is a common test performed as part of the initial evaluation of patients with renal diseases. Understanding the limitations of urine dipstick testing for proteinuria is important. A concentrated urine specimen or an alkaline urine or use of certain medications such as phenazopyridine may cause a false positive result for proteinuria. On the other hand, acidic urine or dilute urine may cause false-negative results. Therefore, urine-specific gravity and urine pH should be considered for interpretation of a urine dipstick result. Urine dipstick testing after iodinated contrast exposure may also result in a false-positive test for proteinuria.[39]

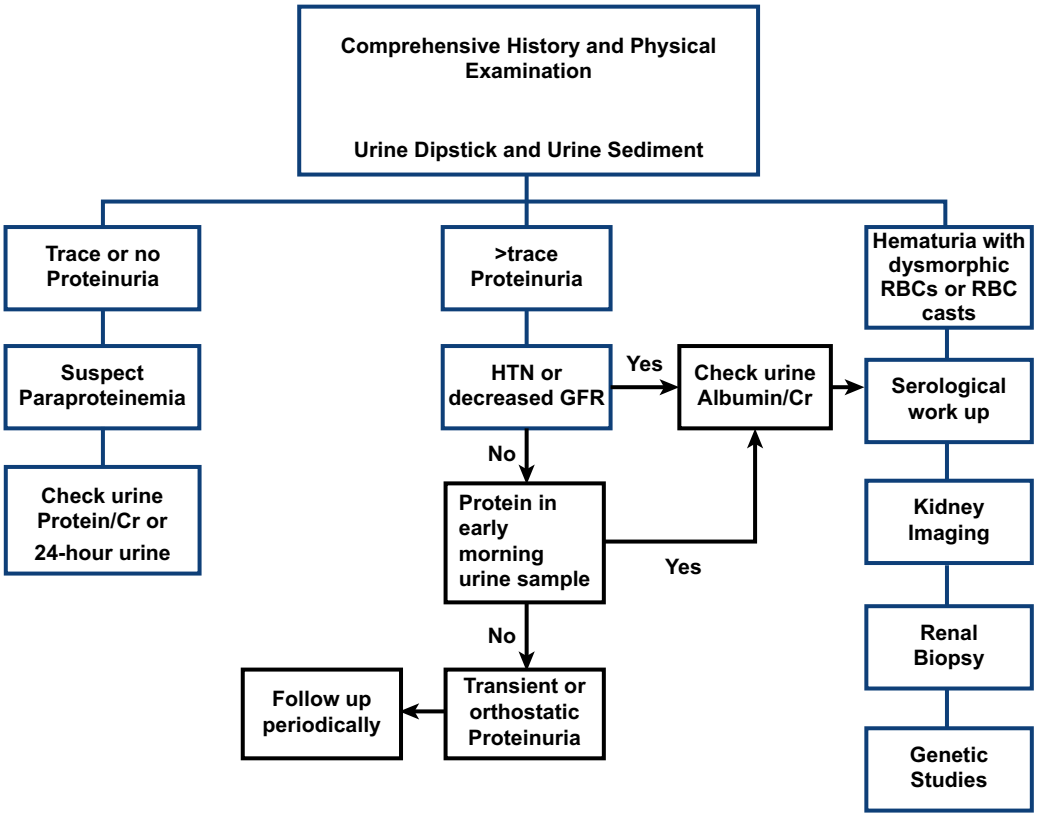


FIGURE 58.3 Approach to non-nephrotic proteinuria.

Urine dipstick cannot detect all proteins. It can only detect albuminuria. Therefore, another example of a false-negative urine dipstick result for proteinuria would be overflow proteinuria found in paraproteinemias, such as multiple myeloma. The presence or absence of other urine abnormalities, such as hematuria or leukocyturia, may also result in a positive test for proteinuria.

A negative urine dipstick for protein excludes proteinuria of a level of more than 1 g/g creatinine. Urine dipstick showing 4+ protein has a more than 90% chance of being associated with proteinuria more than 1 g/g creatinine on a random urine sample. Urine specific gravity and urine pH should be considered specifically in those individuals with 1+ proteinuria. A patient with concentrated and alkaline urine with 1+ proteinuria is less likely to have proteinuria more than 1 g/g creatinine.[40]

URINE ALBUMIN:CREATININE RATIO

Compared with urine dipstick, UACR has superior predictive ability for cardiovascular events.[41] UACR is helpful to identify glomerular damage. The potential pitfall of UACR is missing the overflow proteinuria found in paraproteinemias such as multiple myeloma. Measurement of total proteins by checking urine protein:creatinine ratio (UPCR) or by using 24-hour urine studies or urine protein electrophoresis can address this pitfall. Therefore, other urine studies in addition to UACR are required when paraproteinemia is suspected. Bone pain, anemia, hypercalcemia, and serum globulin gap may be diagnostic clues in patients suspected of having multiple myeloma.[42]

URINE PROTEIN:CREATININE RATIO

Close correlation between random UPCR and 24-hour urine protein excretion has been demonstrated.[43] Compared with UACR, UPCR (which includes albumin and nonalbumin proteins) has similar predictive ability for common complications of chronic kidney disease.[44] A protein gap between urine total protein and urine albumin suggests presence of paraproteins seen in disorders such as multiple myeloma.

UPCR and UACR may be influenced by race, sex, muscle mass, and nutritional status. Given that the urine creatinine concentration is in the denominator of these ratios, it may result in underestimation of proteinuria in patients with large muscle mass and overestimation of proteinuria in patients with poor nutritional status and lower muscle mass.[45,46]

24-HOUR URINE STUDIES

The 24-hour urine study is the gold standard for measurement of proteinuria, however, it is cumbersome and prone to overcollection and undercollection. Quantification of proteinuria based on a spot urine sample has become the common practice. 24-hour urine study is still performed for confirmation purposes or in cases of monitoring for high degree proteinuria when a spot urine sample may not be reliable. In patients with lupus nephritis, spot urine sample was found to be unreliable. 24-hour urine study is suggested for monitoring proteinuria in patients with lupus nephritis.[47] An alternative method is to check overnight 12-hour urine collection, which has been shown to be in agreement with 24-hour urine studies and is more convenient.[47]

URINE SEDIMENT

Microscopic examination of the urine sediment is helpful to narrow the differential diagnoses of non-nephrotic range proteinuria. The presence of dysmorphic RBCs, acanthocytes with blebs protruding from the cell membranes and RBC casts suggest glomerular hematuria. Acanthocyturia >5% is highly suggestive of glomerular hematuria. A patient with non-nephrotic range proteinuria and glomerular hematuria may have primary or secondary glomerulopathy. Identifying leukocytes with an associated negative urine culture (sterile pyuria) may suggest acute or chronic tubulointerstitial disease as the potential etiology for non-nephrotic range proteinuria.

SEROLOGIC EVALUATION

There is no "routine" serologic evaluation recommended for all patients with non-nephrotic range proteinuria. When no clear etiology for the proteinuria is established, however, serologic evaluation for infectious, autoimmune, or neoplastic etiologies would be warranted (Table 58.2). Such serologic evaluation should be guided and tailored based on a comprehensive history and physical examination. Investigation for infectious etiologies such as human immunodeficiency virus (HIV), syphilis, and hepatitis B and C viruses should be considered, especially in those individuals with risk factors, such as history of intravenous drug use, unsafe sexual practice, or exposure to blood products. Many patients with HIV infection may present with proteinuria, therefore, HIV infection should be screened in patients who have non-nephrotic range proteinuria with unclear etiology.[48,49] Patients with hepatitis B- and C-associated glomerulonephritides may present with non-nephrotic range proteinuria, usually with concomitant hematuria.[50,51] Patients with syphilis-associated membranous nephropathy may present with proteinuria ranging from mild to nephrotic range.[52] Autoimmune processes should be suspected in young patients and those with a family history of disorders such as lupus and vasculitis. Serologic tests, including evaluation of antinuclear antibody, anti-dsDNA antibody, antineutrophil cytoplasmic antibody, and serum complements, can be helpful in the diagnostic approach to non-nephrotic range proteinuria. Serologic evaluation for malignancies such as multiple myeloma may also be considered. A subset of patients with myeloma including those with amyloidosis and monoclonal immunoglobulin deposition disease may also present with non-nephrotic range proteinuria.[53,54]

TABLE 58.2 Serologic Evaluation of Non-nephrotic Proteinuria

Endocrine Disorders	Fasting Glucose or Hemoglobin A1c
Infectious etiologies	HIV antibody, hepatitis B surface antigen, hepatitis C antibody, RPR
Rheumatologic diseases	ANA, C3, C4, Anti-ds-DNA, Cryoglobulins, ANCA, anti-MPO, anti-PR3
Paraprotein-related diseases	Serum protein electrophoresis, kappa:lambda free light chain ratio, 24-hour urine protein electrophoresis
Primary renal diseases	Phospholipase A2 receptor antibody

Abbreviations: *ANA*, antinuclear antibodies; *ANCA*, antineutrophil cytoplasmic antibodies; *Anti-dsDNA*, antidouble stranded DNA; *Anti-MPO*, antibodies to myeloperoxidase; *anti-PR3*, antibodies to proteinase-3; *C3*, complement component C3; *C4*, complement component C4; *RPR*, rapid plasma reagin.

KIDNEY IMAGING

Renal ultrasonography is a common imaging modality for initial evaluation of kidney diseases. Other imaging modalities to investigate renal disorders include abdominal plain X-ray, computed tomography scan, magnetic resonance imaging, Doppler ultrasound studies, renal nuclear scans, and pyelography studies. All patients who have a decline in kidney function with unclear etiology should be evaluated with renal imaging studies, especially to exclude obstructive uropathy. Patients with proteinuria and preserved GFR should obtain renal imaging to exclude structural kidney diseases such as a single kidney, congenital anomalies, or cystic diseases. Ultrasonography is critical to assess renal size and echotexture before consideration of a kidney biopsy.

RENAL BIOPSY

Renal biopsy may be considered in the evaluation of non-nephrotic range proteinuria to establish the diagnosis, however, the therapeutic management may be changed in only a small percentage of patients (<15%).[55] Overall, patients with isolated non-nephrotic range proteinuria have a better prognosis than patients with nephrotic range proteinuria. In a Japanese study, 11% of 151 patients with asymptomatic proteinuria developed CKD stage 3 and/or a S[Cr] of more than 1.5 mg/dL within a mean follow-up of approximately 6 years. Proteinuria disappeared in 23% of patients. IgA nephropathy was the dominant diagnosis (68%).[56]

Many nephrologists proceed with renal biopsy in patients who have more than 1 g proteinuria. A lower threshold of 500 mg proteinuria may be used in the presence of systemic diseases such as systemic lupus erythematosus. Periodic follow-up visits are required for those patients with isolated non-nephrotic range proteinuria who do not undergo renal biopsy.

MOLECULAR GENETIC STUDIES

Genetic studies should be considered, especially in those patients with non-nephrotic range proteinuria and a family history of renal disease. Patients with a known family history of Fabry disease or Alport syndrome may proceed to genetic testing without the need for renal biopsy. Family counseling and prenatal diagnosis can be offered according to the genetic test results. Molecular genetic testing is accurate and noninvasive. Genetic study is confirmatory for Fabry disease.[57,58] Non-nephrotic range proteinuria may be the initial manifestation of Fabry disease in those individuals with renal limited disease.[57,58] In patients with a family history of Alport syndrome with a known mutation, molecular genetic testing can be done for that target gene.[59] A positive test for the same mutation will eliminate the need for renal biopsy. DNA sequencing is an option for those patients with other characteristics of Alport syndrome, without the family history of Alport syndrome.[59,60] Therefore, such genetic testing can be offered to a patient who presents with non-nephrotic range proteinuria (less than 1–2 g proteinuria) who does not wish to undergo renal biopsy, especially in cases with a positive family history or nonrenal characteristics of the disease. Genetic testing is also available for patients with FSGS. Absence of family history does not exclude the need for genetic testing, as many of the genes known to cause FSGS have incomplete penetrance.[61] Genetic testing for ApoL1 is also available to confirm the association with FSGS in patients of African descent. The result does not change the direct treatment of affected individuals, however it may affect family counseling, specifically in cases of potential kidney donor evaluation. Renal allograft outcomes have been associated with high-risk ApoL1 genotypes.[62]

TREATMENT

Control of blood pressure to a goal of at least <130/80 mm Hg remains the most important treatment for patients with proteinuria.[63–66] Inhibition of the renin–angiotensin–aldosterone system (RAAS) is first-line antihypertensive therapy for all patients with proteinuric renal disease unless contraindicated.[64] RAAS inhibitors, including ACEIs and ARBs, act to reduce glomerular filtration through vasodilatation of the efferent arteriole through inhibition of angiotensin II. These medications have been shown to decrease proteinuria independent of their effect to control hypertension. Other mechanisms which contribute to the antiproteinuric effect of ACEIs include increased levels of bradykinin, which vasodilates the efferent arteriole, restoration of the size and charge selectivity of the glomerular filtration barrier, and decreased production of transforming growth factor-β. Several clinical trials support the use of RAAS inhibition in the treatment of patients with nondiabetic kidney disease. Combination of a low sodium diet, diuretic therapy, and RAAS inhibition may lead to a greater reduction in proteinuria.[67]

The REIN study[68] evaluated whether administration of ACEI is more effective than conventional therapy at slowing progression of nondiabetic kidney disease. 352 patients were separated into two proteinuria strata. Stratum 1 was 1–3 g/24 h and stratum 2 was >3 g/24 h. Patients were randomly assigned to ramipril or placebo, including standard antihypertensive therapy to achieve a diastolic blood pressure <90 mm Hg. 186 patients in stratum 1 were randomized. The primary outcomes were a change in GFR and time to ESRD or nephrotic range proteinuria >3.5 g/24 h with a median follow-up of 31 months. The decline in GFR per month was not significantly different in patients with non-nephrotic proteinuria. Progression to ESRD, however, was significantly lower in patients who received ACEI with a relative risk reduction of 2.72 [1.27–4.52]. Progression to nephrotic range proteinuria was also significantly lower in the ramipril group. In subgroup analysis, patients with proteinuria >1.5 g/24 h or eGFR <45 m/min/1.73 m^2 benefited more from ACEI therapy.[69] Proteinuria decreased by 13% in the ACEI group and increased by 15% in the placebo arm.[69]

The AASK trial[70] included 1094 African-American patients with CKD secondary to hypertension. Mean protein excretion was 600 mg/24 h in men and 400 mg/24 h in women. Patients were randomly

assigned to ramipril 2.5–10 mg/day, amlodipine 5–10 mg/day, or metoprolol 50–200 mg/day. The primary outcome was the rate of change in GFR, and the secondary outcome was a composite of reduction in GFR of >50 percent or >25 mL/min/1.73 m^2, ESRD or death. Approximately 33% of patients had a UPCR >0.22 (mean protein excretion 1.5 g/24 h in men and 1.2 g/24 h in women). In this subgroup of patients, ramipril led to a 36% decrease in the rate of decline in GFR and a 48% decrease in the composite endpoint. However, patients with UPCR of 0.22 or less had no change in decline in GFR or composite endpoint. The AASK trial provides additional evidence for the benefit of ACEI in patients with non-nephrotic proteinuria.

Mineralocorticoid receptor antagonists (MRAs) can be added to therapy with ACEIs or ARBs to further decrease proteinuria when clinically indicated.[65,71,72] Caution should be used whenever combination RAAS blockade is employed, as rates of hyperkalemia are significantly higher. Combination of ACEI with ARB is no longer used as an antiproteinuric strategy due to higher rates of acute kidney injury and hyperkalemia.[73,74] MRAs should be avoided in patients with advanced CKD due to higher risk of hyperkalemia. A new MRA, finerenone,[75] has been shown to decrease proteinuria with lower rates of hyperkalemia compared with older formulations such as spironolactone and eplerenone.

Nondihydropyridine calcium channel blockers such as verapamil and diltiazem decrease proteinuria through reduction in glomerular filtration pressure. Dihydropyridine calcium channel blockers including amlodipine, felodipine, and nifedipine are effective antihypertensive medications, however, they do not lower proteinuria to the same extent as nondihydropyridine calcium channel blockers because of differential effects on the glomerular capillary bed.[76]

Vitamin D may also have a role in reducing proteinuria through decreasing prorenin gene expression, thus inhibiting the RAAS system.[77] Vitamin D may also decrease proinflammatory cytokines.[77] A randomized controlled trial of diabetic patients treated with the active vitamin D analogue paricalcitol showed a 20% reduction in proteinuria in the active treatment arm.[78] Another study found that treatment with an active vitamin D analogue has an additive effect to reduce proteinuria in patients already treated with RAAS inhibitors.[77]

Endothelin receptor antagonists are being studied to assess their antiproteinuric effects. Activation of the endothelin A receptor (ETA) leads to vasoconstriction of vascular smooth muscle. Inhibition of ETA causes vasodilation of the glomerular capillary bed, which leads to reduced permeability to albumin. Activation of the endothelin B receptor reduces arterial pressure by decreasing sodium and water reabsorption along the nephron. Avosentan, an ETA antagonist, was shown to reduce albuminuria but at the expense of causing edema and decompensated CHF.[79] Atrasentin is an alternative ETA antagonist which may cause less edema and still have similar antiproteinuric effects.[80]

Statin therapy is recommended for all patients with CKD older than age 50.[81] Statins have multiple pleiotropic effects. In some observational studies, statins may also have an antiproteinuric effect independent of their lipid lowering effects. In one retrospective controlled study,[82] 51 patients with Stages 3 and 4 CKD were evaluated over 53 weeks. Patients received treatment with simvastatin or no treatment. At the end of the treatment period, urine protein excretion decreased from 0.96 to 0.48 g/g creatinine in patients who received simvastatin in addition to an ACEI or ARB compared with no change in patients who did not receive statin therapy.

The role of limiting dietary protein intake to reduce proteinuria remains controversial. Some studies suggest that restricting dietary protein intake will help to reduce proteinuria and progression of CKD.[83,84] However, results are mixed. The National Kidney Foundation recommends restricting protein intake to 0.8–1.0 g/kg/day.[85]

Lifestyle modification including smoking cessation and weight reduction may also help to reduce proteinuria.[86,87] Obesity is associated with glomerular hyperfiltration. Obese patients (defined as a BMI >27 kg/m^2) who lost weight in an RCT had reduction in proteinuria compared with those patients who maintained the same weight.[86]

If a renal biopsy is performed, immunosuppression therapy may be a cornerstone of antiproteinuric therapy for patients with acute glomerulonephritis and tubulointerstitial nephritis. These patients often have subnephrotic proteinuria that will not respond to conservative therapy in the absence of specific treatment for the inflammatory renal disease. Immunosuppression options may include corticosteroids, calcineurin inhibitors, mycophenolate mofetil, and rituximab. Both cyclosporine and rituximab[88,89] have been shown to have direct effects on the podocyte to stabilize the actin cytoskeleton which helps to reduce proteinuria independent of their antiinflammatory properties.

CONCLUSION

The development of proteinuria has significant prognostic implications for progression of CKD and increased cardiovascular risk. The type of proteinuria may provide important diagnostic clues to the etiology

of CKD. Evaluation includes review of the urine sediment, serologic evaluation, and renal biopsy if appropriate. Lifestyle modification and antagonism of the RAAS form the cornerstone of conservative management for all patients with proteinuric kidney disease. Immunosuppressive therapy may be indicated depending on the etiology of the patient's renal disease. Additional specific therapies to reduce proteinuria and slow progression of CKD are eagerly awaited.

References

1. Adams F. *The genuine works of Hippocrates*, vol. 2. London: Sydenham Society; 1849. p. 766.
2. Faridi P, Roozbeh J, Mohagheghzadeh A. Ibn-Sina's life and contributions to medicinal therapies of kidney calculi. *Iran J Kidney Dis* 2012;**6**(5):339–45.
3. Bright R. Cases and observations, illustrative of renal disease accompanied with the secretion of albuminous urine. *London Med Gaz* 1835:72–4.
4. Bachmann S. A novel role for Tamm-Horsfall protein (uromodulin) in the renal tubule. *Kidney Int* 2018;**94**(4):652.
5. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. *J Am Med Assoc* 2010; **303**(5):423–9.
6. Carroll MF, Temte JL. Proteinuria in adults: a diagnostic approach. *Am Fam Physician* 2000;**62**:1333.
7. Portman RJ, Kissane JM, Robson AM. Use of beta 2 microglobulin to diagnose tubulointerstitial renal lesions in children. *Kidney Int* 1986;**30**:91.
8. Sesso R, Santos AP, Nishida SK, et al. Prediction of steroid responsiveness in the idiopathic nephrotic syndrome using urinary retinol-binding protein and beta-2 microglobulin. *Ann Intern Med* 1992;**116**:905.
9. D'Amico G, Bazzi C. Pathophysiology of proteinuria. *Kidney Int* 2003;**63**:809–25.
10. Russo LM, Sandoval RM, McKee M, et al. The normal kidney filters nephrotic levels of albumin retrieved by proximal tubule cells: retrieval is disrupted in nephrotic states. *Kidney Int* 2007;**71**:504.
11. Hoyer JR, Seiler MW. Pathophysiology of Tamm-Horsfall protein. *Kidney Int* 1979;**16**:279–89.
12. Ehtesham A, Nihalani D. Glomerular filtration barrier assembly: an insight. *Postdoc J* 2013;**1**:33–45.
13. Dickson LE, Wagner MC, Sandoval RM, Molitoris BA. The proximal tubule and albuminuria: really! *J Am Soc Nephrol* 2014;**25**:443.
14. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2013;**1**:1–136.
15. Schardijn GH, Statius van Eps LW. Beta 2-microglobulin: its significance in the evaluation of renal function. *Kidney Int* 1987; **32**(5):635–41.
16. Barratt J, Topham P. Urine proteomics: the present and future of measuring urinary protein components in disease. *CMAJ* 2007; **177**:361.
17. Waller K, Ward KM, Mahan JD, Wismatt DK. Current concepts in proteinuria. *Clin Chem* 1989;**35**:755–65.
18. Kim MS. Proteinuria. *Clin Lab Med* 1988;**8**:527–40.
19. Konta T, Hao Z, Abiko H. Prevalence and risk factor analysis of microalbuminuria in Japanese general population: the Takahata study. *Kidney Int* 2006;**70**(4):751–6.
20. Garg AX, Kiberd BA, Clark WF, Haynes RB, Clase CM. Albuminuria and renal insufficiency prevalence guides population screening: results from the NHANES III. *Kidney Int* 2002;**61**(6): 2165–75.
21. Amin R, Widmer B, Prevost AT, Schwarze P, Cooper J, Edge J, Marcovecchio L, Neil A, Dalton RN, Dunger DB. Risk of microalbuminuria and progression to macroalbuminuria in a cohort with childhood onset type 1 diabetes: prospective observational study. *BMJ* 2008;**336**(7646):697–701.
22. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR, UKPDS Group. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int* 2003;**63**(1):225–32.
23. Hovind P, Tarnow L, Rossing P, Jensen BR, Graae M, Torp I, Binder C, Parving HH. Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: inception cohort study. *BMJ* 2004;**328**(7448):1105.
24. Pinto-Sietsma SJ, Navis G, Janssen WM, de Zeeuw D, Gans RO, de Jong PE, PREVEND Study Group. A central body fat distribution is related to renal function impairment, even in lean subjects. *Am J Kidney Dis* 2003;**41**(4):733–41.
25. Ritz E, Nowicki M, Fliser D, Horner D, Klimm HP. Proteinuria and hypertension. *Kidney Int Suppl* 1994;**47**:S76–90.
26. Bezinque A, Noyes SL, Kirmiz S, Parker J, Dey S, Kahnoski RJ, Lane BR. Prevalence of proteinuria and other abnormalities in urinalysis in the urology clinic. *Urology* 2017;**103**:34–8.
27. Vaglio A, Buzio L, Cravedi P, Pavone L, Garini G, Buzio C. Prognostic significance of albuminuria in patients with renal cell cancer. *J Urol* 2003;**4**(1):1135–7.
28. Heron M. Deaths: Leading Causes for 2016. National Center for Health Statistics. *Natl Vital Stat Rep* 2018;**67**(6).
29. Peterson JC, Adler S, Burkart JM, Greene T, Hebert LA, Hunsicker LG, King AJ, Klahr S, Massry SG, Seifter JL. Blood pressure control, proteinuria, and the progression of renal disease. The modification of diet in renal disease study. *Ann Intern Med* 1995; **123**(10):754–62.
30. Ruggenenti P, Gaspari F, Perna A, Remuzzi G. Cross sectional longitudinal study of spot morning urine protein:creatinine ratio, 24 hour urine protein excretion rate, glomerular filtration rate, and end stage renal failure in chronic renal disease in patients without diabetes. *BMJ* 1998;**316**(7130):504–9.
31. Grams ME, Li L, Greene TH, Tin A, Sang Y, Kao WHL, Lipkowitz MS, Wright JT, Chang AR, Astor BC, Appel LJ. Estimating time to ESRD using kidney failure risk equations: results from the African American Study of Kidney Disease and Hypertension (AASK). *Am J Kidney Dis* 2015;**65**(3):394–402.
32. Ruggenenti P, Perna A, Gherardi G, Gaspari F, Benini R, Remuzzi G. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril Efficacy in Nephropathy. *Lancet* 1998;**352**(9136):1252–6.
33. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality: a collaborative meta-analysis of general population cohorts. *Lancet* 2010;**9731**:2073–81.
34. van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, de Jong P, Gansevoort RT, Chronic Kidney Disease Prognosis Consortium, van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey AS, de Jong PE, Gansevoort RT, Levey A, El-Nahas M, Eckardt KU, Kasiske BL, Ninomiya T, Chalmers J, Macmahon S, Tonelli M, Hemmelgarn B, Sacks F, Curhan G, Collins AJ, Li S, Chen SC, Hawaii Cohort KP, Lee BJ, Ishani A, Neaton J, Svendsen K, Mann JF, Yusuf S, Teo KK, Gao P, Nelson RG, Knowler WC, Bilo HJ, Joosten H, Kleefstra N, Groenier KH, Auguste P, Veldhuis K, Wang Y, Camarata L, Thomas B, Manley T. Lower estimated glomerular filtration and higher albuminuria are associated with all-cause and

cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2011;**79**(12):1341−52.
35. Carter JL, Tomson CR, Stevens PE, Lamb EJ. Does urinary tract infection cause proteinuria or microalbuminuria? A systematic review. *Nephrol Dial Transplant* 2006;**21**(11):3031−7.
36. Robinson RR. Isolated proteinuria in asymptomatic patients. *Kidney Int* 1980;**18**(3):395−406.
37. Vehaskari VM, Rapola J. Isolated proteinuria: analysis of a school-age population. *J Pediatr* 1982;**101**(5):661−8.
38. Nicot GS, Merle LJ, Charmes JP, et al. Transient glomerular proteinuria, enzymuria, and nephrotoxic reaction induced by radiocontrast media. *J Am Med Assoc* 1984;**252**(17):2432−4.
39. Agarwal R, Panesar A, Lewis RR. Dipstick proteinuria: can it guide hypertension management? *Am J Kidney Dis* 2002;**39**(6): 1190−5.
40. Koeda Y, Tanaka F, Segawa T, et al. Comparison between urine albumin-to-creatinine ratio and urine protein dipstick testing for prevalence and ability to predict the risk for chronic kidney disease in the general population (Iwate-KENCO study): a prospective community-based cohort study. *BMC Nephrol* 2016;**17**(1):46.
41. Kyle RA, Rajkumar SV. Multiple myeloma. *N Engl J Med* 2004; **351**(18):1860−73.
42. Ginsberg JM, Chang BS, Matarese RA, Garella S. Use of single voided urine samples to estimate quantitative proteinuria. *N Engl J Med* 1983;**309**(25):1543−6.
43. Fisher H, Hsu CY, Vittinghoff E, Lin F, Bansal N. Comparison of associations of urine protein-creatinine ratio versus albumin-creatinine ratio with complications of CKD: a cross-sectional analysis. *Am J Kidney Dis* 2013;**62**(6):1102−8.
44. Mattix HJ, Hsu CY, Shaykevich S, Curhan G. Use of the albumin/creatinine ratio to detect microalbuminuria: implications of sex and race. *J Am Soc Nephrol* 2002;**13**(4):1034−9.
45. Carter CE, Gansevoort RT, Scheven L, et al. Influence of urine creatinine on the relationship between the albumin-to-creatinine ratio and cardiovascular events. *Clin J Am Soc Nephrol* 2012;**7**(4): 595−603.
46. Shidham G, Ayoub I, Birmingham D, et al. Limited reliability of the spot urine protein/creatinine ratio in the longitudinal evaluation of patients with lupus nephritis. *Kidney Int Rep* 2018;**3**(5):1057−63.
47. Fine DM, Ziegenbein M, Petri M, et al. A prospective study of protein excretion using short-interval timed urine collections in patients with lupus nephritis. *Kidney Int* 2009;**76**(12):1284−8.
48. Nobakht E, Cohen SD, Rosenberg AZ, Kimmel PL. HIV-associated immune complex kidney disease. *Nat Rev Nephrol* 2016;**12**(5): 291−300.
49. Cohen SD, Kopp JB, Kimmel PL. Kidney diseases associated with human immunodeficiency virus infection. *N Engl J Med* 2017; **377**(24):2363−74.
50. Misiani R, Bellavita P, Fenili D, et al. Hepatitis C virus infection in patients with essential mixed cryoglobulinemia. *Ann Intern Med* 1992;**117**(7):573−7.
51. Lai KN, Li PK, Lui SF, et al. Membranous nephropathy related to hepatitis B virus in adults. *N Engl J Med* 1991;**324**(21):1457−63.
52. Hunte W, al-Ghraoui F, Cohen RJ. Secondary syphilis and the nephrotic syndrome. *J Am Soc Nephrol* 1993;**3**(7):1351−5.
53. Kurita N, Kotera N, Ishimoto Y, et al. AA amyloid nephropathy with predominant vascular deposition in Crohn's disease. *Clin Nephrol* 2013;**79**(3):229−32.
54. Heher EC, Rennke HG, Laubach JP, Richardson PG. Kidney disease and multiple myeloma. *Clin J Am Soc Nephrol* 2013;**8**(11):2007−17.
55. Richards NT, Darby S, Howie AJ, et al. Knowledge of renal histology alters patient management in over 40% of cases. *Nephrol Dial Transplant* 1994;**9**(9):1255−9.
56. Yamagata K, Yamagata Y, Kobayashi M, Koyama A. A long-term follow-up study of asymptomatic hematuria and/or proteinuria in adults. *Clin Nephrol* 1996;**45**(5):281−8.
57. Bennett RL, Hart KA, O'Rourke E, et al. Fabry disease in genetic counseling practice: recommendations of the National Society of Genetic Counselors. *J Genet Couns* 2002;**11**(2):121−46.
58. Nakao S, Kodama C, Takenaka T, et al. Fabry disease: detection of undiagnosed hemodialysis patients and identification of a "renal variant" phenotype. *Kidney Int* 2003;**64**(3):801−7.
59. Martin P, Heiskari N, Zhou J, et al. High mutation detection rate in the COL4A5 collagen gene in suspected Alport syndrome using PCR and direct DNA sequencing. *J Am Soc Nephrol* 1998;**9**(12): 2291−301.
60. Inoue Y, Nishio H, Shirakawa T, et al. Detection of mutations in the COL4A5 gene in over 90% of male patients with X-linked Alport's syndrome by RT-PCR and direct sequencing. *Am J Kidney Dis* 1999; **34**(5):854−62.
61. De Vriese AS, Sethi S, Nath KA, et al. Differentiating primary, genetic, and secondary FSGS in adults: a clinicopathologic approach. *J Am Soc Nephrol* 2018;**29**(3):759−74.
62. Santoriello D, Husain SA, De Serres SA, et al. Donor APOL1 high-risk genotypes are associated with increased risk and inferior prognosis of de novo collapsing glomerulopathy in renal allografts. *Kidney Int* 2018;**94**(6):1189−98.
63. KDIGO 2012 clinical practice guidelines for the management of blood pressure in CKD. *Kidney Int* 2012;**2**:1−405.
64. The SPRINT Research Group. A randomized trial of intensive vs standard blood pressure control. *N Engl J Med* 2015;**373**:2103−16.
65. Cheung AK, Rahman M, Reboussin DM, et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol* 2017;**28**:2812−23.
66. Chang AR, Loser M, Malhotra R, Appel LJ. Blood pressure goals in patients with CKD: a review of evidence and guidelines. *Clin J Am Soc Nephrol* 2019;**14**:161−9.
67. Toblli JE, Bevione P, Gennaro FD, et al. Understanding the mechanism of proteinuria: therapeutic implications. *Int J Nephrol* 2012;**1013**.
68. The Gisen Group. Randomized controlled placebo controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric non-diabetic nephropathy. *Lancet* 1997;**349**:1857−63.
69. Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999;**354**:359.
70. Appel LJ, Wright JT, Greene T, , et alfor the AASK Collaborative Research Group. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010;**363**:918−29.
71. Currie G, Taylor AM, Fujita T, et al. Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: a systematic review and meta-analysis. *BMC Nephrol* 2016;**17**:127.
72. Kim HY, Bae EH, MA SK, Kim SW. Effects of spironolactone in combination with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients with proteinuria. *Kidney Blood Press Res* 2014;**39**:573−80.
73. The ONTARGET Investigators. Telmisartan, Ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;**358**: 1547−59.
74. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;**369**:1892−903.
75. Pei H, Wang W, Zhao D, et al. The use of a novel non-steroidal mineralocorticoid receptor antagonist finerenone for the treatment of chronic heart failure. A systematic review and meta-analysis. *Medicine (Baltim)* 2018;**97**:e0254.
76. Bakris GL, Weir MR, Secic M, et al. Differential effects of calcium antagonist subclasses on markers of nephropathy progression. *Kidney Int* 2004;**65**:1981−2002.
77. Borst MH, Hajhosseiny R, Tamez H, et al. Active vitamin D treatment for reduction of residual proteinuria: a systematic review. *J Am Soc Nephrol* 2013;**24**:1863−71.

78. De Zeeuw D, Agarwal R, Amdahl M, et al. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomizsed controlled trial. *Lancet* 2010:1543–51.
79. Wenzel RR, Littke T, Kuranoff S, et al. Avosentan reduces albumin excretion in diabetics with macroalbuminuria. *J Am Soc Nephrol* 2009;**20**:655–64.
80. Kohan DE, Pollock DM. Endothelin antagonists for diabetic and non-diabetic chronic kidney disease. *Br J Clin Pharmacol* 2013;**76**: 573–9.
81. KDIGO clinical practice guideline for lipid managemnt in chronic kidney disease 2013;**3**:1–303.
82. Satirapoi B, Promrattanakun A, Ouppatham S, et al. The effects of simvastatin on proteinuria and renal function in patients with chronic kidney disease. *Int J Nephrol* 2015:1–6.
83. Hansen HP, Tauber-Lassen E, Jensen BR, et al. Effect of dietary protein restriction on prognosis in patients with diabetic nephropathy. *Kidney Int* 2002;**62**:220–8.
84. Kasiske BL, Lakatua JD, Ma JZ, et al. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am J Kidney Dis* 1998;**31**:954–61.
85. National Kidney Foundation. KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis* 2002;**39**:1–266.
86. Morales E, Valero MA, Leon M, et al. Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies. *Am J Kidney Dis* 2003;**41**:319–27.
87. Phisitkul K, Hegazy K, Chuahirun T, et al. Continued smoking exacerbates but cessation amerliorates progression of early type 2 diabetic nephropathy. *Am J Med Sci* 2008;**335**:284–91.
88. Faul C, Donnelly M, Merscher-Gomez S, et al. The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat Med* 2008;**14**:931–8.
89. Fornoni A, Sageshima J, Wei C, et al. Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. *Sci Transl Med* 2011;**3**:85ra46.

QUESTIONS AND ANSWERS

Question 1

A 47-year-old man is diagnosed with IgA nephropathy. Further evaluation reveals a 24-hour total protein excretion of 2900 mg, S[Cr] 1.4 mg/dL, and eGFR 51 mL/min/1.73 m^2. Which type of proteinuria is most predominant in this patient's 24-hour urine collection?

A. Albuminuria
B. Bence Jones protein
C. Beta-2 microglobulin
D. Tamm–Horsfall Protein

Answer: A

This patient has glomerulonephritis. Therefore, his proteinuria is glomerular in etiology. Albuminuria is the predominant protein seen in patients with diseases of the glomerular filtration barrier.[6,9]

Question 2

A 64-year-old woman presents with back pain, anemia, hypercalcemia, and progressive renal disease. S[Cr] increased from 1.2 mg/dL to 2.1 mg/dL over the past six months. Urinalysis reveals s.g. 1.010, pH 5.5, trace protein, negative heme, negative LE, and negative nitrite. Urine microscopy shows 0–3 rbc/hpf, 0–3 wbc/hpf. A UPCR was 1100 mg/g creat. Which of the following represents the type of proteinuria seen in this patient?

A. Glomerular
B. Tubular
C. Overflow
D. Postrenal

Answer: C

This patient has multiple myeloma and therefore has overflow proteinuria. The positively charged Bence Jones proteins are not detected by routine dipstick, which accounts for the discrepancy in finding only trace protein on dipstick and 1100 mg/g creatinine on the random urine sample.[9,41]

Question 3

A 58-year-old man with a history of hypertension presents for initial evaluation of "moderate albuminuria." UACR is 41 mg/g. At his primary care physician office, the urine albumin:creatinine was 54 mg/g and 36 mg/g on two prior occasions in the past 12 months. His blood pressure in the clinic is 142/91 mm Hg. His current medications include amlodipine 2.5 mg daily. His BMI is 31 kg/m^2. Examination is otherwise unremarkable. In addition to lifestyle modification, including weight reduction, which of the following management strategies is most appropriate for this patient?

A. Increase amlodipine to 5 mg once daily
B. Change from amlodipine to lisinopril
C. Discontinue amlodipine
D. Start chlorthalidone 12.5 mg once daily

Answer: B

Of the answer choices provided, option B is most appropriate in this patient with moderate albuminuria. Although answer choice A would improve blood pressure control, it is unlikely that increasing the dihydropyridiine calcium channel blocker will help reduce proteinuria to the same degree that adding an ACEI (lisinopril) would. Starting a thiazide diuretic may help with blood pressure control, but adding an ACEI would be standard of care given the proteinuria and hypertension. Discontinuation of amlodipine without substituting an alternative antihypertensive agent would not be appropriate therapy.[68,70]

Question 4

36-year-old woman comes to your office for evaluation of moderate albuminuria (38 mg/g) with preserved renal function, S[Cr] 0.7 mg/dL. She brings prior medical records which show UACR of 52 mg/g and 41 mg/g creatinine over the preceding two years. She has no significant past medical history. On physical examination, her BP is 127/80 mm Hg, HR 84 bpm, and BMI 24 kg/m^2. Otherwise, the physical examination is unremarkable. Which of the following is the most appropriate next step in the evaluation of this patient?

A. Start lisinopril 5 mg once daily and bring the patient back to the office in 4 weeks for blood pressure check
B. Review the urinalysis with microscopy
C. Renal biopsy
D. Send molecular genetic testing for Alport syndrome

Answer: B

Review of the urinalysis and microscopy is the next most appropriate step in management of this patient. The presence or absence of microscopic hematuria or cellular casts on urine microscopy will be essential in forming a differential diagnosis of this patient's moderate albuminuria. This patient is normotensive. Therefore, initiation of Lisinopril is not the most appropriate next step. The degree of moderate albuminuria does not warrant renal biopsy or molecular genetic testing, as it would not change management of this patient at this time.[6]

Question 5

Which of the following therapies has been shown to reduce proteinuria in some clinical trials?

A. Paricalcitol
B. Amlodipine
C. Fish oil
D. Vitamin E

Answer: A

Some studies have shown active vitamin D analogues have an additive effect to reduce proteinuria. A randomized controlled trial of diabetic patients treated with the active vitamin D analogue paricalcitol showed a 20% reduction in proteinuria in the active treatment arm. Another study found that treatment with an active vitamin D analogue has an additive effect to reduce proteinuria in patients already treated with RAAS inhibitors.[77,78]

CHAPTER

59

Nutritional Management of Patients with Chronic Kidney Disease

Maulin Shah[a,b], *William E. Mitch*[a]

[a]Nephrology Division, Baylor College of Medicine, Houston, TX, United States; [b]Nephrology Section, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, United States

Abstract

Nutrition management can significantly ameliorate signs and symptoms of progressive chronic kidney disease (CKD). In this chapter, we illustrate how nondialytic, conservative treatment of CKD using protein-restricted diets is safe, improves protein stores, ameliorates toxin production, and delays CKD progression. Providing adequate and appropriate nutrition is much more likely to be successful with the assistance of a skilled dietitian. We describe methods to ascertain dietary compliance as monitoring caloric and protein intakes is essential to ensure utilization of other dietary constituents and to maintain protein stores without exacerbating uremia. Requirements for trace elements, minerals, and vitamins have been poorly studied but are critical for successful implementation of dietary restriction treatment.

INTRODUCTION

Chronic kidney disease (CKD) is a progressive disorder affecting an estimated 26 million American adults. CKD is characterized by disruption of metabolic processes producing electrolyte abnormalities and accumulation of unexcreted toxins. These abnormalities lead to the development of a uremic syndrome characterized by fatigue, loss of lean body mass, and a multitude of nonspecific symptoms.[1–6] We illustrate how nondialytic, conservative treatment of CKD using protein-restricted diets (low-protein diet [LPD]) is safe, improves protein stores, ameliorates toxin production, and delays CKD progression.

PATHOBIOLOGY

The intact nephron hypothesis helps explain why glomerular filtration rate (GFR) is the most accurate estimate of the remaining kidney function in CKD patients. The hypothesis states that each individual nephron functions as an independent unit, so the combined functions of all remaining nephrons will determine the "whole kidney" GFR. This is a useful concept because individual nephrons participate in all physiologic and metabolic functions of the kidney, including regulation of blood pressure, several endocrine functions, the concentrations of ions in extracellular and intracellular fluids, and the excretion of waste products. Losses of these functions produce direct consequences of CKD, including abnormalities arising from the accumulation of unexcreted waste products synthesized during the metabolism of proteins and amino acids. For example, CKD reduces the ability to excrete acid leading to hyperventilation with a compensatory decrease in P_{CO_2} and skeletal muscle metabolic process activation by a mechanism that activates the ubiquitin-proteasome enzymatic process to degrade muscle proteins, causing loss of muscle mass.[7] Accumulated acid is also buffered in bone, releasing calcium and phosphates to aggravate bone demineralization.[5]

PROTEIN

Metabolic Balance and Steady State

Metabolic balance in CKD patients occurs when the intake or production of a substance equals its elimination. The ability of CKD patients to achieve a balance between intake and the excretion plus metabolism of protein-derived compounds has a limit. Specifically, when CKD patients eat unrestricted/high-protein diets (HPDs), metabolism of the excess dietary protein exceeds the kidneys' capacity to excrete uremic toxins

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00059-0

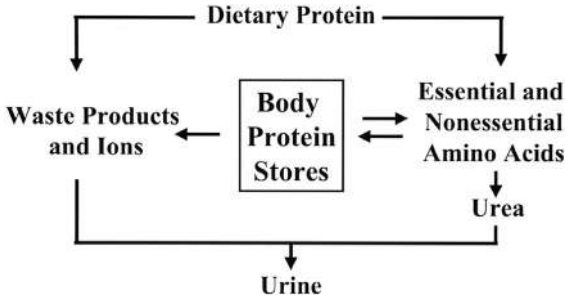


FIGURE 59.1 The summary figure indicates that increasing dietary protein raises the production of both urea and uremic toxins plus ions (such as H+, K+, Na+, and phosphates). The levels of toxins increase when kidney function is impaired. Contrariwise, overly restrictive diets will reduce the intake of essential amino acids and such responses stimulate the loss of body protein stores.

and inorganic ions (such as sodium, potassium, phosphate, etc.).[6] This imbalance is significantly responsible for the development of uremic symptoms (Figure 59.1).

The steady state is a concept related to metabolic balance. A CKD patient is in steady state when his/her internal environment is constant and the intake and/or production of ions or toxic compounds derived from dietary protein equal the excretion and/or metabolism of uremic toxins. CKD patients with a constant BUN and body weight may be in steady state; however, this does not necessarily mean that conditions are normal, as protein is still being converted into urea and toxic compounds. These considerations indicate why the amount of dietary protein being converted into urea must be accounted for when assessing changes occurring in response to alterations in dietary protein intake. Fortunately, this is possible because daily urea production in response to eating protein is either excreted or accumulated in body water. The concentration of urea is the same throughout body water, and the change in body water is calculated from changes in body weight.[8] Metabolic adaptations in response to CKD lead to accumulation of uremic toxins and ions affecting metabolism (such as phosphates, salt, etc.).[6]

The Trade-off Hypothesis

Another important principle, the trade-off hypothesis, refers to the activation of pathophysiologic responses which add to the severity of metabolic abnormalities while introducing consequences of the metabolic trade-off. For example, CKD patients will develop metabolic acidosis unless the source of acid namely dietary protein intake remains controlled. This is important because reducing dietary protein and amino acids limits acid generation in CKD and mitigates activation of pathophysiologic responses.[9,10] The trade-off for buffering acid is stimulation of the degradation of skeletal muscle proteins and amino acids resulting in protein wasting.[11] Furthermore, buffering of acid in bones and the release of phosphates from HPD contribute to the development of uremic bone disease.[5]

Protein Metabolism Contributes to Uremic Symptoms

The metabolism of amino acids and peptides plus pathophysiologic responses to ions that are associated with HPDs contribute to the development of uremia.[12,13] There are at least three major mechanisms that generate uremic toxicity. First, catabolism of dietary proteins, peptides, and amino acids occurs when proteases, amino acid oxidases, and other enzymes are produced by the gastrointestinal tract. Secondly, metabolic processes mediated by bacteria in the gastrointestinal tract can exert primary or secondary changes in the metabolism of proteins, peptides, and amino acids.[14] Investigating the experimental and clinical consequences of the influence of gastrointestinal bacteria is in its infancy. It is likely that this will provide new insights into the consequences of the metabolism of uremic toxins.[14] Third, indirect methods could produce toxic products from the metabolism of proteins, peptides, and amino acids. For example, an LPD improves insulin resistance in both diabetic and nondiabetic advanced CKD stages 4 and 5.[15,16] Lastly, the liver contributes to the metabolism of proteins, peptides, and amino acids. The liver modifies protein metabolism directly or secondarily and is largely responsible for the synthesis of urea.[17]

To date, no single compound or group of uremic toxins has been demonstrated to cause uremic symptoms, in part because identifying and measuring putative uremic toxins is difficult when patients have complex illnesses such as CKD. Generation of amino acid metabolites from eating a protein-rich diet has been implicated as an inducer of uremic symptoms. For example, phenylacetic acid and p-cresol are putative uremic toxins that are derived from the metabolism of phenylalanine that accumulate in CKD patients eating unrestricted amounts of dietary protein.[18,19] Experimentally, p-cresol contributes to inflammation, inhibits inducible nitric oxide synthase, and is linked to the development of atherosclerosis.[20] Another putative uremic toxin is indoxyl sulfate, which is derived from the metabolism of tryptophan. It can inhibit endothelial cell proliferation and interferes with endothelial-dependent wound repair.[19] Following extensive experimental information that indoxyl sulfate is a uremic toxin, a multicenter trial was undertaken to determine if inhibiting it would improve indices of CKD. The outcome of the trial was negative, indicating the complexity of identifying and then testing putative

biochemical mechanisms to determine if the experimental results will maintain the functions of the uremic toxins.[21] Arginine metabolism is another source of uremic toxins. When the mediator of toxicity, asymmetric dimethylarginine (ADMA), was initially examined, it was believed to contribute to impaired kidney functions in CKD patients *via* mechanisms that inhibit nitric oxide synthase and decrease nitric oxide production.[22] ADMA has also been associated with concentration-dependent pressor and bradycardia responses and vasoconstriction. Although these observations seem to identify that ADMA aggravates hypertension, the link between ADMA and blood pressure control has not been established. With ADMA, difficulties in identifying it as a uremic toxin include precise determination of the level of ADMA plus the influence of other mediators of blood pressure control such as the responses to dietary salt or the generation of other compounds that affect blood pressure control in CKD patients.[23] Other potential uremic toxins include guanidino-containing compounds that are present in the sera and tissues of uremic patients eating unrestricted diets. Guanidino compounds (e.g. methylguanidine) can exert neurotoxic responses and contribute to peripheral neuropathy, whereas others (such as γ-guanidinobutyric acid, taurocyamine, homoarginine, and α-keto-δ-guanidinovaleric acid) lower the seizure threshold in experimental animals.[13,24] Experimentally, these compounds are derived from excess dietary protein and, clinically, their metabolic and clinical responses are reduced by restricting dietary protein.

Consequences of High-Protein Diets

HPD contributes to the metabolic problems generated by CKD. Epidemiologically, uric acid production rises in patients eating an HPD. Experimentally increased uric acid levels are associated with the development of hypertension and inflammation.[25–27] Increased intake of protein is clearly associated with excessive intake of phosphates or salt, and these ions can negate the beneficial effects of ACEIs on slowing the progression of CKD.[28,29] Thirdly, an HPD generates metabolic acidosis in CKD patients, which in turn is associated with impaired function of bones, loss of protein stores, and more rapid loss of kidney function.[1–3,9,10,30]

Benefits of Dietary Protein Restriction in CKD

LPD can improve the symptoms and metabolic problems generated by CKD and slowing CKD progression.[12,13,31–34] In a study of almost 1600 CKD patients, Metzger et al. found that each 0.1 g protein/kg/day increase over the average value of 5.6 g protein/day was associated with an increase in the hazard ratio for end-stage renal disease (ESRD) of 1.05.[35] Secondly, Kelly et al. reviewed a meta-analysis of seven studies (~15,000 patients) and concluded that a reduced level of dietary protein was associated with a lower relative risk of death of 0.73, but the authors did not evaluate changes in the progression to ESRD.[36] Thirdly, an updated meta-analysis based on the Cochrane database provided evidence that LPD in nondiabetic CKD patients probably delays but does not halt progression to ESRD. In the latter analysis, LPD diets did not seem to reduce mortality.[37]

Unfortunately, compliance with LPD is difficult and has led to the evaluation of other types of protein substitutes. Substitutes for LPD for the treatment of CKD patients are largely based on supplying the nine essential amino acids (EAA) which are those that must be supplied because the body cannot synthesize them. Specifically, the estimated requirements for the recommended daily allowance (RDA) of the 9 EAAs provided as oral supplements can produce neutral nitrogen balance even when the 11 nonessential amino acids (NEAAs) are absent from the diets.

Alternative substitutes for dietary protein are abbreviated as Ketoacids. Ketoacids have the basic structures of different EAAs, but they have been treated to remove the nitrogen in EAAs. When provided in conjunction with a dietary prescription of 0.3 g protein/kg/day, the Ketoacid mixture improves nutritional indices and slows the progressive loss of kidney function.[38–49] For example, the responses to treating nondiabetic, Romanian, CKD patients for 15 months while they received a Ketoacid supplemented very low−protein diet (VLPD-KA) were favorably compared with results of nondiabetic control CKD patients fed a LPD (0.6 g protein/kg/day). The Ketoacid supplemented regimen was associated with slowing the loss of kidney function plus delaying need for dialysis. There was also evidence for improved nutritional status. There were difficulties in enrolling participants in this study as only about 14% of screened patients were recruited.[48]

There have been too few economic evaluations of the use of LPD to treat CKD patients. Scalone et al. randomly assigned 56 patients with advanced CKD to treatment with the VLPD-KA regimen compared with an equal number of control CKD patients assigned to standard dialysis strategies. At the initiation of the study, patients in both groups were >75 years of age and their creatinine clearances were <10 mL/min. During the first year of the study, the savings were >20,000 €uros and the clinical courses of the two groups of patients including nutritional indices were calculated to be noninferior.[50]

Recommendations for Protein Restriction in CKD

For healthy adults who undergo moderate physical activity and eat sufficient calories, nitrogen balance can be achieved. The minimal amount of dietary protein used to achieve nitrogen balance was similar to the requirements of normal adults according to the 1981 Food and Agriculture Organization/World Health Organization/United Nations University (FAO/WHO/UNU). Specifically, they recommended a dietary protein requirement for normal adults of 0.6 g protein/kg body weight/day. The source of proteins consists of high biological value proteins (i.e. proteins with both EAAs and NEAAs).[51] Two standard deviations from this level (i.e. 0.75 g protein/kg/day) were assigned as a "safe level of intake" because it should meet a protein requirement of 97.5% or more of healthy adults.[52,53] There are three caveats regarding these recommendations. Firstly, the number of patients studied was small. Secondly, some normal adults require less dietary protein and others require more than 0.75 g/kg/day. Thirdly, increasing the dietary protein of CKD patients beyond the safe level simply increases the production of urea and other waste products. For these reasons, the diet of CKD patients must be evaluated for each patient.

In normal individuals, a decrease in dietary protein from 1 to 0.6 g protein/kg/day activates adaptive metabolic responses. Specifically, dietary protein restriction will reduce the irreversible degradation of amino acids and slow the catabolism of muscle proteins. Changes in the rate of protein synthesis in these studies were small, indicating the major factor responsible for loss of protein stores was catabolism rather than changes in protein synthesis.[11,54] Notably, advanced CKD patients uncomplicated by metabolic acidemia, inflammation, or other catabolic conditions become remarkably efficient in adapting to dietary protein restriction.[55] Notably, similar responses were obtained when CKD patients were fed with the VLPD-KA regimen.[38] Furthermore, adaptations to an LPD in CKD patients occur *via* increased efficiency of muscle protein turnover.[56] These results indicate that diets based on 0.6 g protein/kg/day should be sufficient to maintain protein stores during long-term therapy. In our practice, we generally initiate nutritional therapy for patients with stable CKD using a regimen based on LPD to 0.8 g/kg/day as recommended by KDIGO.[57] However, if the patient is developing uremic symptoms or continues with a progressive increase in his/her S[Cr], we recommend dietary restriction to 0.6 g protein/kg/day because it can maintain protein stores and may slow the rate of progression. Unfortunately, Ketoacids are not available in the US. In Table 59.1, we have included our recommendations for different levels of dietary protein in CKD patients.

Despite the benefits discussed, compliance with LPD is low. For example, Moore et al. evaluated results in more than 16,000 adults participating in the National Health and Nutrition Examination Survey (2001–2008). Even at advanced stages of CKD, the dietary protein intake was about 1 g/kg/day.[58] To improve compliance with the change in diets, patients should have regular interactions with a dietician or nutritionist experienced in helping patients achieve compliance. Ignoring the implementation of dietary protein restriction can hasten the need to begin dialysis, which is expensive and interferes with the activities of patients. Moreover, several studies that have examined the outcomes of patients initiating dialysis "early" (at GFRs of 10–12 mL/min) have concluded that earlier dialysis initiation does not improve the mortality associated with CKD nor does it reduce the complications of CKD.[59,60]

Safety of LPD

Concern about the safety of LPD may contribute against routine implementation. Fortunately, there is increasing evidence LPDs are safe. Consequently, a critical goal of restricting dietary protein in CKD patients is to prevent loss of body protein stores. This will occur when there is an imbalance between the rates of protein synthesis and degradation. For example, an increase in the rate of protein synthesis to levels above the rate of protein degradation will produce improvements in protein stores. Alternatively, suppressing protein degradation below the level of protein synthesis will increase protein stores.

In the MDRD Study, 840 nondiabetic patients with different stages of CKD were examined regularly for an average of 2.2 years. Protein intakes were assessed from measurements of urea nitrogen excretion.[61,62] There also were evaluations of energy intake, but they were based on dietary diaries which can be inaccurate.[62,63] Notably, only two of 840 participants were removed from the trial because of concerns about their nutritional status. Overall, assignment to LPD was associated with a small loss of body weight and arm muscle area (an index of muscle mass). In contrast, the serum albumin (S[Alb]) increased significantly.[33,61,62] However, S[Alb] is not a reliable index of deteriorating protein stores.

Although reports indicate that CKD patients have been treated safely during restriction of dietary protein, some investigators have raised concern that LPD will be insufficient for maintaining protein stores.[37,62,64–68] Wolfe et al. used the amino acid turnover method and studied responses of elderly subjects to LPD.

TABLE 59.1 Recommended Nutrient Intake for CKD Patients

Nutrient	Nondialysis CKD	Dialysis ESRD
Protein	GFR 25–50 mL/min/1.73 m^2: 0.8 g/kg/day	>1.2 g/kg/day
	GFR <25 mL/min/1.73 m^2: 0.6 g/kg/day	
	Nephrotic: +1 g/day for each 1 g/day proteinuria	
	Systemic illness: 1.0 g/kg/day[a]	
Energy	30–35 kcal/kg/day[b]	30–35 kcal/kg/day[b]
Carbohydrates	35% of nonprotein calories	35% of nonprotein calories
Fat	Polysaturated to saturated ratio of 2:1	Polysaturated to saturated ratio of 2:1
Sodium	80–100 mmol/day	80–100 mmol/day
Potassium	<1 mmol/kg if elevated	<1 mmol/kg if elevated
Calcium	Should not exceed 2.5 g (dietary + calcium binders)	Should not exceed 2.5 g (dietary + calcium binders)
Phosphorus	800–1000 mg and phosphate binders if elevated	800–1000 mg and binders if elevated

Recommendations are based on ideal body weight.
[a]*>50% high biological value protein (rich in essential amino acids) is recommended.*
[b]*Based on physical activity level. In sedentary elderly adults, recommended energy intake is 30 kcal/kg/day.*

He concluded that elderly subjects exhibit defects in muscle protein synthesis, ultimately leading to loss of protein stores. The investigators concluded that the RDA of 0.8 g protein/kg/day in elderly subjects would be insufficient to maintain protein stores. Instead, the investigators recommended efforts to stimulate protein synthesis to a level that equals or exceeds protein degradation. To improve the rate of protein synthesis, they recommended that the dietary protein intake of elderly subjects be raised to 1.5 g protein/kg/day.[68] Wolfe et al. also reviewed treatment strategies for patients with other catabolic illnesses and concluded that the RDA for patients with CKD plus inflammation, obesity, and similar protein wasting disorders should be raised to 1.5 g/kg/day protein intake.[68] However, implementation of this HPD for CKD patients would be counterproductive as it would result in accumulation of unexcreted toxins, salt, phosphates, acid, and the metabolic consequences of these responses.[37,66]

Not all reports are positive. For example, Menon et al. reported that 10 years after closing the MDRD trial, there was information from the US Renal Data System (USRDS) indicating that random assignment to the VLPD-KA regimen was associated with an increased risk of death.[45] It should be pointed out, however, that during the 8 years after completing the 2-year MDRD Study, there were no data detailing compliance nor was there information about other illnesses, dialysis-related factors, or other treatments arising from the MDRD Study. In addition, there was no ongoing adherence to the Ketoacid regimen because Ketoacids were not supplied following closure of the MDRD trial. Other problems with the Menon et al. analysis have been detailed. In contrast, Chauveau et al. reached a markedly different conclusion about the safety of LPD. They examined the survival and characteristics of 220 stage 4–5 CKD patients who had been treated for an average of 33 months (range 4–230 months) with the VLPD-KA regimen. The outcomes of patients treated concurrently but with no education in LPD were compared with outcomes of patients treated with the VLPD-KA regimen. The latter group had a 1-year survival of 97% and 60% after 5 years of dialysis. Moreover, survival was not impaired following kidney transplantation and was 97% and 95% at 5 and 10 years, respectively.[31] These results were substantially better than those of dialysis patients based on analyses from the French Registry or in the USRDS. Another major advantage of outcomes of the Chauveau study is that compliance with dietary restriction was monitored during long-term therapy by measuring 24-hour urine urea nitrogen excretion. Finally, the influence of dialysis therapy on complications was included in the Chauveau report, but not by the Menon report. Based on these considerations, we conclude that LPDs, including the VLPD-KA regimen, maintain protein stores and do not jeopardize responses of CKD patients who require dialysis or transplantation.

Another special group of CKD patients includes those who excrete more than 5 g protein/day. These patients are special because their treatment requires reducing dietary protein. This is necessary because an HPD increases the degree of proteinuria.[69] In addition, an HPD can increase the likelihood of developing complications of CKD, including progressive kidney failure and cardiovascular disease.[69] It is fortunate nephrotic patients fed

an LPD can activate the adaptive responses to dietary protein restriction that are similar to responses that are activated when the dietary protein of normal adults or CKD patients is reduced. Nephrotic syndrome patients fed 0.8 (plus 1 g dietary protein for each gram of urinary protein excretion) and 35 kcal/kg/day maintained protein stores.[70] Although this amount generally suffices for patients excreting less than 10 g proteinuria, the limitations of LPD in the treatment of patients with excessive proteinuria have not been extensively explored.

In summary, patients with uncomplicated CKD, including those with nephrotic-range proteinuria, activate compensatory responses to dietary protein restriction. The responses include suppression of both amino acid oxidation and protein degradation, which act to preserve lean body mass during long-term dietary protein restriction. Patients eating restricted diets for >1 year can maintain indices of adequate nutrition.[6] It should be emphasized that the responses achieved required repeated monitoring to ensure patients eat a sufficient amount of protein and calories. Finally, if CKD is complicated by acidosis, inflammatory, or catabolic illnesses, patients may not be able to activate adaptive responses to dietary restriction. In these cases, the treatment should concentrate on correcting acidosis, inflammatory conditions, or chronic illnesses.

Diabetic patients may not activate adaptive changes to dietary protein restriction as efficiently as do normal adults or nondiabetic CKD patients, based on the importance of insulin in the regulation of protein and energy metabolism. These patients should emphasize maximizing glucose control to avoid loss of muscle proteins. A recent study of 197 advanced CKD patients with VLPD-KA showed improved uremic symptoms, diabetes control, and weight loss without negative effect on muscle mass or fitness.[71]

Diabetic nephropathy may interfere with the metabolism and progression of CKD. For example, a meta-analysis of 15 randomized controlled trials including nearly 2000 subjects showed LPD may not slow CKD progression in type II diabetic patients.[72] As we await further evidence, diabetic patients should be examined regularly to prevent loss of protein stores.

Plant-Based Dietary Protein Advantages

The source of dietary protein may influence CKD-induced changes in metabolism. In a study of only five patients, providing a vegetarian diet for 1 week led to a decreased S[P] and FGF-23 levels compared with eating meat-based meals.[73] In a study of nearly 3000 CKD patients, the CRIC study group concluded that plant proteins are associated with lower FGF-23 and higher serum bicarbonate levels.[74] Another observational study using the NHANES II database suggested that a diet with higher plant-based proteins is associated with lower mortality in CKD patients.[75]

Monitoring Protein Intake

A major requirement for the implementation of changing dietary proteins is the ability to obtain a regular assessment of the amount of protein eaten by CKD patients. This requirement can be met by collecting a 24-hour urine for the measurement of urea nitrogen, along with a simple calculation of the nitrogen excreted in forms other than urea. This is not a new concept, as Folin reported in 1905 that the principal response to a change in dietary protein is a parallel change in urinary urea excretion.[76] This concept has been confirmed in normal adults and CKD patients.[8,12,13,77] How can this be used to assess the intake of dietary protein (Box 59.1)? First, the patient should be in steady state, signified by constant values of BUN and body weight. Secondly, 24-hour urinary excretion of urea nitrogen is measured. We have noted that the rate of urea production exceeds the steady-state rate of urea excretion, because there is an extrarenal clearance of urea. The latter is presumably mediated by ureases that break down urea to ammonia and carbon dioxide.[12,78] Even when delivered to the liver, the nitrogen in ammonia does not contribute substantially to amino acid synthesis. Instead it is simply reincorporated into urea.[79,80]

BOX 59.1

NITROGEN BALANCE AND ESTIMATED DIETARY PROTEIN

$B_N = I_N - U - NUN$, where $NUN = 0.031$ g N/kg b.w.
If $B_N = 0$, then $I_N = U + 0.031$ g N/kg b.w.
When BUN is constant, $U = UUN$ and
$I_N = UUN + 0.031$ g N/kg b.w.

B_N, nitrogen balance (g N/day); BUN, blood urea nitrogen; I_N, nitrogen intake (g N/day); N, nitrogen; NUN, nonurea nitrogen (g N/day); U, urea nitrogen appearance (g N/day); UUN, 24-hour urinary urea nitrogen (g N/day).

We emphasize these findings because they simplify the evaluation of dietary protein compliance for two reasons. First, the rate of net urea production (i.e. urea appearance) closely parallels dietary nitrogen. Second, urea appearance is easily calculated because the concentration of urea is equal throughout body water.[8,81] Because water represents approximately 60% of body weight in nonedematous patients, changes in the urea nitrogen pool in a patient with CKD can be calculated by multiplying 60% of nonedematous body weight in kilograms by the serum urea nitrogen concentration in grams per liter. Thirdly, the nitrogen balance (B_N) is estimated by adding the urea excretion to the nonurea nitrogen excretion. The latter includes the amount of nitrogen in feces plus the nitrogen in urinary creatinine, uric acid, protein, etc. Note that the average excretion is estimated as 0.031 g nitrogen/kg/day. It does not vary significantly with changes in protein intake.[12] For this determination, nitrogen is used rather than protein weight because assessing changes in the intake/metabolism of all proteins would hopelessly complicate the calculation. Fortunately, the nitrogen content of all proteins is 16%, which avoids the pitfalls of measuring the nitrogen content of all the body's proteins. A neutral or positive B_N indicates that protein stores are maintained or increased, whereas a negative B_N indicates protein mass is declining. If the BUN is increasing more rapidly than the S[Cr], the amount of protein in the diet should be adjusted based on measurements of urea production.[12]

In summary, the urea appearance is calculated as the change in the urea nitrogen pool (positive or negative) plus urinary urea nitrogen excretion and the nonurea nitrogen excretion. If serum urea nitrogen and weight are stable, urea nitrogen accumulation is zero, and the urinary nitrogen appearance equals the excretion rate. The sum of urea nitrogen and nonurea nitrogen (i.e. 0.031 g nitrogen/kg/day) should equate to dietary intake of nitrogen unless there are complications (such as gastrointestinal bleeding). There are two caveats to the use of this method to estimate dietary protein. First, there must be completion of the 24-hour urine collection for urinary urea excretion because urea clearance varies throughout the day and an incomplete collection will underestimate dietary compliance. Secondly, the nonurea nitrogen average of 0.031 g N/kg/day is not reliable for patients receiving total parenteral nutrition or eating completely digestible foods (e.g. astronauts).[12] When the nitrogen balance has been calculated, the investigator must interpret the values. If the total amount of excreted nitrogen exceeds the prescribed protein intake by more than 20%, then the patient should be evaluated to determine if the increase in nitrogen excreted is due to dietary noncompliance, unexpected catabolism, or gastrointestinal bleeding.[12]

Another potential use of the method of assessing dietary protein would be to evaluate a patient's caloric intake. This is possible because a skilled dietitian can use a patient's dietary history to estimate the ratio of calories to protein. The second step is to calculate dietary protein intake from the 24-hour urea nitrogen production as described earlier. Third, the calories per protein intake can be used to estimate calorie intake from the ratio of protein to calorie intake. These simple calculations should be used regularly in patients treated with restricted diets because calorie intake must be sufficient to maintain body protein stores.[12]

Other methods of assessing intake, including dietary histories, are less accurate. For example, when the food records and anthropometry of CKD patients were evaluated, it was found that energy intake was seriously underestimated when assessed by diet records.[63,82]

Other methods of assessing the adequacy of the LPD for CKD patients include assessing amino acid turnover and repeated evaluations of anthropometric indices and/or levels of markers of nutritional status. There are problems with both methods. The amino acid turnover method requires an intravenous injection of a labeled amino acid, followed by repeated measurements of the dilution of the labeled amino acids in muscles. After the steady state is established, the rates of protein synthesis and degradation in skeletal muscles can be calculated during a day-long evaluation. Note that this technique, unlike the measurement of nitrogen balance, reflects only a portion of the metabolism for that day, while the nitrogen balance requires measuring metabolic responses throughout the body over 5–7 days. The most frequently used but least reliable method of evaluating changes in protein stores relies on estimating changes in protein stores from anthropometric measurements or from changes in serum protein levels. The accuracy of these methods has not been rigorously determined and their utility is limited.[12]

Protein-Energy Wasting Markers

There is no consensus about ideal markers of protein-energy wasting in CKD patients. Generally, a composite of health standards including body weight, S[Alb] or prealbumin levels, questions about general health status, and anthropometric measures are used to detect loss of protein stores. The problems in using these methods to detect loss of protein stores are the measurements. To interpret changes in body weight, the measurement should be obtained with the same amount of clothes and integrated with a dietary history plus estimates of dietary protein and caloric intake. There are also confounding interpretations of changes in S[Alb] because inflammation exerts a reciprocal reaction. Low

values of S[Alb] could be due to inflammation rather than an inadequate or unbalanced diet. The same problems affect the interpretation of serum prealbumin levels. Finally, anthropometric measurements are user-dependent, greatly increasing the variability in values, unless the same individual is measuring the same parameters (e.g. skinfold thickness and arm circumference).[83]

In determining whether patients are losing protein stores, we recommend a standardized assessment of body weight and dietary protein intake. S[Alb] can be measured with the caveat that low values should trigger evaluations for sources of inflammation.

INORGANIC DIETARY CONSIDERATIONS

Sodium

Diets rich in protein are also rich in sodium, chloride, potassium, phosphates, and precursors of uric acid and other acid equivalents. Excess dietary salt not only counteracts strategies to treat hypertension but also suppresses the benefits of ACEI therapy on the progression of CKD.[29,84,85] For these reasons, dietary salt should be included in evaluating patients with CKD. Specifically, the 24-hour excretion of sodium should stimulate an adjustment of the diet to achieve a daily sodium excretion less than 100 mEq/day (2–2.5 g sodium)[86] (Table 59.1).

Potassium

CKD patients with hyperkalemia should be initially screened for disorders that raise the S[K] (e.g. metabolic acidosis and insulin resistance), and there should be an estimate of daily potassium excretion from a 24-hour urine collection. Pathophysiological causes of hyperkalemia should be approached by restricting the 24-hour urinary potassium to 1.5 g/day (39 mEq/day, Table 59.1).[86] Fortunately, dietary potassium restriction for treating high levels of S[K] is generally unnecessary because responses to CKD include increases in gastrointestinal potassium excretion and aldosterone responses. We emphasize the benefits of these adaptations because diets planned for CKD patients are frequently based on fruits and vegetables, which have a high potassium content but also promote clinically important reductions in blood pressure. For example, the DASH (Dietary Approaches to Stop Hypertension) Study demonstrated that an increase in dietary potassium content and a decrease in dietary salt led to significant decreases in systolic and diastolic blood pressures, especially in African-American patients. The influence of the DASH diet has not been tested in CKD patients.[87–89]

Metabolic Acidosis

CKD patients frequently develop metabolic acidosis. As with other uremic toxins, restriction of dietary protein decreases acid production by limiting the intake of sulfur-containing and positively charged amino acids. These amino acids are metabolized to produce hydrogen ions.[1,2] Preventing this complication of CKD is beneficial because metabolic acidosis stimulates the degradation of muscle proteins and EAAs, and metabolic acidosis is associated with the development of several metabolic defects.[9,10] In normal individuals, the development of metabolic acidosis suppresses albumin synthesis and aggravates renal osteodystrophy,[5,90] while persistent acidosis in CKD patients can accelerate the loss of kidney function.[1–3] Considering the multiple adverse responses problems, it is not surprising that acidosis changes the metabolism of several hormones and vitamins and stimulates protein losses in CKD patients.[11,30,55,91–97]

These examples exhibit a recurring theme. CKD patients have a type of "protein intolerance" because meals with a high dietary protein content may lead to uremic toxicity due to the accumulation of unexcreted metabolites of protein and inorganic ions in patients with CKD. These problems can be largely avoided by manipulating the diet of CKD patients, but it is difficult to change dietary habits. At the minimum, patients require the assistance of a skilled dietitian. The dietitian can adjust components of the diet based on measuring compliance and provide "feedback" to help patients obtain a sufficient amount of dietary protein and calories to maintain body protein stores, while avoiding problems from excess dietary protein.

VITAMINS AND TRACE ELEMENTS IN CKD

Vitamins and trace elements are required for energy utilization, organ function, and cell growth and protection (for example, from oxygen radicals). Consequently, patients with CKD should receive a sufficient amount of these nutrients incorporated into their planned diets (Table 59.2). Besides an insufficient diet, inadequate supplies of vitamins and trace minerals can result from decreased intestinal absorption of micronutrients, or metabolic responses to uremia interfering with the influence of vitamins and minerals. In addition, there could be circulating inhibitors of vitamins, loss of protein-bound elements with proteinuria, and medicines that

TABLE 59.2 Recommended Vitamin and Trace Element Intake for CKD Patients

Nutrient	Nondialysis CKD
Thiamine (B_1)	1.2 mg/day
Riboflavin (B_2)	1.3 mg/day
Niacin (B_3)	16 mg/day
Pantothenic acid (B_5)	5 mg/day
Pyridoxine (B_6)	5 mg/day
Biotin (B_7)	30–100 μg/day
Folate (B_9)	1 mg/day
Cobalamin (B_{12})	2.4 μg/day
Ascorbic Acid (C)	70 mg/day
Vitamin A (retinoids)	No addition
Vitamin D	Individualized
Vitamin E	15 mg/day
Vitamin K	No addition
Zinc	No addition

antagonize some vitamins.[98] Unfortunately, the RDA for these nutrients has not been defined for CKD patients.

We recommend that CKD patients receive a supplement of the water-soluble vitamins containing B-complex and C vitamins.[98] These recommendations are based on reports that restricted protein diets may cause deficiency conditions. For example, riboflavin, found in meats and dairy products, acts as a cofactor for flavin mononucleotide and flavin adenine dinucleotide. Riboflavin deficiency can produce sore throat, stomatitis, or glossitis that may be mistaken for uremic symptoms.[98] Folic acid, found in fruits and vegetables, improves responses to erythropoietin treatment, and deficiency may suppress homocysteine production.[98] Pyridoxine, found in meats, vegetables, and cereals, contributes to amino acid metabolism. When deficient, problems similar to advanced uremia, such as peripheral neuropathy or altered immune function, are encountered. Consequently, it is recommended that patients with advanced CKD (stage 4 or 5) receive 5 mg pyridoxine daily.[98] Vitamin B_{12} is required for synthesis of nucleic acids and is available in meats and dairy products. There are large stores in the liver. As with other B vitamins, a supplement of vitamin B_{12} is recommended for CKD patients.[98] Vitamin C (ascorbic acid) is contained in meat, dairy, and many fruits and vegetables. A deficiency state is unusual. Ascorbic acid protects against antioxidant reactions and is involved in collagen formation. As high doses of vitamin C are metabolized to oxalate which can precipitate in soft tissues (including the kidney), we recommend limiting the dose of vitamin C to the RDA.[98] The remaining water-soluble vitamins, including biotin, niacin, and pantothenic acid, have not been extensively studied in CKD patients, leading us to limit their intake to the RDA.

The requirements for fat-soluble vitamins have not been established for CKD patients. There is a possibility that certain fat-soluble vitamins may cause complications. Plasma vitamin A (retinol) levels in CKD patients are frequently increased because there are high levels of retinol-binding protein. Vitamin A excess could explain the origin of the vitamin A-associated syndrome, consisting of anemia, dry skin, pruritis, bone reabsorption, and liver dysfunction, but the mechanisms underlying these problems have not be elucidated.[98] There is even less known about the requirements for vitamin E, but its plasma levels in CKD patients are apparently normal. It has been suggested that vitamin E might suppress lipid peroxidation/oxidant stress and block progression of arteriosclerosis.[99] Vitamin D relates to metabolic bone disease in CKD and will not be discussed in this chapter. There is inadequate information regarding vitamin K dosing in CKD patients.[98] Consequently, multivitamin preparations containing fat-soluble vitamins should be avoided in CKD, unless there is evidence of deficiency.

The requirements for trace elements in CKD patients also have not been sufficiently studied. One potential exception is zinc. Zinc is involved in gastrointestinal metabolic functioning following small intestine absorption. Zinc absorption is increased with HPD, and there is binding of zinc to proteins and various amino acids in foods. These relationships could contribute to zinc deficiency in patients who have zinc losses when urinary protein excretion is increased. Some but not all reports indicate that patients with CKD and poor taste discrimination (dysgeusia) or with impaired sexual function may be improved by giving zinc supplements.[98] Some of the commonly used medications for CKD patients (calcium and iron supplements and phosphate binders) can hinder the intestinal absorption of zinc. Finally, drugs such as ACEIs, ARBs, and thiazides can increase zincuria.[100,101]

The requirements for trace elements and the consequences of adverse reactions to their supplements have not been fully studied in CKD patients. Consequently, we do not recommend giving supplements of trace elements routinely to CKD patients unless there is evidence of low intake or deficiency. An exception would be for CKD patients receiving long-term parenteral or enteral nutrition. These individuals should routinely be given trace elements but still require careful monitoring of circulating levels. As with vitamins, the appearance of skin rashes, neurologic abnormalities, or unexplained problems in CKD patients should prompt a search for trace element deficiency conditions.[10]

ENERGY INTAKE OF CKD PATIENTS

In normal adults and CKD patients, inadequate energy intake leads to loss of body weight, but the mechanism resulting in this response is complex. First, the magnitude of the energy deficit is difficult to measure. Secondly, there are many possible metabolic defects such as changes in hormones (e.g. insulin). In detecting insufficient calories, the resting energy expenditure (REE), defined as the amount of energy expressed in Kcal required for a 24-hour period when the individual is at rest, is a reliable method. In 1981, a report of the results of about 11,000 REE determinations of healthy adults was analyzed by the FAO/WHO/UNU.[51] They reported that there was considerable variability in the determinations, and, hence, that caution is needed in making decisions about energy requirements. Besides the requirement for REE, energy requirements are also affected by physical activity, general health, and the presence of catabolic conditions (e.g. acidosis, high values of BUN or S[P], and the presence of insulin resistance). Generally, patients with stage 3 CKD or more advanced disease spontaneously limit daily physical activity. The contribution of uremia *per se* in increasing energy expenditure is controversial.[12] As a caveat, it has been noted that energy expenditure may not fall when caloric intake of CKD patients is reduced, indicating there is poor adaptation to a low-calorie intake.[102] In addition, obese CKD patients with S[Cr] values greater than 2.4 mg/dL or with metabolic acidosis can develop insulin resistance and impaired energy utilization.[103]

The contribution of a low energy intake to nutritional deficiencies in CKD patients is unclear. CKD patients who were eating 16–20 g/day of protein plus a supplement of EAA did not increase their protein stores (measured as nitrogen balance) when energy intake was varied between 22 and 50 kcal/kg/day.[104] Other investigators have concluded that energy requirements of CKD patients eating an LPD should be 35 kcal/kg/day, to utilize dietary protein maximally to maintain body protein stores.[102] Unfortunately, there are only a few studies of energy requirements of CKD patients. We believe that the energy intake of CKD patients who are at or below their ideal body weight should be 35 kcal/kg/day. Equally important, overweight patients should have energy intake restricted to lose adipose tissue. This is recommended because obesity causes insulin resistance, which impairs the utilization of protein and calories. In contrast, for patients who are losing weight, the number of dietary calories should be increased.[12] In all cases, energy intake of CKD patients should be monitored by assessing changes in body weight, calorie intake, and the presence of specific adipose sites. This is especially emphasized in patients with truncal obesity because calorie supplements will increase body fat rather than protein stores. Results from the MDRD Study of CKD patients revealed that when energy intakes were below 35 kcal/kg/day, loss of body mass was infrequent. Only two patients were withdrawn from the trial because of nutritional considerations.[63,82] Still, these conclusions must be considered tentative because energy intake was assessed from diet diaries, a method that can lead to erroneous results.[63,82]

CONCLUSIONS

CKD patients can respond to dietary modification with a reduction in the signs and symptoms of uremia. Dietary modification in CKD leads to reductions in waste product accumulation, plus mitigation of the uremic syndrome that includes correction of acidosis, amelioration of protein-energy wasting, suppression of uremic bone disease, and improvement in blood pressure control. There are remarkable similarities in the responses to dietary protein restriction when examined in normal adults and CKD patients, including activation of adaptive metabolic processes. This accounts, in part, for why restriction of diet proteins in patients with CKD is nutritionally safe unless there are complicating factors. Our recommendations for dietary management in CKD are summarized in Tables 59.1 and 59.2. Achieving compliance, however, can be difficult. Success and implementation is improved by the assistance of a skilled and interested dietitian.

Regarding initiation of LPDs, we recommend introducing dietary changes when signs/symptoms of CKD arise or when blood chemistry values indicate the presence of complications of CKD. We recognize that patients with CKD may spontaneously decrease their dietary intake, but this should not be a signal to increase protein in diets, as it would result in worsening complications of CKD. Whether dietary manipulation influences the progressive loss of GFR is still controversial. But instituting an LPD can substantially delay the need for dialysis, and there are other benefits including improved responsiveness to ACEI. The latter includes avoidance of excess dietary salt or phosphates that blunt ACEI responses.

References

1. Goraya N, Simoni J, Jo C, Wesson DE. Dietary acid reduction with fruits and vegetables or bicarbonate attenuates kidney injury in patients with a moderately reduced glomerular filtration rate due to hypertensive nephropathy. *Kidney Int* 2012;**81**(1):86–93.
2. Scialla JJ, Appel LJ, Astor BC, et al. Estimated net endogenous acid production and serum bicarbonate in african americans with chronic kidney disease. *Clin J Am Soc Nephrol* 2011;**6**(7):1526–32.

3. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol* 2009;**20**(9):2075–84.
4. Meyer TW, Hostetter TH. Uremia. *N Engl J Med* 2007;**357**(13): 1316–25.
5. Bushinsky DA. The contribution of acidosis to renal osteodystrophy. *Kidney Int* 1995;**47**:1816–32.
6. Hung A. Effects of chronic kidney disease on metabolism and hormonal function. In: Ikizler TA, Mitch WE, editors. *Handbook of nutrition and the kidney*. 7th ed. Philadelphia: Lppincott-Williams and Wilkins; 2018.
7. Wang XL, Mitch WE. Mechanisms of muscle wasting in chronic kidney diseases. *Nat Rev Nephrol* 2014;**10**:504–16.
8. Maroni BJ, Steinman T, Mitch WE. A method for estimating nitrogen intake of patients with chronic renal failure. *Kidney Int* 1985; **27**:58–65.
9. Reaich D, Channon SM, Scrimgeour CM, Daley SE, Wilkinson R, Goodship THJ. Correction of acidosis in humans with CRF decreases protein degradation and amino acid oxidation. *Am J Physiol* 1993;**265**:E230–5.
10. Reaich D, Mitch WE. Metabolic acidosis as a stimulus for protein and amino-acid catabolism. *Nephrol Dial Transplant* 1995; **10**(Suppl.):27–32.
11. Garibotto G, Russo R, Sofia A, et al. Skeletal muscle protein synthesis and degradation in patients with chronic renal failure. *Kidney Int* 1994;**45**:1432–9.
12. Perez JJ, Mitch WE. Requirements for protein, calories, and fat in the predialysis patient. In: Ikizler TA, Mitch WE, editors. *Handbook of nutrition and the kidney*. 7th ed. Philadelphia: Lppincott-Williams and Wilkins; 2018.
13. Fouque D, Mitch WE. Dietary approaches to kidney diseases. In: Skorecki K, Chertow GM, Marsden PA, Taal MW, Yu ASL, editors. *Brenner and rector's the kidney*. 10 ed. Philadelphia: Elsevier; 2016. p. 1955–86.
14. Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. *J Am Soc Nephrol* 2014;**25**(4):657–70.
15. Gin H, Aparicio M, Potaux L, et al. Low-protein, low-phosphorus diet and tissue insulin sensitivity in insulin-dependent diabetic patients with chronic renal failure. *Nephron* 1991;**57**(4):411–5.
16. Bergstrom J, Furst P, Ahlberg M, Noree L-O. The role of dietary and energy intake in chronic renal failure. In: Canzler VH, editor. *Topical questions in nutritional therapy in nephrology and gastroenterology*. Stuttgart: Georg Thieme Verlag; 1978. p. 1–16.
17. Tizianello A, DeFerrari G, Garibotto G, Robaudo C. Amino acid metabolism and the liver in renal failure. *Am J Clin Nutr* 1980; **33**:1354–62.
18. Kalantar-Zadeh K, Horwich TB, Oreopoulos A, et al. Risk factor paradox in wasting diseases. *Curr Opin Clin Nutr Metab Care* 2007;**10**(4):433–42.
19. Dou L, Bertrand E, Cerini C, et al. The uremic solutes p-cresol and indoxyl sulfate inhibit endothelial proliferation and wound repair. *Kidney Int* 2004;**65**(2):442–51.
20. Vanholder R, Schepers E, Pletinck A, Nagler EV, Glorieux G. The uremic toxicity of indoxyl sulfate and p-cresyl sulfate: a systematic review. *J Am Soc Nephrol* 2014;**25**(9):1897–907.
21. Schulman G, Berl T, Beck GJ, et al. Randomized placebo-controlled EPPIC trials of AST-120 in CKD. *J Am Soc Nephrol* 2015;**26**(7):1732–46.
22. Fleck C, Schweitzer F, Karge E, Busch M, Stein G. Serum concentrations of asymmetric (ADMA) and symmetric (SDMA) dimethylarginine in patients with chronic kidney diseases. *Clin Chim Acta* 2003;**336**(1–2):1–12.
23. Kielstein JT, Zoccali C. Asymmetric dimethylarginine: a cardiovascular risk factor and a uremic toxin coming of age? *Am J Kidney Dis* 2005;**46**(2):186–202.
24. Arnold R, Issar T, Krishnan AV, Pussell BA. Neurological complications in chronic kidney disease. *JRSM Cardiovasc Dis* 2016;**5**. 2048004016677687.
25. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake and the risk of gout in men. *N Engl J Med* 2004;**350**:1093–103.
26. Bellomo G, Venanzi S, Verdura C, Saronio P, Esposito A, Timio M. Association of uric acid with change in kidney function in healthy normotensive individuals. *Am J Kidney Dis* 2010;**56**:264–72.
27. Johnson RJ, Segal MS, Srinivas T, et al. Essential hypertension, progressive renal disease, and uric acid: a pathogenetic link? *J Am Soc Nephrol* 2005;**16**(7):1909–19.
28. Zoccali C, Ruggenenti P, Perna A, et al. Phosphate may promote CKD progression and attenuate renoprotective effect of ACE inhibition. *J Am Soc Nephrol* 2011;**22**(10):1923–30.
29. Vegter S, Perna A, Postma MJ, Navis G, Remuzzi G, Ruggenenti P. Sodium intake, ACE inhibition, and progression to ESRD. *J Am Soc Nephrol* 2012;**23**(1):165–73.
30. DeFronzo RA, Beckles AD. Glucose intolerance following chronic metabolic acidosis in man. *Am J Physiol* 1979;**236**:E328–34.
31. Chauveau P, Couzi L, Vendrely B, et al. Long-term outcome on renal replacement therapy in patients who previously received a keto acid-supplemented very-low-protein diet. *Am J Clin Nutr* 2009;**90**:969–74.
32. Mitch WE, Remuzzi G. Diets for patients with chronic kidney disease, still worth prescribing. *J Am Soc Nephrol* 2004;**15**: 234–7.
33. Levey AS, Adler S, Caggiula AW, et al. Effects of dietary protein restriction on the progression of advanced renal disease in the Modification of Diet in Renal Disease Study. *Am J Kidney Dis* 1996;**27**:652–63.
34. Wang M, Chou J, Chang Y, et al. The role of low protein diet in ameliorating proteinuria and deferring dialysis initiation: what is old and what is new. *Panminerva Med* 2017;**59**(2):157–65.
35. Metzger M, Yuan WL, Haymann JP, et al. Association of a low-protein diet with slower progression of CKD. *Kidney Int Rep* 2018;**3**(1):105–14.
36. Kelly JT, Palmer SC, Wai SN, et al. Healthy dietary patterns and risk of mortality and ESRD in CKD: a meta-analysis of cohort studies. *Clin J Am Soc Nephrol* 2017;**12**(2):272–9.
37. Hahn D, Hodson EM, Fouque D. Low protein diets for non-diabetic adults with chronic kidney disease. *Cochrane Database Syst Rev* 2018;**10**:CD001892.
38. Masud T, Young VR, Chapman T, Maroni BJ. Adaptive responses to very low protein diets: the first comparison of ketoacids to essential amino acids. *Kidney Int* 1994;**45**:1182–92.
39. Mariani G, Barsotti G, Ciardella F, et al. Albumin metabolism and nutritional status of uremic patients on a long-term very-low-protein diet supplemented with essential amino acids and keto analogues. *J Nucl Med Allied Sci* 1984;**28**:237–44.
40. Ciardella F, Morelli E, Cupisti A, et al. Metabolic effects of a very-low-protein, low-phosphorus diet supplemented with essential amino acids and keto analogues in end-stage renal diseases. *Contrib Nephrol* 1988;**65**:72–80.
41. Teschan PE, Beck GJ, Dwyer JT, et al. Effect of a ketoacid-aminoacid-supplemented very low protein diet on the progression of advanced renal disease: a reanalysis of the MDRD feasibility study. *Clin Nephrol* 1998;**50**:273–83.
42. Aparicio M, Chauveau P, dePrecigout V, Bouchet J-L, Lasseur C, Combe C. Nutrition and outcome on renal replacement therapy of patients with chronic renal failure treated by a supplemented very low protein diet. *J Am Soc Nephrol* 2000;**11**:719–27.
43. Di Iorio BR, Minutolo R, De Nicola L, et al. Supplemented very low protein diet ameliorates responsiveness to erythropoietin in chronic renal failure. *Kidney Int* 2003;**64**:1822–8.

44. Bellizzi V, Di Iorio BR, De NL, et al. Very low protein diet supplemented with ketoanalogs improves blood pressure control in chronic kidney disease. *Kidney Int* 2007;**71**(3):245–51.
45. Menon V, Kopple JD, Wang X, et al. Effect of a very low-protein diet on outcomes: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. *Am J Kidney Dis* 2008;**53**: 208–17.
46. Peuchant E, mas-Beauvieux MC, Dubourg L, et al. Antioxidant effects of a supplemented very low protein diet in chronic renal failure. *Free Radic Biol Med* 1997;**22**(1–2):313–20.
47. Garneata L, Mircescu G. Effect of low-protein diet supplemented with keto acids on progression of chronic kidney disease. *J Ren Nutr* 2013;**23**(3):210–3.
48. Garneata L, Stancu A, Dragomir D, Stefan G, Mircescu G. Ketoanalogue-supplemented vegetarian very low-protein diet and CKD progression. *J Am Soc Nephrol* 2016;**27**(7):2164–76.
49. Di Iorio BR, Di ML, Marzocco S, et al. Very low-protein diet (VLPD) reduces metabolic acidosis in subjects with chronic kidney disease: the "nutritional light signal" of the renal acid load. *Nutrients* 2017;**9**(1).
50. Scalone L, Borghetti F, Brunori G, et al. Cost-benefit analysis of supplemented very low-protein diet versus dialysis in elderly CKD5 patients. *Nephrol Dial Transplant* 2010;**25**(3):907–13.
51. FAO/WHO/UNU. Energy and protein requirements. In: *Technical report series 724*. 1st ed. Geneva: World Health Organization; 1985.
52. Avesani CM, Kamimura MA, Draibe SA, Cuppari L. Is energy intake underestimated in nondialyzed chronic kidney disease patients? *J Ren Nutr* 2005;**15**(1):159–65.
53. Carrero JJ, Stenvinkel P, Cuppari L, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). *J Ren Nutr* 2013;**23**(2):77–90.
54. Garlick PJ, McNurlan MA, Ballmer PE. Influence of dietary protein intake on whole-body protein turnover in humans. *Diabetes Care* 1991;**14**(12):1189–98.
55. Williams B, Hattersley J, Layward E, Walls J. Metabolic acidosis and skeletal muscle adaptation to low protein diets in chronic uremia. *Kidney Int* 1991;**40**:779–86.
56. Garibotto G, Sofia A, Parodi EL, et al. Effects of low-protein, and supplemented very low-protein diets, on muscle protein turnover in patients with CKD. *Kidney Int Rep* 2018;**3**(3):701–10.
57. Group KDIGOKCW. KDIGO 2012 clinical practice guidelines for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:1–150.
58. Moore LW, Byham-Gray LD, Scott PJ, et al. The mean dietary protein intake at different stages of chronic kidney disease is higher than current guidelines. *Kidney Int* 2013;**83**:724–32.
59. Traynor JP, Simpson K, Geddes CC, Deighan CJ, Fox JG. Early initiation of dialysis fails to prolong survival in patients with end-stage renal failure. *J Am Soc Nephrol* 2002;**13**:2125–32.
60. Cooper BA, Branley P, Bulfone L, et al. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med* 2010; **363**(7):609–19.
61. Kopple JD, Levey AS, Greene T, et al. Effect of dietary protein restriction on nutritional status in the modification of diet in renal disease (MDRD) study. *Kidney Int* 1997;**52**:778–91.
62. Group MS, Kopple JD, Greene T, et al. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD Study. *Kidney Int* 2000;**57**:1688–703.
63. Block G. A review of validations of dietary assessment methods. *Am J Epidemiol* 1982;**115**:492–505.
64. Kelly RA, Mitch WE. Creatinine, uric acid and other nitrogenous waste products: clinical implication of the imbalance between their production and elimination in uremia. *Semin Nephrol* 1983; **3**:286–94.
65. Kopple JD, Fouque D. Pro: the rationale for dietary therapy for patients with advanced chronic kidney disease. *Nephrol Dial Transplant* 2018;**33**(3):373–8.
66. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. *N Engl J Med* 2017;**377**(18):1765–76.
67. Robertson L, Waugh N, Robertson A. Protein restriction for diabetic renal disease. *Cochrane Database Syst Rev* 2007;(4):CD002181.
68. Wolfe RR, Miller SL, Miller KB. Optimal protein intake in the elderly. *Clin Nutr* 2008;**27**(5):675–84.
69. Cortinovis M, Perico N, Remuzzi G. Nephrotic syndrome: nutritional consequences and dietary management. In: Ikizler TA, Mitch WE, editors. *Handbook of nutrition and the kidney.* 7th ed. Philadelphia: Lppincott-Williams and Wilkins; 2018.
70. Maroni BJ, Staffeld C, Young VR, Manatunga A, Tom K. Mechanisms permitting nephrotic patients to achieve nitrogen equilibrium with a protein-restricted diet. *J Clin Investig* 1997;**99**: 2479–87.
71. Bellizzi V, Calella P, Hernandez JN, et al. Safety and effectiveness of low-protein diet supplemented with ketoacids in diabetic patients with chronic kidney disease. *BMC Nephrol* 2018;**19**(1):110.
72. Rughooputh MS, Zeng R, Yao Y. Protein diet restriction slows chronic kidney disease progression in non-diabetic and in type 1 diabetic patients, but not in type 2 diabetic patients: a meta-analysis of randomized controlled trials using glomerular filtration rate as a surrogate. *PLoS One* 2015;**10**(12):e0145505.
73. Moe SM, Zidehsarai MP, Chambers MA, et al. Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. *Clin J Am Soc Nephrol* 2011; **6**(2):257–64.
74. Scialla JJ, Appel LJ, Wolf M, et al. Plant protein intake is associated with fibroblast growth factor 23 and serum bicarbonate levels in patients with chronic kidney disease: the Chronic Renal Insufficiency Cohort study. *J Ren Nutr* 2012;**22**(4):379–388 e371.
75. Chen X, Wei G, Jalili T, et al. The associations of plant protein intake with all-cause mortality in CKD. *Am J Kidney Dis* 2016; **67**(3):423–30.
76. Folin O. Laws governing the clinical composition of urine. *Am J Physiol* 1905;**13**:67–115.
77. Cottini EP, Gallina DL, Dominguez JM. Urea excretion in adult humans with varying degrees of kidney malfunction fed milk, egg or an amino acid mixture: assessment of nitrogen balance. *J Nutr* 1973;**103**:11–9.
78. Franch HA, Mitch WE. Navigating between the Scylla and Charybdis of prescribing dietary protein of chronic kidney diseases. *Annu Rev Nutr* 2009;**29**:341–64.
79. Mitch WE, Lietman PS, Walser M. Effects of oral neomycin and kanamycin in chronic renal failure: I. urea metabolism. *Kidney Int* 1977;**11**:116–22.
80. Mitch WE, Walser M. Effects of oral neomycin and kanomycin in chronic uremic patients. II. Nitrogen balance. *Kidney Int* 1977;**11**: 123–7.
81. Mitch WE, Wilcox CS. Disorders of body fluids, sodium and potassium in chronic renal failure. *Am J Med* 1982;**72**:536–50.
82. Kloppenburg WD, De Jong PE, Huisman RM. The contradiction of stable body mass despite low reported dietary energy intake in chronic haemodialysis patients. *Nephrol Dial Transplant* 2002; **17**:1628–33.
83. Mitch WE. Malnutrition: a frequent misdiagnosis for hemodialysis patients. *J Clin Investig* 2002;**110**:437–9.
84. Wilcox CS. Dietary salt intake for patients with hypertension or kidney disease. In: Mitch WE, Ikizler TA, editors. *Handbook of nutrition and the kidney.* 6th ed. Philadelphia: Lippincott, Williams and Wilkins; 2009. p. 233–42.
85. Kotchen TA, Cowley Jr AW, Frohlich ED. Salt in health and disease–a delicate balance. *N Engl J Med* 2013;**368**(13):1229–37.

86. Lipkowitz MS, Wilcox CS. Dietary salt intake for patients with hypertension or kidney disease. In: Ikizler TA, Mitch WE, editors. *Handbook of nutrition and the kidney.* 7th ed. Philadelphia: Lppincott-Williams and Wilkins; 2018.
87. Sacks FM, Svetkey LP, Vollmar WM, et al. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *N Engl J Med* 2001;**344**:3—10.
88. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997;**336**(16):1117—24.
89. Svetkey LP, Simons-Morton D, Vollmer WM, et al. Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. *Arch Intern Med* 1999;**159**(3):285—93.
90. Ballmer PE, McNurlan MA, Hulter HN, Anderson SE, Garlick PJ, Krapf R. Chronic metabolic acidosis decreases albumin synthesis and induces negative nitrogen balance in humans. *J Clin Investig* 1995;**95**:39—45.
91. Brungger M, Hulter HN, Krapf R. Effect of chronic metabolic acidosis on the growth hormone/IGF-1 endocrine axis: new cause of growth hormone insensitivity in humans. *Kidney Int* 1997;**51**: 216—21.
92. Brungger M, Hulter HN, Krapf R. Effect of chronic metabolic acidosis on thyroid hormone homeostasis in humans. *Am J Physiol* 1997;**272**:F648—53.
93. Krapf R, Vetsch R, Vetsch W, Hulter HN. Chronic metabolic acidosis increases the serum concentration of 1,25-dihydroxyvitamin D in humans by stimulating its production rate. *J Clin Investig* 1992;**90**:2456—63.
94. Kalhoff H, Diekmann L, Kunz C, Stock GJ, Manz F. Alkali therapy versus sodium chloride supplement in low birthweight infants with incipient late metabolic acidosis. *Acta Paediatr* 1997;**86**: 96—101.
95. Boirie Y, Broyer M, Gagnadoux MF, Niaudet P, Bresson J-L. Alterations of protein metabolism by metabolic acidosis in children with chronic renal failure. *Kidney Int* 2000;**58**:236—41.
96. Reaich D, Channon SM, Scrimgeour CM, Goodship THJ. Ammonium chloride-induced acidosis increases protein breakdown and amino acid oxidation in humans. *Am J Physiol* 1992;**263**:E735—9.
97. Papadoyannakis NJ, Stefanides CJ, McGeown M. The effect of the correction of metabolic acidosis on nitrogen and protein balance of patients with chronic renal failure. *Am J Clin Nutr* 1984;**40**: 623—7.
98. Hanafusa N, Kopple JD. Trace elements and vitamins. In: Ikizler TA, Mitch WE, editors. *Handbook of nutrition and the kidney.* 7th ed. Philadelphia: Lppincott-Williams and Wilkins; 2018.
99. Lonn E, Bosch J, Yusuf S, et al. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *J Am Med Assoc* 2005;**293**(11):1338—47.
100. Cousins RJ. Absorption, transport, and hepatic metabolism of copper and zinc: special reference to metallothionein and ceruloplasmin. *Physiol Rev* 1985;**65**(2):238—309.
101. Kimmel PL. Zinc and chronic renal disease. *Semin Dial* 1989;**2**(4): 253—9.
102. Monteon FJ, Laidlaw SA, Shaib JK, Kopple JD. Energy expenditure in patients with chronic renal failure. *Kidney Int* 1986;**30**: 741—7.
103. Thomas SS, Zhang L, Mitch WE. Molecular mechanisms of insulin resistance in chronic kidney disease. *Kidney Int* 2015;**88**:1233—9.
104. Kopple JD, Monteon FJ, Shaib JK. Effect of energy intake on nitrogen metabolism in nondialyzed patients with chronic renal failure. *Kidney Int* 1986;**29**:734—42.

QUESTIONS AND ANSWERS

Question 1

A 60-year-old man with stage 4 CKD with estimated GFR 20 mL/min/1.73 m^2 who weighs 65 kg is prescribed a 0.6 g protein/kg/day diet. His BUN and body weight are stable. Assess compliance if 24-hour urine collection contains 7 g of urea nitrogen.

Answer: Nitrogen balance (B_N) = nitrogen intake (I_N) − (urea nitrogen) UUN − (nonurea nitrogen) NUN

Assuming compliance $B_N = 0$ then I_N = UUN + NUN

UUN = 7 g N/day, NUN = 0.031 N/kg b.w. = 0.031 * 65 = 2.02 g N/day

I_N = 7 g N/day + 2.02 g N/day = 9.02 g N/day

Because protein is 16% nitrogen, protein intake = 9.02 g N/day/0.16% N/g protein = 56.38 g protein which is >20% of prescribed intake of 0.6 g protein/kg/day * 65 kg = 39 g protein.

He is not compliant with LPD.

Question 2

A 55-year-old woman with stage 3 CKD with estimated GFR of 45 mL/min/1.73 m^2 who weighs 80 kg presents for nutritional recommendations. She has nephrotic syndrome with 8 g proteinuria/day. What protein restriction do you prescribe?

Answer: Protein restriction for stage III CKD should be 0.8 g/kg/day. In this case, we also need to account for losses of 8 g/day from proteinuria. Her recommended protein intake should be 8 g/day + 0.8 g/kg * 80 kg = 72 g protein/day.

Question 3

An 85-year-old man with stage 5 CKD with estimated GFR 10 mL/min/1.73 m^2 presents for evaluation. He has mild symptoms of uremia. His serum electrolytes are within normal range. He is normotensive and euvolemic on examination. He asks your recommendation whether he should initiate dialysis. What are your recommendations?

Answer: Initiating hemodialysis earlier may be associated with higher cost and disease burden compared with medical management. There is no mortality benefit with dialysis compared with medical management. You can recommend a VLPD-KA regimen if available or LPD and assess his symptoms on follow-up.

Question 4

A 32-year-old woman with stage 3 CKD with estimated GFR 45 mL/min/1.73 m^2 asks you for vitamin supplementation to optimize nutrition. She follows an LPD of 0.8 g/kg/day and is not receiving parenteral nutrition. Which of the following do you recommend?

A. Prescribe fat-soluble vitamins (vitamin A, D, E, and K) but not water-soluble vitamins
B. Prescribe water-soluble vitamins (B-complex and C) but not fat-soluble vitamins
C. Prescribe trace elements only
D. Prescribe fat-soluble vitamins, water-soluble vitamins, and trace elements

Answer: B

Excessive vitamin C could lead to oxalate nephropathy so prescription should be lower than RDA.

Question 5

Which of the following are consequences of metabolic acidosis?

A. Stimulates muscle protein degradation
B. Improves protein stores
C. Suppresses albumin synthesis
D. Aggravates renal osteodystrophy
E. Ameliorates effects of uremia on bone
F. Accelerates CKD progression
G. Promotes insulin resistance and glucose intolerance
H. Leads to zinc accumulation
I. Impairs thyroid hormone responses
J. Aggravates trace element deficiencies
K. Impairs growth hormone
L. Impairs response to 1,25 dihydroxyvitamin D3

Answer: A, C, D, F, G, I, K, and L

Refer to section on metabolic acidosis.

Question 6

A 40-year-old man feels well but is concerned because his S[Cr] has increased from 2 to 3 mg/dL despite a prescribed diet of 0.8 g protein/kg/day and daily lisinopril. Which of the following factors must be evaluated?

A. The presence of edema and changes in body weight and blood pressure
B. Fluid ingestion at bedtime
C. Increased intake of phosphates
D. A 24-hour urine collection to measure intake of dietary protein
E. Urine sediment examination

Answer: A, C, D, and E

The presence of edema, hypertension, and higher blood pressure suggests the patient's salt intake has increased. This factor and/or an increase in phosphate intake can suppress the beneficial effect of ACEI in slowing the progression of CKD. If the dietary protein intake has increased, it might overcome the benefits of LPDs on the progression of CKD. The increase in S[Cr] could reflect kidney cell damage signified by granular casts in the urine sediment.

CHAPTER

60

Management of Anemia in Chronic Kidney Disease

Blaise Abramovitz[a], *Jeffrey S. Berns*[b]

[a]Renal-Electrolyte Division, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States; [b]Renal-Electrolyte and Hypertension Division, Department of Medicine, Perelman School of Medicine of the University of Pennsylvania School of Medicine, Philadelphia, PA, United States

Abstract

Anemia is one of the most common complications of chronic kidney disease (CKD). As kidney disease advances, the incidence and prevalence of anemia increases. Anemia of CKD is multifactorial in etiology. The most common causes are erythropoietin deficiency, iron deficiency, and inflammation. Observational studies have suggested an increased risk of cardiovascular and renal complications, lower quality of life, and higher mortality as being associated with a lower hemoglobin (Hb) concentration. However, large randomized controlled trials have demonstrated that normalization of Hb concentration with an erythropoiesis-stimulating agent (ESA) is associated with either no benefit or an increased risk of cardiovascular complications and/or death, due to either the high Hb, the higher ESA doses needed to achieve this, or both. Contemporary approaches to anemia management embrace individualized therapy aimed at minimizing transfusions and use of the lowest possible dose of ESA together with treatment of iron deficiency and inflammation.

INTRODUCTION

Anemia is one of the most common complications of chronic kidney disease (CKD).[1,2] As kidney disease advances, the incidence and prevalence of anemia increases. Anemia of CKD is multifactorial in etiology. The most common causes are erythropoietin deficiency, iron deficiency, and inflammation. Observational studies, primarily in hemodialysis patients, suggested that an increased risk of cardiovascular and renal complications, lower quality of life (QoL), and higher mortality are associated with a lower hemoglobin (Hb) level.[3–7] Based on these observations, it became commonplace in both patients on dialysis and those with CKD not on dialysis to at least partially, if not fully, correct the anemia. In more recent years, however, large randomized controlled trials (RCTs) have demonstrated that complete, as opposed to partial, correction of anemia with an erythropoiesis-stimulating agent (ESA) is associated with either no benefit or an increased risk of cardiovascular complications and/or death compared with lower Hb levels, due either to these higher Hb levels, the higher ESA doses needed to achieve higher Hb concentrations, or some combination of both.[8–13] Thus, contemporary approaches to anemia management now more typically embrace using the lowest possible dose of ESA together with treatment of iron deficiency and inflammation with a goal of maintaining Hb levels around 10–11 g/dL in most patients.

DIAGNOSIS AND EVALUATION OF ANEMIA IN CKD PATIENTS

Evaluating patients both for the clinical effects of anemia and assessing potential causes of anemia is critical. The diagnosis of anemia of CKD rests on an appropriate clinical and laboratory evaluation. The evaluation is reviewed in more detail in two guideline documents from the Kidney Disease: Improving Global Outcomes (KDIGO) and the European Renal Best Practice groups.[14,15]

A diagnosis of anemia is generally made when the Hb concentration falls below about 13.5 g/dL in adult men and about 12.0 g/dL in adult children. As will be discussed below, however, these Hb concentrations should trigger an assessment of the cause of anemia but not necessarily treatment, and there is now a general consensus that an Hb concentration >10 g/dL does

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00060-7

not warrant specific therapy in most patients with anemia related to CKD. Screening for anemia should occur annually in patients with stage 3 CKD and at least twice a year in patients with stage 4 or 5 (nondialysis) CKD. Aside from a complete blood count, initial evaluation of anemia should include assessment of reticulocyte count, ferritin, transferrin saturation (TSAT), vitamin B_{12}, and red blood cell folate levels. Consideration should also be given to screening for fecal occult blood. Measurement of circulating erythropoietin levels is not useful in most patients with CKD and anemia and is not recommended. Once a patient has been diagnosed with anemia, but is not yet being treated with an ESA and/or iron therapy, monitoring of anemia should generally occur about every 3 months in patients with stages 3–5 who are not on dialysis.

The serum ferritin concentration is a commonly used indicator of storage iron. Ferritin is also an acute-phase reactant and, thus, is affected by inflammation. As such, ferritin values are of greatest predictive value when low (<100 ng/mL) but are of more limited value when elevated. TSAT measures circulating iron that is available for erythropoiesis. It is derived by dividing serum iron by total iron binding capacity and then multiplying by 100. Evaluating anemia based on serum iron alone is not recommended. Unfortunately, studies indicate that serum iron parameters poorly predict either tissue iron or Hb response to intravenous (IV) iron therapy.[16,17]

GENERAL APPROACH TO TREATMENT OF ANEMIA IN CKD

Before availability of recombinant human erythropoietin (epoetin alfa) in 1989, the treatment of CKD anemia comprises blood transfusions, iron, and, in patients on dialysis, anabolic steroids. Most patients were very anemic, with Hb concentrations commonly as low as 5–7 g/dL in advanced CKD and end-stage renal disease (ESRD). The goal of treatment was to raise the Hb to levels that afforded some improvement in symptoms such as lack of energy, fatigue, decreased physical functioning, and an inability to perform the daily activities of life. The introduction of epoetin alfa in 1989 had a transformative effect on the management of the anemia of CKD. Very soon thereafter, almost all anemic patients on dialysis were receiving epoetin alfa therapy and the numbers of nondialysis anemic patients with CKD receiving ESA treatment increased dramatically.

As noted above, observational studies, mostly among patients on hemodialysis, suggested an association between anemia and cardiovascular events and mortality in CKD patients with and without concurrent ESA treatment.[3–11] These studies found that lower levels of Hb were associated with worse outcomes, higher mortality risk, and increased rate of hospitalizations compared with patients with higher Hg concentrations.[3,7] Small studies also found that left ventricular hypertrophy was inversely associated with Hb concentrations.[18,19] Some studies indicated that patients with nondialysis CKD and anemia had a higher risk of progression of kidney disease and an increased risk of adverse cardiovascular events, congestive heart failure (CHF), and increased hospitalizations.[20–22] These observations led many physicians to use epoetin alfa to push Hb concentrations higher and higher toward the normal range with the expectation that doing so would improve patient well-being, cardiovascular outcomes, and mortality.

This began to change, however, with publication of the Normal Hematocrit Cardiac Trial (NHCT) trial in HD patients, in 1998. While this chapter is focused on patients with CKD who are not on dialysis, it is important to consider the NHCT study because its results informed future studies among patients who were not on dialysis. The NHCT was an RCT of HD patients with established heart disease, comparing a hematocrit target of 42% to one of 30%. The study was stopped by the Data Safety Monitoring Board because of concern for increased mortality in the patients randomized to the higher hematocrit group, although the observed difference was not statistically significant. Additionally, patients in the higher hematocrit group had a nearly statistically significantly higher rate of nonfatal myocardial infarction (MI) or death.[10] In a subsequent analysis, it was reported that randomization to the higher Hb target did increase the risk for the primary endpoint (RR 1.28; 95% CI = 1.06–1.56; p = 0.0112; 99.92% CI = 0.92–1.78), the risk of death (RR 1.27; 95% CI = 1.04–1.54), nonaccess thrombotic events (p = 0.041), and hospitalization rate (p = 0.04), while "physical function" did not improve (p = 0.88).[23,24] As discussed in the next section, subsequent studies in patients with CKD not on dialysis further informed our management of anemia in these patients.

ESA USE IN THE TREATMENT OF ANEMIA IN PATIENTS WITH CKD

The US Food and Drug Administration (FDA) approved epoetin alfa, a short-acting ESA, in 1989. Other short-acting ESAs are available in other countries, which differ in structure, dosing, safety, and immunogenicity. The epoetins are typically administered once weekly or every other week in patients with CKD who are not on dialysis. Darbepoetin alfa, approved in the US and elsewhere in 2001, is a hyperglycosylated erythropoietin analogue with a terminal half-life that is several fold

TABLE 60.1 Erythropoiesis-Stimulating Agents (ESAs)

	Commonly Used Initial Subcutaneous Dose
Short-Acting ESAs	
Various epoetins, including epoetin alfa-epbx	4000–10,000 weekly
Long-Acting ESAs	
Darbepoetin alfa	0.45 mcg/kg every 1–2 weeks or 0.75 mcg/kg every 2–4 weeks
Methoxy polyethylene glycol-epoetin	0.6 mcg/kg every 2–4 weeks

Adapted from reference 27.

longer than epoetin alfa. Darbepoetin alfa can be dose as infrequently as once or twice per month.[25] Methoxy polyethylene glycol-epoetin is another long-acting ESA with an extended half-life that can also be administered once or twice per month.[26] With expiration of patents for epoetin alfa has come the introduction of competitor products called "biosimilar" epoetins. Biosimilars are biologic therapeutic agents that are similar, but not identical, to the original biological agent. The epoetin biosimilar that is available in the US, epoetin alfa-epbx, is dosed the same as the original epoetin alfa formulation. Table 60.1 provides a comparison of dosing schedules of ESAs.[27,28] Unlike many hemodialysis patients, ESAs are administered subcutaneously in patients with CKD.

Treatment of anemia with an ESA in patients with CKD must balance the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients. Current guidelines and consensus statements generally support the initiation of ESA therapy in many patients when Hb <10 g/dL, emphasizing though that whether to treat with an ESA should be individualized based on the rate of fall of Hb concentration, iron status and prior response to iron therapy, the risk of needing a transfusion, and the risks attributable to anemia and those related to ESA therapy. ESA treatment should generally not be undertaken until concurrent iron deficiency has been appropriately treated, with TSAT >20% and serum ferritin >100 ng/mL. On initiation of ESA therapy, the Hb concentration is often measured monthly until the target level has been achieved after which assessment monitoring every 2–3 months is appropriate, depending on clinical circumstances. ESA dose adjustments should typically be made no more often than once every 2–4 weeks because the effect of dose changes will generally not be seen within a shorter interval.

For most patients, ESA treatment is used to maintain Hb concentrations of 10–11.5 g/dL, with slightly higher concentrations targeted in selected patients who might benefit from higher levels and understand and are willing to accept the potential risks. The US FDA labeling for ESAs identifies avoidance of transfusion as the sole indication for ESA use and states that, for nondialysis CKD patients, one should consider ESA treatment only when the Hb level is <10 g/dL and reduce or interrupt the ESA dose if the Hb level exceeds 10 g/dL. Targeting Hb concentrations >13 g/dL is not recommended. KDIGO Guidelines recommend that ESAs be used with caution or not at all in patients with active malignancy (Grade 1B recommendation), a history of stroke (Grade 1B recommendation), or a history of malignancy (Grade 2C recommendation).[15] Individual responses to ESA treatment vary; those who do not respond as expected should be investigated for iron deficiency, infection, inflammatory conditions, and other disorders associated with ESA hyporesponsiveness.[29] Hyporesponsiveness has been associated with poorer outcomes compared with patients with better response to ESA treatment.[30,31] In all patients, the lowest possible dose that maintains the target Hb concentration should be used.

The above recommendations stem largely from results of three randomized controlled clinical trials in patients with CKD not on dialysis which found inconsistent effects on QoL and either no mortality benefit or risk of harm among patients randomized to treatment groups targeting higher compared with lower Hb concentrations. The Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta trial enrolled approximately 600 nondialysis CKD subjects who were randomized into either an early anemia treatment group or a delayed anemia treatment group.[9] The early treatment group received epoetin beta therapy immediately for a normal target Hb of 13–15 g/dL, whereas the delayed anemia treatment group did not receive treatment until their Hb was <10.5 g/dL with treatment aimed at maintaining an Hb of 10.5–11.5 g/dL. There was no improvement in time to first cardiac event in the early treatment/higher target Hb group compared with the delayed/lower target Hb group, but dialysis was required in more patients in the higher than the lower Hb group. QoL measure scores were improved for the higher compared with lower Hb group subjects.

The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial was an open-label RCT that studied 1432 nondialysis CKD subjects who were randomized to receive epoetin alfa targeted to achieve an Hb of 13.5 g/dL or 11.3 g/dL.[11] The primary endpoint, a composite of death, MI, CHF, hospitalization (excluding hospitalization during which renal replacement therapy occurred), and stroke, occurred more often

in the high Hb group compared with the low Hb group (HR 1.34; 95% CI 1.03−1.74; p = 0.03). Among other secondary endpoints, QoL showed improvement in both groups but was not significantly better in the higher compared with lower Hb groups. More subjects in the high Hb group experienced at least one serious adverse event compared with the low Hb group. Secondary analyses from the CHOIR trial suggest the higher ESA doses needed to achieve and sustain higher Hb concentrations may contribute to the increased risk of adverse events in the high target Hb arm.[32,33]

The Trial to Reduce Cardiovascular Events with Aranesp Therapy study, the only large placebo-controlled study of ESAs in CKD, randomized 4038 subjects with type 2 diabetes mellitus and CKD (eGFR 20−60 mL/min/1.73 m^2) to receive darbepoetin alfa to achieve a target Hb of 13 g/dL or placebo with rescue darbepoetin administered if the Hb level was <9 g/dL.[8] The primary endpoints were composite outcomes of death or cardiovascular event (nonfatal MI, CHF, stroke, or hospitalization for myocardial ischemia) and death or ESRD. The median follow-up for this study was 29 months. Both groups had similar risks of death or cardiovascular event (HR 1.05; 95% CI 0.94−1.17; p = 0.41) and death or ESRD (HR 1.06; 95% CI 0.95−1.19; p = 0.29). There was a significantly higher risk of stroke in the group assigned to darbepoetin alfa compared with placebo, especially in patients with a prior history of a stroke. Death due to cancer in those with a prior history of cancer was also increased.

These three studies, along with changes in FDA-approved product labeling in the US, have led clinicians to avoid attempts at Hb normalization and tempered enthusiasm for use of ESAs to improve QoL. Instead, practice has evolved to use of lower ESA doses and targeting of Hb levels in the range of 10−11.5 g/dL in many patients.

EVALUATING AND CORRECTING PERSISTENT FAILURE TO REACH OR MAINTAIN TARGET HB

ESA hyporesponsiveness, which is much more common among hemodialysis patients than those with CKD not on dialysis, is diagnosed in patients who are not able to achieve or maintain the desired Hb concentration despite receiving higher than expected ESA doses.[29] Patients with initial ESA hyporesponsiveness during the first several months of treatment are more likely to experience an adverse cardiovascular outcome or die than patients who respond better to initial dosing.[30,34] In patients with initial or acquired ESA hyporesponsiveness, evaluation for specific causes of poor ESA response should be undertaken. The most common factors leading to ESA hyporesponsiveness are shown in Table 60.2.[35] It is now generally recommended, given concerns that high ESA doses may contribute to some of the adverse events noted in clinical trials, that ESA doses not be repeatedly increased in hyporesponsive patients beyond 2−3 times the initial dose.

IRON SUPPLEMENTATION TO TREAT CKD ANEMIA

Adequate iron stores and availability of iron to support erythropoiesis are essential, whether patients are receiving an ESA or not. Iron deficiency is common in patients with CKD.[36−38] Iron status (iron stores and available iron in the circulation) should be evaluated in anemic patients with CKD. The gold standard for evaluating iron stores is the assessment of stainable iron in a bone marrow biopsy, a test that is only very rarely performed for this purpose. Instead, measurement of serum ferritin, a marker of storage iron, is

TABLE 60.2 Factors Involved in Erythropoiesis-Stimulating Agent (ESA) Hyporesponsiveness

Easily Correctable	Potentially Correctable	Other Factors
Absolute iron deficiency	Infection/Inflammation	Hemoglobinopathies
Vitamin B_{12}/Folate deficiency	Malnutrition	
Inadequate dialysis	Hemolysis	
ACEI/ARB use (uncommon)	Bleeding	
	Severe hyperparathyroidism (uncommon)	
	Pure red cell aplasia	
	Malignancy	
	Bone marrow disorders	

ACEI, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker.
Adapted from reference 35.

commonly used. A serum ferritin ≤30 ng/mL is consistent with an absence of bone marrow iron. Ferritin is also an acute-phase reactant, and because patients with CKD patients may have chronic inflammation, elevated serum ferritin levels must be interpreted cautiously. TSAT is the most common method for assessing iron availability in the circulation for incorporation into red blood cells.

Iron deficiency may be either absolute, i.e. there is an absence or deficiency of bone marrow iron which limits erythropoiesis, or functional, in which bone marrow iron is present but due to inflammatory blockade or other factors is not readily available to support erythropoiesis. Functional iron deficiency may also be seen in patients receiving ESAs with stimulation of erythropoiesis beyond that which available iron can support. Absolute iron deficiency in patients with CKD is typically characterized by TSAT <20% and serum ferritin levels <200 mg/dL. Functional iron deficiency, in contrast, is characterized by TSAT >20−30% and serum ferritin >200−300 mg/dL. Despite having adequate bone marrow iron stores, some patients with CKD and anemia will nonetheless experience an increased red blood cell production and Hb concentration when administered IV iron.[16,39]

Untreated iron deficiency is a major cause of hyporesponsiveness to ESA treatment.[40,41] As high ESA doses may contribute to adverse outcomes, maximizing ESA responsiveness with adequate iron stores is essential so that the lowest possible ESA dose can be used. Therefore, before initiating ESA therapy, a patient's iron status must be assessed and iron deficiency, if present, should be treated. Options for therapy depend on the stage of CKD and include oral and IV therapies. A trial of oral iron therapy is often undertaken in patients with CKD who are not on dialysis, although IV iron is more effective in repleting and maintaining sufficient iron stores and leads to greater Hb increases,[42] and thus should be used if oral iron is poorly tolerated or less effective than desired.

IRON AGENTS DOSING AND FREQUENCY IN CKD

Decisions to initiate iron therapy must weigh both the benefits (avoidance of transfusions and reduction of anemia-related symptoms) and potential adverse effects of iron supplementation. The 2012 KDIGO Clinical Practice Guidelines for anemia in CKD recommend initiation in nondialysis CKD patients not on ESA therapy if an increase in Hb concentration is desired and TSAT is ≤30% and ferritin is ≤500 ng/mL. A trial of oral iron therapy can be undertaken for 1−3 months before using IV iron therapy, although some use IV iron instead of oral iron to avoid adverse effects of oral iron and ensure adequate iron supplementation. Selection of route of iron therapy depend on severity of iron deficiency, availability of venous access, response to prior oral or IV iron therapy, tolerance of side effects with prior oral iron treatment, patient compliance, and cost.

Dosing strategies for oral iron generally provide approximately 200 mg of elemental iron daily, which is equivalent to ferrous sulfate 325 mg three times daily, the most commonly used oral iron preparation. Each pill provides 65 mg of elemental iron. Other oral iron formulations are available, but none has been convincingly demonstrated to be more effective or better tolerated than iron sulfate. Gastrointestinal side effects may limit use of oral iron. If goals of iron supplementation are not met with oral iron after a 1- to 3-month trial, it is appropriate to consider IV iron supplementation, as recommended (Grade 2C) in the 2012 KDIGO Anemia Guidelines.[15] IV iron can be administered as a single large dose or repeated smaller doses depending on the specific IV iron preparation used (discussed further below). The initial course of IV iron is typically prescribed to provide approximately 1000 mg initially, with additional doses if this fails to achieve the desired increase in Hb level and/or decrease in ESA dose. TSAT and ferritin are typically monitored every 3 months once anemia treatment with iron is initiated, with monthly monitoring of the Hb.

A new oral iron preparation, ferric citrate, was approved by the US FDA in 2017 for the treatment of iron deficiency anemia in patients with CKD who are not on dialysis. It had previously been approved as a phosphate binder for patients on dialysis. Ferric citrate contains the equivalent of 210 mg of ferric iron. Two double-blind RCTs comparing ferric citrate to placebo in subjects with nondialysis-dependent CKD demonstrated greater improvement in Hb and iron indices with ferric citrate and similar side effects compared with placebo.[43,44] Ferric citrate is more expensive than iron sulfate but may be useful in selected patients, although studies comparing the efficacy and side effects of these two oral iron preparations have not yet been reported.

USE OF INTRAVENOUS IRON IN THE TREATMENT OF CKD ANEMIA

Several IV iron preparations are available for treatment of iron deficiency among patients with CKD. A high molecular weight formulation of iron dextran, which was associated with more common occurrence of severe side effects compared with other agents, is no longer available. Alternatives include ferric carboxymaltose, ferric gluconate, ferumoxytol, iron sucrose, iron

isomaltoside (not available in the US), and low molecular weight iron dextran. Iron sucrose and ferric gluconate required repeated administration, whereas the other agents can provide a total iron dose of 1000 mg or more in one or two infusions, which is more convenient and preferred for patients with CKD who may be preserving veins for possible hemodialysis vascular access placement. Iron sucrose may be given in doses of 100–300 mg and ferric gluconate in doses of 125–175.5 mg. A 25-mg test dose before infusion of a full dose of iron dextran is required; test doses are not required with the other agents but are often recommended in patients with multiple drug allergies or history of prior reactions to IV iron.

IV iron can cause allergic reactions, including life-threatening anaphylaxis. Such reactions appear to be very uncommon and occur with roughly equal frequency with any of the currently available IV preparations. Other uncommon symptoms with iron infusion include urticaria, palpitations, and dizziness. Because of mostly theoretical concerns that bacterial infections may worsen following IV administration, it is generally recommended that iron infusions be deferred in patients with active bacterial infections or at least are on appropriate antimicrobial therapy.

CONCLUSION

Anemia is one of the most common complications of CKD. As kidney disease advances, the incidence and prevalence of anemia increases. Anemia of CKD is multifactorial in etiology with erythropoietin deficiency, iron deficiency, and inflammation being the most important contributing causes. Observational studies have suggested an increased risk of cardiovascular and renal complications, lower QoL, and higher mortality as being associated with a lower Hb level. While it is likely that this positive impact of anemia management is present comparing Hb concentrations of 9–11 g/dL with Hb concentrations prevalent before ESAs became available, large RCTs have demonstrated that correction of anemia with an ESA is associated with either no benefit or an increased risk of cardiovascular complications and/or death. Some studies have also suggested that exposure to high doses of ESA may contribute to some adverse events arising from anemia treatment. Contemporary approaches to anemia management now embrace individualizing anemia management using the lowest possible dose of ESA together with treatment of iron deficiency and any underlying inflammation. In the not too distant future, oral prolyl hydroxylase inhibitors that stabilize and prevent degradation of hypoxia-inducible factor leading to both enhanced erythropoietin production and improved iron utilization are likely to be approved for management of anemia in patients with CKD.[45,46] Their role in management of anemia in this patient population is likely to be determined based on their cost compared with already available agents and demonstration of long-term safety.

References

1. McClellan W, Aronoff SL, Bolton WK, Hood S, Lorber DL, Tang KL. The prevalence of anemia in patients with chronic kidney disease. *Curr Med Res Opin* 2004;**20**:1501–10.
2. Hsu CY, McCulloch CE, Curhan GC. Epidemiology of anemia associated with chronic renal insufficiency among adults in the United States: results from the Third National Health and Nutrition Examination Survey. *J Am Soc Nephrol* 2002;**13**:504–10.
3. Locatelli F, Pisoni RL, Combe C, Bommer J, Andreucci VE, Piera L, Greenwood R, Feldman HI, Port FK, Held PJ. Anaemia in haemodialysis patients of five European countries: association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2004;**19**:121–32.
4. Robinson BM, Joffe MM, Berns JS, Pisoni RL, Port FK, Feldman HI. Anemia and mortality in hemodialysis patients: accounting for morbidity and treatment variables updated over time. *Kidney Int* 2005;**68**:2323–30.
5. Collins AJ, Ma JZ, Ebben J. Impact of hematocrit on morbidity and mortality. *Semin Nephrol* 2000;**20**:345–9.
6. Collins AJ, Li S, St Peter W, Ebben J, Roberts T, Ma JZ, Manning W. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephrol* 2001;**12**:2465–73.
7. Regidor DL, Kopple JD, Kovesdy CP, Kilpatrick RD, McAllister CJ, Aronovitz J, Greenland S, Kalantar-Zadeh K. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. *J Am Soc Nephrol* 2006;**17**:1181–91.
8. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, Lewis EF, McGill JB, McMurray JJ, Parfrey P, Parving HH, Remuzzi G, Singh AK, Solomon SD, Toto R. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;**362**:2019–32.
9. Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006;**355**:2071–84.
10. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;**339**:584–90.
11. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;**355**:2085–98.
12. Singh AK. Is there a deleterious effect of erythropoietin in end-stage renal disease? *Kidney Int* 2011;**80**:569–71.
13. Singh AK. What is causing the mortality in treating the anemia of chronic kidney disease: erythropoietin dose or hemoglobin level? *Curr Opin Nephrol Hypertens* 2010;**19**:420–4.
14. Locatelli F, Bárány P, Covic A, de Francisco A, del Vecchio L, Goldsmith D, Hörl W, London G, Vanholder R, van Biesen W. Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European renal best practice position statement. *Nephrol Dial Transplant* 2013;**28**:1346–59.

15. KDIGO Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl* 2012;**2**(4): 279–335.
16. Stancu S, Bârsan L, Stanciu A, Mircescu G. Can the response to iron therapy be predicted in anemic nondialysis patients with chronic kidney disease? *Clin J Am Soc Nephrol* 2010;**5**:409–16.
17. Singh AK, Coyne DW, Shapiro W, Rizkala AR. Predictors of the response to treatment in anemic hemodialysis patients with high serum ferritin and low transferrin saturation. *Kidney Int* 2007;**71**: 1163–71.
18. Levin A, Singer J, Thompson CR, Ross H, Lewis M. Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention. *Am J Kidney Dis* 1996;**27**:347–54.
19. Levin A, Thompson CR, Ethier J, Carlisle EJ, Tobe S, Mendelssohn D, Burgess E, Jindal K, Barrett B, Singer J, Djurdjev O. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis* 1999;**34**:125–34.
20. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The impact of anemia on cardiomyopathy, morbidity, and mortality in end-stage renal disease. *Am J Kidney Dis* 1996;**28**:53–61.
21. Rigatto C, Parfrey P, Foley R, Negrijn C, Tribula C, Jeffery J. Congestive heart failure in renal transplant recipients: risk factors, outcomes, and relationship with ischemic heart disease. *J Am Soc Nephrol* 2002;**13**:1084–90.
22. Xue JL, St Peter WL, Ebben JP, Everson SE, Collins AJ. Anemia treatment in the pre-ESRD period and associated mortality in elderly patients. *Am J Kidney Dis* 2002;**40**:1153–61.
23. Coyne DW. The health-related quality of life was not improved by targeting higher hemoglobin in the Normal Hematocrit Trial. *Kidney Int* 2012;**82**:235–41.
24. Fishbane S, Wish JB. A physician's perseverance uncovers problems in a key nephrology study. *Kidney Int* 2012;**82**:135–7.
25. Galle J, Claes K, Kiss I, Winearls CG, Herlitz H, Guerin A, di Giulio S, Suranyi MG, Bridges I, Addison J, Farouk M. An observational cohort study of extended dosing (once every 2 weeks or once monthly) regimens with darbepoetin alfa in patients with chronic kidney disease not on dialysis: the EXTEND study. *Nephrol Dial Transplant* 2012;**27**:2303–11.
26. Koch M, Henrich D, Faust J, Nawka J, Rath T, Wanner C. Initial use of once-monthly administration of C.E.R.A. is effective and safe in correcting renal anemia in non-dialysis patients: the MERCUR trial. *Clin Nephrol* 2012;**78**:189–97.
27. Hörl WH. Differentiating factors between erythropoiesis-stimulating agents: an update to selection for anaemia of chronic kidney disease. *Drugs* 2013;**73**:117–30.
28. Macdougall IC, Walker R, Provenzano R, de Alvaro F, Locay HR, Nader PC, Locatelli F, Dougherty FC, Beyer U. C.E.R.A. corrects anemia in patients with chronic kidney disease not on dialysis: results of a randomized clinical trial. *Clin J Am Soc Nephrol* 2008;**3**:337–47.
29. Drüeke T. Hyporesponsiveness to recombinant human erythropoietin. *Nephrol Dial Transplant* 2001;**16**:25–8.
30. Solomon SD, Uno H, Lewis EF, Eckardt KU, Lin J, Burdmann EA, de Zeeuw D, Ivanovich P, Levey AS, Parfrey P, Remuzzi G, Singh AK, Toto R, Huang F, Rossert J, McMurray JJ, Pfeffer MA. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. *N Engl J Med* 2010;**363**:1146–55.
31. Tsuruya K, Uemura Y, Hirakata H, Kitazono T, Tsubakihara Y, Suzuki M, Ohashi Y. Association between responsiveness to methoxy polyethylene glycol-epoetin beta and renal survival in patients with non-dialysis-dependent chronic kidney disease: a pooled analysis of individual patient-level data from clinical trials. *Nephrology* 2017;**22**:769–75.
32. Inrig JK, Barnhart HX, Reddan D, Patel UD, Sapp S, Califf RM, Singh AK, Szczech LA. Effect of hemoglobin target on progression of kidney disease: a secondary analysis of the CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) trial. *Am J Kidney Dis* 2012;**60**:390–401.
33. McCullough PA, Barnhart HX, Inrig JK, Reddan D, Sapp S, Patel UD, Singh AK, Szczech LA, Califf RM. Cardiovascular toxicity of epoetin-alfa in patients with chronic kidney disease. *Am J Nephrol* 2013;**37**:549–58.
34. Rossert J, Gassmann-Mayer C, Frei D, McClellan W. Prevalence and predictors of epoetin hyporesponsiveness in chronic kidney disease patients. *Nephrol Dial Transplant* 2007;**22**:794–800.
35. Kliger AS, Foley RN, Goldfarb DS, Goldstein SL, Johansen K, Singh A, Szczech L. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for anemia in CKD. *Am J Kidney Dis* 2013;**62**:849–59.
36. Besarab A, Coyne DW. Iron supplementation to treat anemia in patients with chronic kidney disease. *Nat Rev Nephrol* 2010;**6**:699–710.
37. Fernández Rodríguez A, Guerra Prieto MF, Camino Calderón E, Solera Santos J. Iron-deficiency anemia and adult celiac disease. *An Med Interna* 1999;**16**:208–9.
38. Kalantar-Zadeh K, Höffken B, Wünsch H, Fink H, Kleiner M, Luft FC. Diagnosis of iron deficiency anemia in renal failure patients during the post-erythropoietin era. *Am J Kidney Dis* 1995; **26**:292–9.
39. Chung M, Chan JA, Moorthy D, Hadar N, Ratichek SJ, Concannon TW, Lau J. *Biomarkers for assessing and managing iron deficiency anemia in late-stage chronic kidney disease: identification of future research needs from comparative effectiveness review no. 83*. 2013. Rockville (MD).
40. Sunder-Plassmann G, Hörl WH. Importance of iron supply for erythropoietin therapy. *Nephrol Dial Transplant* 1995;**10**:2070–6.
41. Fishbane S, Frei GL, Maesaka J. Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. *Am J Kidney Dis* 1995;**26**:41–6.
42. Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: an updated systematic review and meta-analysis. *Am J Kidney Dis* 2016;**68**:677–90.
43. Block GA, Fishbane S, Rodriguez M, Smits G, Shemesh S, Pergola PE, Wolf M, Chertow GM. A 12-week, double-blind, placebo-controlled trial of ferric citrate for the treatment of iron deficiency anemia and reduction of serum phosphate in patients with CKD Stages 3-5. *Am J Kidney Dis* 2015;**65**:728–36.
44. Fishbane S, Block GA, Loram L, Neylan J, Pergola PE, Uhlig K, Chertow GM. Effects of ferric citrate in patients with nondialysis-dependent CKD and iron deficiency anemia. *J Am Soc Nephrol* 2017;**28**:1851–8.
45. Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: a potential new treatment for anemia in patients with CKD. *Am J Kidney Dis* 2017;**69**:815–26.
46. Hasegawa S, Tanaka T, Nangaku M. Hypoxia-inducible factor stabilizers for treating anemia of chronic kidney disease. *Curr Opin Nephrol Hypertens* 2018;**27**:331–8.

QUESTIONS AND ANSWERS

Question 1

A 60-year-old man with a history of hypertension, diabetes mellitus, and proteinuric CKD stage 4 is seen in follow-up. He has noticed increasing fatigue, without any other signs of uremia. He has had no changes in his medications, no recent illnesses. A recent echocardiogram demonstrated no acute changes. Current medications include lisinopril, aspirin, insulin, ferrous sulfate 325 mg three times a day, lansoprazole, and calcium acetate. Blood pressure is 120/80 mm Hg, heart rate 100 beats per minute. Lungs are clear, there are no murmurs, abdomen is soft, nontender, without evidence of hepatosplenomegaly, and there is trace peripheral edema. The following labs are obtained:

S[Na] 140 mEq/L
S[K] 4.4 mEq/L
S[Cl] 100 mEq/L
tCO2 22 mEq/L
BUN 38 mg/dL
S[Cr] 2.9 mg/dL
WBC 5.5/μL
Hb 8 g/dL
Hct 24%
Platelets 250/μL
TSAT 10%
Ferritin 20 ng/mL

What would be the next step in management?

A. Discontinue proton pump inhibitor
B. Discuss avoiding taking ferrous sulfate with meals or calcium acetate
C. Discontinue ACEI
D. Increase ferrous sulfate dose
E. Initiate IV iron therapy

Answer: E

The clinical presentation is consistent with severe iron deficiency anemia as evidenced by the symptoms and laboratory findings. The patient has a low Hb concentration with a low TSAT and a very low ferritin level. Although proton pump inhibitors, calcium phosphate, and ingesting iron with meals may interfere with iron absorption (A, B), the patient has symptomatic anemia; therefore, discontinuing the proton pump inhibitor and avoiding iron with meals and calcium acetate will not adequately address his severe anemia. Discontinuing his ACEI is not necessary, though ACEI are associated with ESA hyporesponsiveness (C). Increasing his ferrous sulfate dose (D), if he is indeed adherent, is also not correct as he is receiving the recommended daily dose of 200 mg of elemental iron (each 325mg of ferrous sulfate has 65mg of elemental iron). Given his symptoms, it would be best to initiate IV iron therapy (E) and measure his response to IV iron repletion following a dose of 1000 mg (in either split doses or one large dose). If his Hb does not improve and his TSAT remains $\leq$30% and his ferritin is $\leq$500 ng/mL, this dose may be repeated once. If there is no improvement following administration of 2 g of IV iron, then sources of ongoing blood loss should be investigated.

Question 2

A 45-year-old woman with a past medical history of systemic lupus, hypertension, and lupus nephritis (in remission), with CKD stage 3, presents for routine follow-up. She has no complaints and has been adherent with her medications, which include mycophenolate mofetil 1500 mg twice a day, plaquenil, lisinopril, and aspirin. Blood pressure is 110/70 mm Hg, heart rate is 70 beats per minute. Her physical examination demonstrates normal findings, clear lungs, no murmurs, no hepatosplenomegaly, and no evidence of peripheral edema. The following labs are obtained:

S[Na] 140 mEq/L
S[K] 4.0 mEq/L
S[Cl] 100 mEq/L
tCO2 24 mEq/L
BUN 25 mg/dL
S[Cr] 1.5 mg/dL
WBC 3.5/μL
Hb 9.8 g/dL
Hct 28.5%
Platelets 300/μL
TSAT 35%
Ferritin 250 ng/mL

What would be the next step in management of the anemia?

A. Decrease mycophenolate mofetil dose
B. Start oral iron therapy
C. Discontinue ACEI
D. Repeat CBC, TSAT, ferritin within 12 months and check B12/folate, TSH to investigate other causes of anemia
E. Initiate ESA therapy

Answer: D

This is an asymptomatic anemic patient with lupus nephritis which is in remission. Decreasing her mycophenolate mofetil dose may be indicated if she had leukopenia or infection, but not in this case (A). Her TSAT and ferritin levels are adequate and do not indicate iron deficiency (B). There is no indication to hold her ACEI in this case as it is not independently associated with a low Hb (C). In the absence of a clear

explanation for a low Hb, and in the absence of symptoms, there is no indication to initiate ESA therapy in this patient (E). Investigation of other underlying causes of anemia is indicated for this patient (D).

Question 3

A 55-year-old man with a history of hypertension and CKD stage 5 of unknown etiology has been followed regularly in renal clinic. He has not had any uremic symptoms but has noticed that his blood pressure, which had previously been well controlled, has become elevated recently to 160/90 mm Hg consistently. He denies headaches, change in vision, chest pain, and shortness of breath. He denies recent changes to his medications, and he does not take over-the-counter medications or recreational drugs. His medications include diltiazem, furosemide, darbepoetin alfa 40 μg monthly, sodium bicarbonate, ferrous sulfate 325 mg three times a day, sevelamer, calcitriol 0.5 μg three times a week, and simvastatin. Blood pressure is 170/100 mm Hg, heart rate is 75 beats per minute. His physical examination demonstrates jugular venous pressure 7 cm, clear lungs, no murmurs, no hepatosplenomegaly, and no evidence of peripheral edema. The following labs are obtained:

S[Na] 140 mEq/L
S[K] 4.5 mEq/L
S[Cl] 104 mEq/L
tCO2 21 mEq/L
BUN 49 mg/dL
S[Cr]5.5 mg/dL
WBC 6.5/μL
Hb 14 g/dL
Hct 42%
Platelets 300/μL
TSAT 30%
Ferritin 420 ng/mL
Chemistries have been stable for the last 6 months; however, the Hb has increased from 10 g/dL three months ago to 14 g/dL on the same dose of darbepoetin alfa.

What would be the next step in management?

A. Discontinue darbepoetin alfa
B. Decrease darbepoetin alfa dose
C. Discontinue iron
D. Increase antihypertensive therapy

Answer: A

This is a patient with hypertension likely related to therapy with ESA. Normal subjects and CKD patients (both treated and not treated with dialysis) on ESA therapy have demonstrated elevated systolic and diastolic blood pressures in previous studies. The correct answer would be A, stop the darbepoetin alfa and monitor blood pressure carefully. As it is likely that it will take some time to see an improvement in blood pressure in the short-term, it would also be prudent to increase antihypertensive therapy temporarily (D), but the patient would likely not need prolonged increased hypertensive therapy. Decreasing the darbepoetin alfa dose will not be beneficial as the Hb level is elevated and the patient does not need further therapy. Holding the iron therapy is also reasonable as the patient is not iron deficient (C), but the first thing to stop is the darbepoetin alfa.

Question 4

A 67-year-old woman with a history of hypertension, diabetes mellitus, and proteinuric CKD stage 5 presents with a history of increasing fatigue sustained an ankle fracture 6 months ago following a mechanical fall. She is having difficulty with walking up and down her stairs. On follow-up visit, her Hgb was 7.0 g/dL. She was sent to the hospital and had a blood transfusion. No evidence was found for ongoing blood loss. She subsequently had a cardiac stress test that was normal. Following the blood transfusion, her fatigue improved. She has returned for follow-up in renal clinic. Her medications have not changed since her hospitalization and include carvedilol, lisinopril, lansoprazole, calcitriol 0.5 μg on three times a week, sevelamer 1600 mg with meals, darbepoetin alfa 40 μg monthly, sodium bicarbonate, and simvastatin. Her blood pressure is 110/75 mm Hg, heart rate is 70 beats per minute. The rest of her physical examination demonstrates clear lungs, no murmurs, no hepatosplenomegaly, and no evidence of peripheral edema. The following labs are obtained:

S[Na] 140 mEq/L
S[K] 5.0 mEq/L
S[Cl] 110 mEq/L
tCO2 22 mEq/L
BUN 40 mg/dL
S[Cr] 5.0 mg/dL
S[Ca] 8.5
S[P] 8.0 mg/dL
iPTH = 2000 pg/mL
WBC 7.5/μL
Hb 8.5 g/dL
Hct 26%
Platelets 228/μL
TSAT 30%
Ferritin 420 ng/mL

What would be the next step in management?

A. Discontinue lisinopril
B. Discontinue lansoprazole

C. Control hyperparathyroidism by discontinuing calcitriol, discussing adherence to low phosphorus diet and binders, and starting cinacalcet
D. Increase darbepoetin alfa frequency

Answer: C

This is a patient with severe hyperparathyroidism with symptomatic anemia despite normal iron stores and ESA therapy who subsequently required a blood transfusion. Hyperparathyroidism is a cause of ESA hyporesponsiveness; therefore, C is the correct answer: control hyperparathyroidism. Although lisinopril may be a cause of ESA hyporesponsiveness and may also be held if her blood pressure is monitored (A), it is not the first step in this patient's management. Lansoprazole does not affect ESA response (B), and increasing darbepoetin will not improve this patient's Hb until the hyperparathyroidism is under control (D).

Question 5

A 70-year-old woman with a history of hypertension, hypothyroidism, and IgA nephropathy with CKD stage 4 who presents with a history of progressive fatigue returns to renal clinic. She has an Hb of 6 g/dL. Three months ago, her Hb was 9.5 g/dL. She denies shortness of breath or chest pain but does have dyspnea on exertion and has noticed some light-headedness at times. Her medications include labetalol, synthroid, epoetin alfa three times a week, calcium acetate 500 mg with meals, and calcitriol 0.25 μg three times a week. Her blood pressure is 100/70 mm Hg, heart rate is 70 beats per minute. The rest of her physical examination is unremarkable. The following labs are obtained STAT:

S[Na] 140 mEq/L
S[K] 4.0 mEq/L
S[Cl] 105 mEq/L
tCO2 22 mEq/L
BUN 40 mg/dL
S[Cr] 4.0 mg/dL
S[Ca] 8.5 mg/dL
S[P] 5.0 mg/dL
WBC 8.0/μL
Hb 6 g/dL
Hct 18%
Platelets 228/μL

Before a blood transfusion, you request the following labs be obtained. Which laboratory test is most likely to be abnormal?

A. TSH
B. Parvovirus PCR
C. Anti-EPO antibodies
D. iPTH
E. Iron studies to include TSAT, ferritin

Answer: C

The dramatic drop in Hb level in this patient raises concerns about ongoing blood loss, but in the absence of bleeding, the more likely cause of this dramatic decrease in hematocrit is anti-EPO antibodies (C) developing as a consequence of ESA therapy. Although pure red blood cell aplasia is rare, it has been seen in patients who have been on formulations of epoietin alpha. The other causes of ESA hyporesponsiveness should also be investigated. If the first set of studies is normal, evaluation by a hematologist will be necessary as bone marrow disorders, and malignancy could also be a cause of severe anemia in this patient.

Question 6

A 75-year-old woman with a past medical history of Hodgkin lymphoma successfully treated with chemotherapy and radiation 20 years ago, with hypertension and CKD stage 4 presents for follow-up in renal clinic. Her labs have been stable over three years, except at her last visit 6 months ago, she was found to be anemic with an Hb of 7.5 g/dL. She was initiated on oral iron for iron deficiency anemia, and once her iron stores had improved, she was started on darbepoetin alfa monthly. She has been on ESA therapy for 3 months now, and each month, her TSAT and ferritin have been adequate, yet her Hb has not substantially improved and is still 7.8 g/dL. Her current dose of darbepoetin is twice the initial dose recommended by the manufacturer. She is fatigued but has not had shortness of breath or dyspnea on exertion, and she denies light-headedness.

What is the next step in this patient's management?

A. Increase her darbepoetin dose
B. Initiate a trial of IV iron therapy
C. Initiate Vitamin C therapy
D. Referral to hematology for evaluation of anemia

Answer: A

Attempting an increase in darbepoetin dose sounds reasonable (A), given the lack of response to the current dose of ESA. The darbepoetin dose should be adjusted monthly but should not exceed four times the initial dose recommendations based on weight. Given her history of Hodgkin lymphoma, she is at increased risk for developing myelodysplastic syndrome, which is a cause of ESA hyporesponsiveness, as is any bone marrow disorder. If there is no improvement in her Hb within one month with the increased dose of darbepoetin, then referral to a hematologist is indicated (D). Answer B is not correct because her TSAT and ferritin are adequate. Answer C, Vitamin C adjuvant therapy, is associated with Hb improvements in patients treated with dialysis who are on ESA therapy; however, the effects of Vitamin C on predialysis CKD patients are unknown.

CHAPTER

61

Management of Hypertension in Chronic Kidney Disease

Mahboob Rahman[a], *Paul Drawz*[b], *George Thomas*[c], *Jeffrey Turner*[d]

[a]University Hospitals Cleveland Medical Center, Case Western Reserve University, Louis Stokes Cleveland VA Medical Center, Cleveland, OH, United States; [b]Division of Renal Diseases and Hypertension, University of Minnesota Medical School, Minneapolis, MN, United States; [c]Cleveland Clinic Foundation, Cleveland, OH, United States; [d]Yale University, New Haven, CT, United States

Abstract

Hypertension is common in patients with chronic kidney disease (CKD) and contributes to risk of progression of CKD and cardiovascular disease. Many factors including alterations in salt and water balance, the sympathetic nervous system, and the renin–angiotensin–aldosterone system underlie the pathophysiology of hypertension in this setting. Careful measurement of blood pressure, including out-of-office measurement, is important. Goal blood pressure for patients with CKD is less than 130/80 mm Hg. Restriction of dietary salt intake is an important nonpharmacologic intervention, and inhibitors of the renin–angiotensin axis are the cornerstone of drug therapy, especially in patients with proteinuria.

Hypertension is common in patients with chronic kidney disease (CKD) with a prevalence rate of 60–90% in several studies.[1] Hypertension contributes to the high risk for cardiovascular disease and to progressive loss of kidney function over time in this population. Therefore, optimal management of hypertension is an important aspect of the care of the patient with CKD. However, blood pressure (BP) control rates remain suboptimal. Only 34–67% of adults with hypertension and CKD have controlled BP (<140/90 mm Hg).[2,3]

MECHANISMS OF HYPERTENSION IN CKD

The kidneys play a central role in regulating BP by maintaining sodium and water homeostasis and through regulation of the renin–angiotensin–aldosterone system (RAAS). In addition, factors that affect the sympathetic nervous system and endothelial function are important contributors to the pathogenesis of hypertension in CKD patients.

Salt and Water Balance

Hypertension due to impaired sodium and water retention is a final common pathway of several interconnected pathologies that occur in CKD. In the steady state, salt and water intake is precisely balanced with salt and water excretion by the kidneys. When salt and water intake is increased, such that it exceeds the steady state excretion rate, a transient period of positive sodium balance will occur. This results in an increase in total body water, extracellular water, and arterial BP. The rise in BP stimulates an increase in sodium and water excretion by the kidneys, such that homeostasis is achieved, and sodium and water intake will again be balanced by salt and water excretion.[4,5] In this system, the BP costs of achieving sodium balance with increasing amounts of sodium intake varies among individuals. In some a rise in BP is minimal or nonexistent, whereas in others, significant sustained hypertension occurs.[6] The latter is referred to as salt-sensitive hypertension. The magnitude of salt-sensitive hypertension increases with increasing loss of kidney function.[7–9] In these settings, there is an increase in mean arterial pressure required to achieve sodium balance with higher levels of sodium intake. This salt-sensitivity phenomenon is due to an inability to adequately downregulate neurohormones that promote increased renal sodium reabsorption in these pathologic settings. On the other hand, in some models of CKD, salt sensitivity is not demonstrated, due to a homogenous increase in preglomerular resistance. Representative clinical scenarios

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00061-9

include bilateral renal artery stenosis and coarctation of the aorta, in which hypertension is a significant feature; however, salt sensitivity is not present. This is due to the preservation of the ability to downregulate neurohormones that promote renal sodium reabsorption with increased salt intake.

The mechanisms that result in a shift to the right of the pressure natriuresis curves, the so called "resetting of pressure natriuresis," are less well understood. This response is critical in any form of sustained hypertension, whether essential hypertension or hypertension in the setting of CKD is considered.[10] Resetting in pressure natriuresis is not due to changes in renal blood flow or glomerular filtration. Rather, increases in renal interstitial hydrostatic pressure lead to the downregulation of proximal tubule sodium transporters, particularly Na+ H+ isoform 3.[11] In addition, it has been speculated that sustained abnormalities in pressure natriuresis may be related to abnormalities in renal vasoconstriction[12] and endothelial dysfunction related to abnormalities in nitric oxide.[13]

Renin–Angiotensin–Aldosterone System

The RAAS is a major regulator of BP due to its effects on salt and water retention and due to its direct effects on vasoconstriction. Key concepts have emerged regarding the role of RAAS in the pathogenesis of hypertension in CKD. The presence of an intrarenal RAAS that operates independently of systemic RAAS plays an important pathophysiologic role. Important signaling pathways for the intrarenal RAAS include the Wnt/β-catenin pathway and sympathetic nervous system stimulation of β-1 adrenergic receptors.

The RAAS is tightly regulated in health and responds to dietary sodium intake. In the presence of high salt intake, there is increased delivery of sodium and chloride to the macula densa of the thick ascending limb. This signals inhibition of renin production by the juxtaglomerular cells of the afferent arteriole, which then inhibit the downstream production of angiotensin II and aldosterone, potent stimuli for vasoconstriction and renal tubular sodium reabsorption. However, in CKD there is hyperactivation of the RAAS that is stimulated independently of sodium intake.[14,15] Mounting evidence demonstrates that this is mediated through the intrarenal RAAS system.[16,17] The kidney is unique compared to most other organs in the body, in that it has all the necessary components to generate intrarenal angiotensin II along the cells of the nephron. Much higher tissue concentrations of angiotensin II in the kidney have been demonstrated that could not be explained by delivery of systemically produced angiotensin II *via* the arterial blood flow alone.[14,18] In addition, several kidney disease models have demonstrated activation of intrarenal RAAS as opposed to systemic RAAS.[19–24] Therefore, it appears that intrarenal RAAS is an important mechanism by which hypertension is both initiated and maintained in CKD.

Sympathetic Nervous System

Activation of the sympathetic nervous system is an important contributor to the development of hypertension in CKD patients. The kidneys are both the source (*via* afferent pathways) and the target (*via* efferent pathways) of this activity, and higher sympathetic nervous system activity is associated with increased vascular tone and BP.[25] Direct stimulation of renal afferent pathways by uremic solutes[26,27] may also mediate increased sympathetic nervous system activity in CKD.[28] Sympathetic overactivity is also transmitted back to the kidney *via* efferent neural pathways resulting in β1 adrenergic receptor–mediated renin release in the juxtaglomerular cells and α1 adrenergic receptor–mediated renal arteriole vasoconstriction. Both of these mechanisms are important in sustaining hypertension in CKD patients.

Vascular Endothelial Dysfunction

Endothelial dysfunction is common in CKD, contributing to hypertension as well as end-organ damage. Although there are numerous pathways by which endothelial function is affected, two important mechanisms include impairments in nitric oxide, a potent vasodilator, and deficiencies of renalase, a secreted amine important for catecholamine metabolism.[29–31]

MEASUREMENT OF BLOOD PRESSURE IN CKD

Office Blood Pressure

For over 100 years, BP measurement in the office has been the preferred method for assessing BP, diagnosing hypertension, and evaluating response to therapy. The original auscultatory method has been mostly replaced by oscillometric devices that detect pulsatile blood flow and indirectly calculate BP.[32] Many modern oscillometric devices are programmable to enable a defined rest period, and multiple measurements are typically taken at one minute intervals. BP measured using one of these newer devices is referred to as automated office BP. Although the evidence is limited, automated office BP may be slightly lower than manual office BP, and automated office BP may correlate better with ambulatory daytime BPs.[33] Most recent clinical trials use automated office BP.[34] Regardless of the technique (manual vs. automated), measurement of BP in the office should

follow guidelines from the American College of Cardiology/American Heart Association.[32,35] Important considerations include preparing the patient (including about five minutes of quiet rest, and proper positioning with the arm supported at heart level), use of an approved device with the proper cuff size, and averaging two or more readings used to estimate the BP for that clinic visit.

Home BP

Measurement of BP outside the office setting has been increasingly recognized as a valuable adjunct in the management of hypertension.[32,36] This can be done by monitoring BP at home, or by 24-hour ambulatory BP monitoring. Although it does require some patient education, home BP monitoring is typically less cumbersome than ambulatory BP monitoring. Patients should be instructed on proper technique, including use of a validated monitor, proper positioning, and the necessity of adequate quiet rest prior to taking readings.[32] Patients should bring their monitor to clinic to assess their technique using their home device compared to clinic BP. Patients are typically instructed to take two BP readings in the morning before taking medications and two BP readings in the evening. The average of all readings over a week is then used to assess BP control.[32] Home BP monitoring may improve BP control. In the Targets and Self-Management for the Control of Blood Pressure in Strokes and at Risk Groups (TASMIN-SR) study, 552 patients with a BP $\geq$130 mm Hg were randomized to usual care or self-management (which included measurement of BP in the home and self-titration of medications).[37] After 12 months, among the 146 patients with CKD, the systolic BP in the intervention group at 12 months was 8.4 mm Hg (95% CI 1.1−15.8) lower than the control group.[37] A recent meta-analysis found a similar benefit to home BP monitoring but indicated that combining home BP monitoring with other interventions, such as a plan for medication titration and education, may be necessary to achieve lower BPs.[38] In summary, home BP monitoring should be considered in the diagnosis (to identify white coat and masked hypertension) and management of hypertension in patients with CKD.

Ambulatory BP Monitoring

Ambulatory BP monitoring (ABPM) is considered the gold standard for assessing out-of-office BP. The monitors are similar to automated oscillometric devices used in the clinic and are programmed to record BP throughout the day and night for a 24-hour period.[32] ABPM provides an estimate of daytime, 24 hour, and nighttime BP, and the relative decrease in BP from day to night, which is referred to as dipping status.[39] Compared to daytime BP, nighttime BP is more strongly associated with all-cause mortality, cardiovascular mortality, and cardiovascular events.[40−42]

White-Coat and Masked Hypertension

Out-of-office BPs, either home or ambulatory, can be combined with clinic BPs to categorize patients as normotensive (normal clinic and out-of-office BP), white-coat hypertension (elevated clinic BP with normal out-of-office BP), masked hypertension (normal clinic BP with elevated out-of-office BP), and sustained hypertension (elevated clinic and out-of-office BP). In observational studies in the general population, patients with white-coat hypertension have risk of cardiovascular outcomes that are similar to those with controlled clinic and out-of-office BPs, whereas masked hypertension is associated with increased risk for adverse outcomes.[43,44]

Patients with low estimated glomerular filtration rate (eGFR) and proteinuria are more likely to have elevated nighttime BP and a nondipping pattern.[45] Similarly, masked and sustained hypertensions are associated with lower eGFR and proteinuria.[46] Masked hypertension is associated with higher risk of target organ damage and clinical cardiovascular disease outcomes. In 1492 patients with CKD enrolled in the Chronic Renal Insufficiency Cohort study, 28% had masked hypertension. Compared to controlled clinic and ambulatory BP, masked hypertension was associated with higher left ventricular mass index (+2.52 g/m^2; 95% CI 0.9−4.1) and pulse wave velocity (+0.92 m/s; 95% CI 0.5−1.3).[46] In a longitudinal study of 489 hypertensive patients seen in a nephrology clinic in Italy, compared to controlled clinic and ambulatory BP, white-coat hypertension was associated with similar risk for cardiovascular outcomes, end-stage renal disease (ESRD), and all-cause mortality while masked hypertension was associated with increased risk of cardiovascular outcomes (hazard ratio [HR] 3.17; 95% 1.5−6.7), ESRD (HR 3.93; 95% CI 1.8−8.7), and all-cause mortality (HR 3.45; 95% CI 1.5−7.9).[47] Based on these studies and others, it appears that the well-established increased risk associated with masked hypertension in the general population also applies to patients with CKD.

Current national guidelines recommend out-of-office BP to confirm the diagnosis of hypertension prior to initiating treatment and to guide therapy in patients receiving antihypertensive medications.[32,36]

TREATMENT OF HYPERTENSION IN CKD PATIENTS

The goal of hypertension management in patients with CKD is to achieve and maintain BP less than 130/80 mm Hg[32] (Figure 61.1). This is supported by

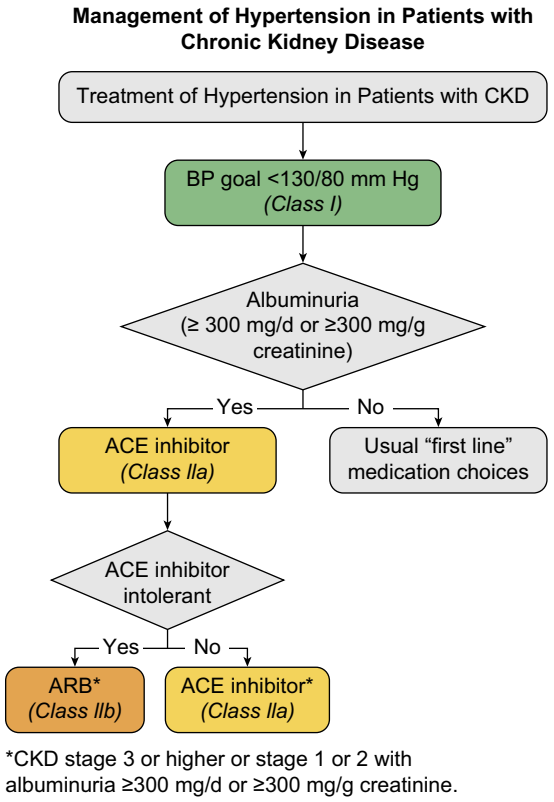


FIGURE 61.1 Overview of management of hypertension in CKD.[32] *Reprinted with permission from the Journal of the American College of Cardiology.*

observational data that suggest there is a linear relationship between BP and clinical outcomes in patients with CKD.[48] More importantly, intensive treatment of BP has been shown to reduce risk of cardiovascular disease and mortality in this patient population.[34,49] The Systolic Blood Pressure Treatment Trial (SPRINT) provided valuable information about intensive BP control in patients with CKD. SPRINT was a multicenter clinical trial that randomized 9361 hypertensive patients to a standard treatment arm (target systolic BP less than 140 mm Hg) or an intensive treatment arm (target systolic BP less 120 mm Hg). Of study participants, 28% had CKD at baseline. In the CKD participants[50] the mean BP over the duration of follow-up (3.2 years) was 123/66 mm Hg, requiring an average of 2.9 antihypertertensive medications. Participants assigned to the intensive treatment group had lower risk of all-cause mortality (HR, 0.72; 95% CI, 0.53–0.99) and of developing the primary cardiovascular outcome (HR, 0.81; 95% CI, 0.63–1.05), consistent with findings in the overall study population. However, there was no difference in the primary renal outcome (ESRD or 50% decline in eGFR), perhaps due to the small number of patients who reached this endpoint. There was an acute decline in glomerular filtration rate (GFR) in the first six months in the intensive treatment group, suggestive of a hemodynamic effect of lowering BP, seen in previous clinical trials. The urinary biomarker profile measured in SPRINT supported a hemodynamically mediated decline in GFR rather than tubular injury. In summary, the SPRINT study demonstrated that intensive BP control can be achieved and maintained and is associated with lower risk of mortality and cardiovascular disease in patients with CKD.

Other studies have shown that benefits of intensive treatment of BP on preserving renal function are seen after long-term follow-up in patients with proteinuria.[50,51] Whether intensive treatment of BP slows decline in kidney function in patients without significant proteinuria remains unclear.[50]

Nonpharmacologic Interventions

Patients with CKD and hypertension should be advised to lose weight, follow a healthy diet, reduce salt intake, participate in regular physical activity, not smoke, and have moderate alcohol intake.[32,52] Most of these recommendations are based on expert opinion, observational data, and randomized trials in the general population. However, there is some evidence of the effectiveness of these interventions in patients with CKD. A meta-analysis of 11 observational studies and 2 randomized trials demonstrated that weight loss interventions resulted in lower systolic BP along with a reduction in proteinuria.[53] Dietary sodium restriction is especially important to consider given CKD patients' decreased ability to excrete sodium. Among CKD patients with proteinuria, randomized trials have shown that decreased sodium intake reduces BP and proteinuria.[54,55] The Dietary Approaches to Stop Hypertension diet is recommended to lower BP in the general population. It should be considered with caution, however, in patients with advanced CKD, especially those with elevated serum potassium concentration (S[K]).[56]

Antihypertensive Drug Therapy in CKD

Selection of antihypertensive medications for CKD patients should take into account the presence of proteinuria, comorbid conditions, individual patient characteristics, and side-effect profile. Each specific class of antihypertensive medication has advantages and disadvantages, as well as indications and contraindications.

RAAS Blockers

RAAS blockers including angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARB) are recommended as first-line therapy for treatment of hypertension in patients with

proteinuric CKD.[32] These agents are effective in reducing proteinuria and slowing progression of CKD by improving glomerular hemodynamics, restoring the altered glomerular barrier function, and limiting the nonhemodynamic effects of angiotensin II and aldosterone, such as fibrosis and vascular endothelial dysfunction. These protective effects are, at least in part, independent of the reduction in systemic BP.[57] In patients with nondiabetic kidney disease, there is good evidence that treatment with ACEI results in slower decline in GFR, and this risk reduction is more pronounced in patients with higher degrees of proteinuria.[58] In patients with type 1 diabetes, treatment with captopril in those with overt proteinuria was associated with a 50% decrease in the risk of the combined endpoint of death, dialysis, or renal transplantation.[59] Patients with moderately increased albuminuria and treated with an ACEI also had reduced incidence of progression to overt proteinuria.[60] In type 2 diabetes, treatment with an ARB in patients with overt nephropathy was associated with a significant 20% and 16% decrease in risk, respectively, of the combined endpoint of death, ESRD, or doubling of serum creatinine concentration (S[Cr]).[61] Side effects of ACEI and ARB include cough (more with ACEI), angioedema (more with ACEI), and development of hyperkalemia. ACEI or ARB therapy can cause a modest rise in S[Cr] due to reduction in intraglomerular pressure. An elevation in S[Cr] up to 30% that stabilizes in the first 2 months is not necessarily a reason to discontinue therapy. Continued rise in S[Cr] should prompt evaluation for excessive fall in BP (especially with volume depletion due to concomitant diuretic use) and/or possible bilateral renal artery stenosis. There is no level of GFR or S[Cr] at which ACEI or ARB is absolutely contraindicated. This decision should be made on an individual basis. Risks for hyperkalemia should always be kept in mind at lower GFR levels. It would be prudent to check S[Cr] and S[K] within the first week or two after initiation or intensification of RAAS inhibition in CKD patients. RAAS blockers are contraindicated in pregnancy due to known teratogenic effects.

Aliskiren is a direct renin inhibitor that prevents conversion of angiotensinogen to angiotensin I. There are limited data to support the use of aliskiren in patients with CKD. Combination therapy with ACEI, ARB, or direct renin inhibitors is not recommended. Studies demonstrated worse renal outcomes, hypertension, and hyperkalemia with use of dual RAAS blockade.[62,63]

Diuretics

Because patients with CKD are particularly sensitive to sodium and water retention, diuretics are an integral component of management of hypertension. Diuretics may also help to reduce the risk of hyperkalemia in CKD patients treated with an ACEI or ARB. Many patients with CKD have resistant hypertension, and diuretics are important in this setting to achieve BP control. Thiazide diuretics also likely decrease peripheral vascular resistance and contribute to long-term benefit in BP control, in addition to acute benefits in volume expansion.

Thiazide-type diuretics include hydrochlorothiazide, chlorthalidone, indapamide, and metolazone. Chlorthalidone is more potent and has a longer duration of action compared to hydrochlorothiazide.[64] Chlorthalidone may be associated with a higher risk of developing hyponatremia and hypokalemia, particularly in the elderly.[65] Thiazide diuretics are generally considered to be ineffective when estimated GFR is less than 30 mL/min/1.73 m^2, due to decreased filtered sodium load reaching the distal tubule. Loop diuretics are preferred in this setting. However, some studies indicate that chlorthalidone is effective in lowering BP even in patients with low GFR.[66] Metolazone remains effective in patients with renal dysfunction, but due to unpredictable bioavailability, it is generally used for short durations of treatment, in combination with loop diuretics. Short-acting loop diuretics (such as furosemide) should be dosed at least twice daily to be effective. Patients with CKD may require higher doses of diuretics due to decreased secretion of diuretics by renal tubules in the setting of impaired renal function. Electrolytes should be monitored while patients are on diuretic therapy. Diuretics should be used cautiously in patients with a history of acute gout, unless already on uric acid-lowering therapy.

Mineralocorticoid Antagonists

There is now strong evidence supporting the use of spironolactone as add-on therapy in patients with resistant hypertension.[67] In patients with CKD, studies have shown enhanced antiproteinuric effects of an ACEI or ARB when combined with mineralocorticoid antagonists.[68] This added benefit is likely due to the impact on aldosterone escape (non−ACE-mediated activation of angiotensin II and production of aldosterone) and attenuation of aldosterone-mediated renal fibrosis. Combination therapy entails the risk of hyperkalemia and therefore should be used with caution in patients with significant renal dysfunction, with close monitoring of renal function and S[K]. Side effects specific to spironolactone include gynecomastia and breast tenderness due to estrogen-like effects, which are not seen with eplerenone.

Calcium Channel Blockers

Calcium channel blockers include dihydropyridines (such as amlodipine, nifedipine) and nondihydropyridines (such as verapamil and diltiazem).

Dihydropyridines act on vascular smooth muscle causing vasodilation. They also have a preferential effect on afferent glomerular arteriolar vasodilation, which can result in increased albuminuria when used as monotherapy.[69] Nondihydropyridines act on the myocardium, with negative chronotropic and inotropic effects. They have a vasodilatory effect on both afferent and efferent glomerular arterioles, resulting in decreased albuminuria. Although both classes of calcium channel blockers can lower BP, nondihydropyridines may be preferable in patients with albuminuria, especially when there is a contraindication to use of an ACEI or ARB. Although combination therapy with dihydropyridine and nondihydropyridine calcium channel blockers has been proposed due to differential mechanisms of action, this has not been studied in CKD patients.

Pedal edema may be a limiting factor to use of dihydropyridine calcium channel blockers due to arteriolar dilation and redistribution of fluid from the vascular space into the interstitium. The risk of edema is dose-dependent. Diuretic therapy may not be beneficial for calcium channel blocker-induced edema because it is not plasma volume mediated. The addition of an ACEI or ARB, on the other hand, may reduce the severity of edema.[70] Nondihydropyridines may increase the risk of atrioventricular block or bradycardia and should not be combined with beta blocker therapy.

Beta Blockers

Beta blockers are not recommended as first-line therapy for hypertension management in the absence of specific indications. They are useful in the setting of cardiac comorbidities including ischemic heart disease, congestive heart failure, and tachyarrhythmias. Extended release metoprolol and vasodilating beta blockers such as carvedilol have been shown to have mortality benefits in patients with congestive heart failure.[71] Abrupt cessation of beta blockers should be avoided, and concomitant use with nondihydropyridine calcium channel blockers is not recommended due to the risk of bradycardia and heart block.

Alpha Blockers

Alpha-1 blockers act by peripheral vasodilation and may be particularly useful in men with symptomatic benign prostatic hyperplasia. Therapy with the alpha-1 blocker doxazosin was associated with increased risk of cardiovascular events (especially congestive heart failure), compared to therapy with chlorthalidone.[72] Therefore, alpha-1 blockers are not recommended as first-line therapy for hypertension in CKD patients. Adverse effects include postural hypotension and risk of falls, particularly in the elderly.

Centrally Acting Alpha Agonists

Centrally acting alpha agonists include clonidine, methyldopa, and guanfacine. Centrally acting alpha agonists act by decreasing central sympathetic outflow, resulting in vasodilation. Centrally acting alpha agonists are generally used as adjunctive therapy in CKD patients with resistant hypertension who are already treated with multiple medications. Methyldopa has a long record of safety in pregnancy and is therefore widely used in this setting. Abrupt discontinuation of clonidine should be avoided because of the risk of rebound hypertension.

Vasodilators

Vasodilators, such as hydralazine and minoxidil, have direct vasodilatory effects on vascular smooth muscle, resulting in BP reduction. These agents are often third- or fourth-line agents after other medications have resulted in inadequate BP control or have intolerable side effects. Hydralazine has a short duration of action and frequent dosing is needed. Use of hydralazine is also associated with a drug-induced lupus-like syndrome in some patients treated with higher doses. Minoxidil is associated with pericardial effusion and severe volume expansion. Minoxidil should ideally be used with a high dose of a loop diuretic.

Choice of Drug Therapy and Combination Antihypertensive Drug Therapy in CKD

In proteinuric CKD, an ACEI or an ARB should be used as first-line therapy to lower BP and slow rate of progression of CKD.[32] The antihypertensive effect of an RAAS blocker may be enhanced by diuretic use. As a next step, a nondihydropyridine calcium channel blocker can be added for additional reduction in proteinuria. In patients with proteinuric CKD without overt edema, a diuretic or a nondihydropyridine calcium channel blocker can be considered as second-line therapy.

In patients with nonproteinuric CKD, there is no strong evidence that RAAS blockers are more beneficial than other agents. Any of the first-line agents for the treatment of hypertension can be used.[32] Diuretics remain useful as a part of combination therapy.

RESISTANT HYPERTENSION

Resistant hypertension is defined as BP that is not at goal despite the use of at least three antihypertensive medication classes, preferably including a diuretic, or BP that is at goal but requires prescription of four or

more medications.[73] The prevalence of apparent treatment resistant hypertension has been estimated to be as high as 40% in patients with CKD.[74] Patients with resistant hypertension are at higher risk for decline in kidney function (28% increased risk for decline in GFR and ESRD) and developing cardiovascular events (38% increased risk of composite of myocardial infarction, stroke, peripheral arterial disease, congestive heart failure, and all-cause mortality) compared with those without treatment-resistant hypertension.[74]

A careful and systematic evaluation of patients can result in identification of barriers to BP control and aid in the crafting of an optimal antihypertensive medication regimen in a given patient.[73] This starts with excluding factors that cause "pseudo-resistance," by obtaining standardized measurement of BP as described above and measuring out-of-office BP readings to exclude a "white-coat" effect. Assessment of the patient's adherence to the therapeutic regimen is very important. Some studies have indicated medication nonadherence rates as high as 50%.[75] Patients with CKD have complex medication regimens that may predispose them to more side effects. A high pill burden increases the possibility of nonadherence. It is also important to identify use of any pharmacologic agents that may increase BP, such as erythropoietin or cyclosporine, and reinforce lifestyle factors including dietary sodium reduction, moderation in alcohol use, engagement in regular physical activity, and weight management. An evaluation for causes of secondary hypertension may be needed if indicated by clinical features or initial laboratory assessments.

Several pharmacologic principles should be considered in the management of the patient with resistant hypertension. Dosing regimens should be optimized to maintain antihypertensive efficacy. Agents with complementary mechanisms of action should be used in combination to obtain maximum BP reduction. It is particularly important to choose the appropriate diuretic. In general, patients with preserved kidney function (GFR >30 mL/min) respond better to thiazide diuretics. Loop diuretics are preferred in patients with more advanced CKD (GFR <30 mL/min). The use of mineralocorticoid antagonists such as spironolactone is now standard as the fourth-line agent in patients with resistant hypertension. However, special considerations in CKD patients include the risk of hyperkalemia especially if used in combination with an ACEI or ARB. Ultimately, patient characteristics will determine the best combination of antihypertensive drug therapy. Consultation with a hypertension specialist may be considered in patients with true refractory hypertension.

Suboptimal control rates of hypertension and limited advances in pharmacologic options have increased interest in the use of device therapy as potential complementary or alternative treatment modalities for patients with hypertension. Experimental device therapies have included catheter-based renal denervation and baroreceptor-activation therapy.[76,77] Better understanding is needed regarding the safety, efficacy, and durability of their effects. This is especially true in CKD patients, as all large clinical trials studying device therapy have excluded patients with moderate to severe CKD and ESRD. Additionally, studies do not show a uniform BP lowering response with device therapy. Patient subgroups that are more likely to respond need to be identified, and practical clinical markers that can assess adequacy of the intervention are needed. None of the device therapies are currently approved for clinical use in the US. Appropriate evaluation of patients with resistant hypertension, with emphasis on lifestyle modifications and appropriate antihypertensive medication use, remain the cornerstone of management of these patients.

CONCLUSION

Hypertension is common in patients with CKD and contributes to the high risk of morbidity and mortality in this population. Many factors including abnormalities in salt and water balance, renin–angiotensin–aldosterone axis, and sympathetic nervous system contribute to hypertension in patients with CKD. A systematic and thorough approach is required to manage hypertension. This includes careful measurement of office BP, consideration of out-of-office BP measures, and reinforcement of nonpharmacologic interventions to lower BP. The target BP of less than 130/80 mm Hg can often be achieved and maintained with combination antihypertensive drug therapy, including RAAS inhibitors and diuretics. Importantly, good BP control can reduce risk of cardiovascular and progressive kidney disease in patients with CKD.

References

1. Taler SJ, Agarwal R, Bakris GL, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for management of blood pressure in CKD. *Am J Kidney Dis* 2013;**62**(2):201–13.
2. Muntner P, Anderson A, Charleston J, et al. Hypertension awareness, treatment, and control in adults with CKD: results from the chronic renal insufficiency cohort (CRIC) study. *Am J Kidney Dis* 2010;**55**(3):441–51.
3. Schneider MP, Hilgers KF, Schmid M, et al. Blood pressure control in chronic kidney disease: a cross-sectional analysis from the German Chronic Kidney Disease (GCKD) study. *PLoS One* 2018; **13**(8):e0202604.
4. Bonventre JV, Leaf A. Sodium homeostasis: steady states without a set point. *Kidney Int* 1982;**21**(6):880–3.
5. Ivy JR, Bailey MA. Pressure natriuresis and the renal control of arterial blood pressure. *J Physiol* 2014;**592**(18):3955–67.

6. Hall JE, Mizelle HL, Hildebrandt DA, Brands MW. Abnormal pressure natriuresis. A cause or a consequence of hypertension? *Hypertension* 1990;**15**(6 Pt 1):547–59.
7. Wadei HM, Textor SC. The role of the kidney in regulating arterial blood pressure. *Nat Rev Nephrol* 2012;**8**(10):602–9.
8. Koomans HA, Roos JC, Boer P, Geyskes GG, Mees EJ. Salt sensitivity of blood pressure in chronic renal failure. Evidence for renal control of body fluid distribution in man. *Hypertension* 1982;**4**(2): 190–7.
9. Koomans HA, Roos JC, Dorhout Mees EJ, Delawi IM. Sodium balance in renal failure. A comparison of patients with normal subjects under extremes of sodium intake. *Hypertension* 1985;**7**(5):714–21.
10. Guyton AC. The surprising kidney-fluid mechanism for pressure control–its infinite gain! *Hypertension* 1990;**16**(6):725–30.
11. O'Connor PM, Cowley Jr AW. Modulation of pressure-natriuresis by renal medullary reactive oxygen species and nitric oxide. *Curr Hypertens Rep* 2010;**12**(2):86–92.
12. Hall JE. The kidney, hypertension, and obesity. *Hypertension* 2003; **41**(3 Pt 2):625–33.
13. Granger JP, Alexander BT. Abnormal pressure-natriuresis in hypertension: role of nitric oxide. *Acta Physiol Scand* 2000;**168**(1): 161–8.
14. Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. *Pharmacol Rev* 2007;**59**(3): 251–87.
15. Nakano D, Kobori H, Burford JL, et al. Multiphoton imaging of the glomerular permeability of angiotensinogen. *J Am Soc Nephrol* 2012;**23**(11):1847–56.
16. Burns KD, Harris RC. Signaling and growth responses of LLC-PK1/Cl4 cells transfected with the rabbit AT1 ANG II receptor. *Am J Physiol* 1995;**268**(4 Pt 1):C925–935.
17. Siragy HM, Carey RM. Role of the intrarenal renin-angiotensin-aldosterone system in chronic kidney disease. *Am J Nephrol* 2010; **31**(6):541–50.
18. Casarini DE, Boim MA, Stella RC, Krieger-Azzolini MH, Krieger JE, Schor N. Angiotensin I-converting enzyme activity in tubular fluid along the rat nephron. *Am J Physiol* 1997;**272**(3 Pt 2): F405–409.
19. Hollenberg NK, Price DA, Fisher ND, et al. Glomerular hemodynamics and the renin-angiotensin system in patients with type 1 diabetes mellitus. *Kidney Int* 2003;**63**(1):172–8.
20. Ruiz-Ortega M, Gonzalez S, Seron D, et al. ACE inhibition reduces proteinuria, glomerular lesions and extracellular matrix production in a normotensive rat model of immune complex nephritis. *Kidney Int* 1995;**48**(6):1778–91.
21. Pimentel Jr JL, Montero A, Wang S, Yosipiv I, el-Dahr S, Martinez-Maldonado M. Sequential changes in renal expression of renin-angiotensin system genes in acute unilateral ureteral obstruction. *Kidney Int* 1995;**48**(4):1247–53.
22. Mazzali M, Kim YG, Suga S, et al. Hyperuricemia exacerbates chronic cyclosporine nephropathy. *Transplantation* 2001;**71**(7): 900–5.
23. Allred AJ, Chappell MC, Ferrario CM, Diz DI. Differential actions of renal ischemic injury on the intrarenal angiotensin system. *Am J Physiol Renal Physiol* 2000;**279**(4):F636–645.
24. Gabow PA, Chapman AB, Johnson AM, et al. Renal structure and hypertension in autosomal dominant polycystic kidney disease. *Kidney Int* 1990;**38**(6):1177–80.
25. Converse Jr RL, Jacobsen TN, Toto RD, et al. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992; **327**(27):1912–8.
26. Johansson M, Elam M, Rundqvist B, et al. Increased sympathetic nerve activity in renovascular hypertension. *Circulation* 1999; **99**(19):2537–42.
27. Klein IH, Ligtenberg G, Neumann J, Oey PL, Koomans HA, Blankestijn PJ. Sympathetic nerve activity is inappropriately increased in chronic renal disease. *J Am Soc Nephrol* 2003;**14**(12): 3239–44.
28. Matsukawa T, Gotoh E, Minamisawa K, et al. Effects of intravenous infusions of angiotensin II on muscle sympathetic nerve activity in humans. *Am J Physiol* 1991;**261**(3 Pt 2):R690–696.
29. Baylis C. Nitric oxide deficiency in chronic kidney disease. *Am J Physiol Renal Physiol* 2008;**294**(1):F1–9.
30. Aucella F, Maas R, Vigilante M, et al. Methylarginines and mortality in patients with end stage renal disease: a prospective cohort study. *Atherosclerosis* 2009;**207**(2):541–5.
31. Desir GV. Renalase deficiency in chronic kidney disease, and its contribution to hypertension and cardiovascular disease. *Curr Opin Nephrol Hypertens* 2008;**17**(2):181–5.
32. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;**71**(19): e127–248.
33. Drawz P. Clinical implications of different blood pressure measurement techniques. *Curr Hypertens Rep* 2017;**19**(7):54.
34. Wright Jr JT, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**(22):2103–16.
35. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005;**45**(1):142–61.
36. Siu AL, Force USPST. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2015;**163**(10):778–86.
37. McManus RJ, Mant J, Haque MS, et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. *J Am Med Assoc* 2014; **312**(8):799–808.
38. Tucker KL, Sheppard JP, Stevens R, et al. Self-monitoring of blood pressure in hypertension: a systematic review and individual patient data meta-analysis. *PLoS Med* 2017;**14**(9):e1002389.
39. Drawz PE, Abdalla M, Rahman M. Blood pressure measurement: clinic, home, ambulatory, and beyond. *Am J Kidney Dis* 2012; **60**(3):449–62.
40. Fagard RH, Celis H, Thijs L, et al. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension* 2008;**51**(1):55–61.
41. Hansen TW, Li Y, Boggia J, Thijs L, Richart T, Staessen JA. Predictive role of the nighttime blood pressure. *Hypertension* 2011;**57**(1): 3–10.
42. Roush GC, Fagard RH, Salles GF, et al. Prognostic impact from clinic, daytime, and night-time systolic blood pressure in nine cohorts of 13,844 patients with hypertension. *J Hypertens* 2014; **32**(12):2332–40. discussion 2340.
43. Asayama K, Thijs L, Li Y, et al. Setting thresholds to varying blood pressure monitoring intervals differentially affects risk estimates associated with white-coat and masked hypertension in the population. *Hypertension* 2014;**64**(5):935–42.
44. Stergiou GS, Asayama K, Thijs L, et al. Prognosis of white-coat and masked hypertension: international database of home blood pressure in relation to cardiovascular outcome. *Hypertension* 2014;**63**(4): 675–82.

45. Agarwal R, Light RP. GFR, proteinuria and circadian blood pressure. *Nephrol Dial Transplant* 2009;**24**(8):2400–6.
46. Drawz PE, Alper AB, Anderson AH, et al. Masked hypertension and elevated nighttime blood pressure in CKD: prevalence and association with target organ damage. *Clin J Am Soc Nephrol* 2016; **11**(4):642–52.
47. Minutolo R, Gabbai FB, Agarwal R, et al. Assessment of achieved clinic and ambulatory blood pressure recordings and outcomes during treatment in hypertensive patients with CKD: a multicenter prospective cohort study. *Am J Kidney Dis* 2014;**64**(5):744–52.
48. Peralta CA, Norris KC, Li S, et al. Blood pressure components and end-stage renal disease in persons with chronic kidney disease: the Kidney Early Evaluation Program (KEEP). *Arch Intern Med* 2012; **172**(1):41–7.
49. Cheung AK, Rahman M, Reboussin DM, et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol* 2017;**28**(9):2812–23.
50. Appel LJ, Wright Jr JT, Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *N Engl J Med* 2010;**363**(10):918–29.
51. Sarnak MJ, Greene T, Wang X, et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. *Ann Intern Med* 2005;**142**(5):342–51.
52. Chapter 2: lifestyle and pharmacological treatments for lowering blood pressure in CKD ND patients. *Kidney Int Suppl* 2012;**2**(5): 347–56.
53. Navaneethan SD, Yehnert H, Moustarah F, Schreiber MJ, Schauer PR, Beddhu S. Weight loss interventions in chronic kidney disease: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2009;**4**(10):1565–74.
54. Vogt L, Waanders F, Boomsma F, de Zeeuw D, Navis G. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. *J Am Soc Nephrol* 2008;**19**(5):999–1007.
55. Slagman MC, Waanders F, Hemmelder MH, et al. Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. *BMJ* 2011;**343**:d4366.
56. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. DASH-sodium collaborative research group. *N Engl J Med* 2001;**344**(1):3–10.
57. Atkins RC, Briganti EM, Lewis JB, et al. Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. *Am J Kidney Dis* 2005;**45**(2):281–7.
58. Agodoa LY, Appel L, Bakris GL, et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *J Am Med Assoc* 2001;**285**(21):2719–28.
59. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993;**329**(20): 1456–62.
60. Viberti G, Mogensen CE, Groop LC, Pauls JF. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. *J Am Med Assoc* 1994; **271**(4):275–9.
61. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;**345**(12):861–9.
62. Investigators O, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;**358**(15):1547–59.
63. Fried LF, Emanuele N, Zhang JH. Combined angiotensin inhibition in diabetic nephropathy. *N Engl J Med* 2014;**370**(8):779.
64. Ernst ME, Carter BL, Goerdt CJ, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension* 2006;**47**(3):352–8.
65. Dhalla IA, Gomes T, Yao Z, et al. Chlorthalidone versus hydrochlorothiazide for the treatment of hypertension in older adults: a population-based cohort study. *Ann Intern Med* 2013;**158**(6): 447–55.
66. Agarwal R, Sinha AD, Pappas MK, Ammous F. Chlorthalidone for poorly controlled hypertension in chronic kidney disease: an interventional pilot study. *Am J Nephrol* 2014;**39**(2):171–82.
67. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 2015;**386**(10008): 2059–68.
68. Bomback AS, Kshirsagar AV, Amamoo MA, Klemmer PJ. Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. *Am J Kidney Dis* 2008;**51**(2):199–211.
69. Bakris GL, Weir MR, Secic M, Campbell B, Weis-McNulty A. Differential effects of calcium antagonist subclasses on markers of nephropathy progression. *Kidney Int* 2004;**65**(6):1991–2002.
70. Makani H, Bangalore S, Romero J, Wever-Pinzon O, Messerli FH. Effect of renin-angiotensin system blockade on calcium channel blocker-associated peripheral edema. *Am J Med* 2011;**124**(2): 128–35.
71. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002;**106**(17):2194–9.
72. Diuretic versus alpha-blocker as first-step antihypertensive therapy: final results from the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *Hypertension* 2003;**42**(3):239–46.
73. Carey RM, Calhoun DA, Bakris GL, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American heart association. *Hypertension* 2018;**72**(5): e53–90.
74. Thomas G, Xie D, Chen HY, et al. Prevalence and prognostic significance of apparent treatment resistant hypertension in chronic kidney disease: report from the chronic renal insufficiency cohort study. *Hypertension* 2016;**67**(2):387–96.
75. Strauch B, Petrak O, Zelinka T, et al. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. *J Hypertens* 2013; **31**(12):2455–61.
76. Symplicity HTNI, Esler MD, Krum H, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010;**376**(9756):1903–9.
77. van Kleef M, Bates MC, Spiering W. Endovascular baroreflex amplification for resistant hypertension. *Curr Hypertens Rep* 2018; **20**(5):46.

QUESTIONS AND ANSWERS

Question 1

A 74-year-old woman presents to hypertension clinic. She is a retired physician and is concerned about her risk for cardiovascular disease. She asks which type of BP measurement is best for assessing hypertension-related cardiovascular risk. You recommend:

A. Clinic BP
B. Home BP
C. Ambulatory BP
D. Kiosk BP at pharmacies

Answer: C

Ambulatory BP has the advantage of estimating 24-hour BP, nighttime BP, and the relative decrease in BP from day to night, which is referred to as dipping status. Nighttime BP is of particular interest. Compared to daytime BP, nighttime BP is more strongly associated with all-cause mortality, cardiovascular mortality, and cardiovascular events (C is correct). Although clinic BP has been used to assess eligibility for nearly all randomized controlled trials in hypertension and as the target BP in treat to target studies, ambulatory BP is more strongly associated with adverse outcomes than clinic BP (A is incorrect). Home BP allows for identification of white-coat and masked hypertension but does not assess nighttime BP (B is incorrect). Most kiosk BP monitors are not well validated (D is incorrect).

Question 2

A 62-year-old woman with CKD stage 4 from diabetic nephropathy presents to clinic for follow-up. She reports an increase in dietary sodium intake in recent weeks. An average of her recent home BP measurements is 154/92 mm Hg. Her current medications include furosemide 40 mg daily and lisinopril 20 mg daily. Her examination is notable for an elevated jugular venous pressure at 10 cm, crackles at her lung bases bilaterally, and 2+ edema of her lower extremities. Which of the following statement is most correct about hypertension in CKD?

A. Net sodium intake is always greater then net sodium excretion in CKD
B. Pressure natriuresis response does not change in CKD
C. Upregulation of the renin−angiotensin−aldosterone system and the sympathetic nervous system commonly impair sodium excretion in CKD
D. Low plasma renin activity and high serum aldosterone is a typical finding in CKD patients with hypertension

Answer: C

Impaired sodium excretion due to the upregulation of the renin−angiotensin−aldosterone system and the sympathetic nervous system is a common mechanism underlying hypertension in CKD (Answer C is correct). Typically the severity of these abnormalities associates with the severity of CKD. Despite this, sodium homeostasis is still maintained (at the cost of elevated BP and volume overload) in CKD except for ESRD patients (Answer A is incorrect). Pressure natriuresis is defined by the relationship of BP and sodium excretion. Typically, the pressure natriuresis curve is shifted to the right in CKD, such that a higher BP is required to reach sodium homeostasis (Answer B is incorrect). Finally, low plasma renin activity, and high serum aldosterone is typical of primary hyperaldosteronism, but this is not a typical finding in CKD (Answer D is incorrect).

Question 3

A 45-year-old man is seen for routine follow-up. He has a history of dyslipidemia and takes atorvastatin once daily. He is otherwise well. On physical examination his BP is 138/78 mm Hg and pulse is 74 bpm. He has a regular rhythm without murmurs, gallops, or rubs; no bruits; and peripheral pulses are equal. You instruct him on lifestyle modifications including exercise and a low-salt diet. Three months later, he returns and his BP is 136/76 mm Hg. According to the 2017 American College of Cardiology/American Heart Association guidelines, the next step in the diagnosis and management of this patient's elevated BP is

A. Initiate antihypertensive therapy with chlorthalidone 12.5 mg once daily
B. Initiate antihypertensive therapy with carvedilol 6.25 mg twice daily
C. Obtain out-of-office BP and initiate treatment if daytime ambulatory or home BP is $\geq$130/80 mm Hg
D. Make a diagnosis of elevated BP

Answer: C

This patient presents with elevated BP on two occasions separated by 3 months. The ACC/AHA guidelines recommend confirming elevated clinic BP with out-of-office measurements (correct Answer C) prior to initiating antihypertensive therapy (A and B are incorrect). The recommendation for out-of-office BPs is based on observational evidence of low risk for adverse outcomes with white-coat hypertension (elevated clinic BP with normal ambulatory/home BP). Similarly, the guidelines recommend out-of-office BP measurement in patients with elevated office BP (120−129/<80 mm Hg) to screen for masked hypertension (normal clinic BP with elevated ambulatory/home BP). The ACC/AHA guidelines define elevated BP as a systolic BP of

120−129 mm Hg and a diastolic BP <80 mm Hg (D is incorrect).

Question 4

A 50-year-old man with a past medical history of CKD stage 3 presents because he was found to have elevated BP readings on a routine physical examination a month ago and on subsequent home readings. His BP today in the office is 148/93 mm Hg. A complete physical examination is otherwise unremarkable. Renal function panel obtained today reveals S[Cr] 1.4 mg/dL (stable over the last 2 years). Urinalysis indicates proteinuria. You recommend the following:

A. Repeat the BP measurement in a week to confirm the diagnosis of hypertension
B. Start carvedilol
C. Start chlorthalidone
D. Start lisinopril
E. Start clonidine

Answer: D

This patient's diagnosis of HTN is already established based on more than one office visit and out-of-office readings. He does not need further measurement for confirmation (Answer A is incorrect). Per 2017 ACC/AHA guideline recommendations, in patients with proteinuric CKD, treatment with ACEI or ARB is recommended to improve renal outcomes (Answer D is correct; Answer C is incorrect). Beta blockers are no longer considered first-line antihypertensive in the absence of heart failure or coronary artery disease (Answer B is incorrect). Clonidine is not a first-line agent for hypertension management (Answer E is incorrect).

Question 5

A 65-year-old man is referred for further management of hypertension. He was just diagnosed with stage 1 hypertension and started on hydrochlorothiazide 25 mg daily with excellent BP control. His examination today is unremarkable. His BP is 129/79 mm Hg. His renal function panel shows a S[Cr] 1.0 mg/dL, Na of 138 mEq/L, and K of 4 mEq/L. He has done extensive reading about hydrochlorothiazide vs. chlorthalidone. He asks you about your recommendations. When comparing hydrochlorothiazide and chlorthalidone, which one of the following is correct?

A. Hydrochlorothiazide has a longer duration of action
B. Chlorthalidone may be associated with a higher risk of hyponatremia and hypokalemia in the elderly
C. Hydrochlorothiazide has been associated with a mortality benefit
D. Hydrochlorothiazide is a more potent BP medication
E. Chlorthalidone was not used in large hypertension studies

Answer: B

Chlorthalidone is more potent and has a longer duration of action compared to hydrochlorothiazide, including lowering nighttime BP (Answer A and D are incorrect). Mortality benefits and reduced cardiovascular morbidity have also been reported with use of chlorthalidone compared to hydrochlorothiazide (Answer C is incorrect). One study showed an increased risk of hospitalization for hyponatremia and hypokalemia with the use of chlorthalidone in the elderly (Answer B is correct). Chlorthalidone has been used in large hypertension trials, including the SPRINT trial, where the preferred thiazide diuretic was chlorthalidone (Answer E is incorrect).

Question 6

A 75-year-old man with hypertension and stage 3 CKD who is in good overall health is seen in your office. He has recently read online that new guidelines recommend lower BP goals (<130/80 mm Hg) compared to previous guidelines (<140/90 mm Hg). He asks about your opinion regarding more intensive compared to "usual" BP control targets.

Which of the following is NOT true about intensive compared to standard BP treatment goals?

A. Intensive treatment BP goals are associated with lower risk of heart disease and mortality in older patients
B. Intensive treatment BP goals will likely require use of more antihypertensive medications than standard goals
C. Intensive treatment BP goals will reduce the risk of progression of kidney disease in all patients with CKD
D. Intensive treatment goals of BP may be associated with more side effects

Answer: C

The SPRINT study rigorously compared a standard BP goal (<140 mm Hg systolic) with an intensive treatment goal (<120 mm Hg). Participants assigned to the intensive treatment goal had lower risk of cardiovascular outcomes and mortality (Option A is correct). Intensive BP therapy was associated with more use of antihypertensive drug therapy and higher risk of some side effects (Options B and D are correct). However, there was no difference in risk of progression of kidney disease between the two groups. This is consistent with other studies that do not show a benefit of intensive BP control in CKD patients without proteinuria (Option C is incorrect).

CHAPTER

62

Management of Mineral and Bone Disorders in Chronic Kidney Disease

Kristen L. Nowak, Michel Chonchol

Division of Renal Diseases and Hypertension, University of Colorado Denver Anschutz Medical Campus, Aurora, CO, United States

Abstract

The pathophysiology of chronic kidney disease—mineral and bone disorder (CKD-MBD), a common clinical syndrome in patients with CKD with consequences affecting mineral metabolism, bone mineralization, and extracellular calcification, is complex. Diagnosis and management of CKD-MBD requires particular attention to the biochemical/hormonal factors affecting calcium, phosphorus, vitamin D, parathyroid hormone, and fibroblast growth factor-23 metabolism, as well as consideration of bone and vascular calcification. Nephrologists, patients, and the public need future well-designed randomized trials to further guide the diagnosis and management of CKD-MBD.

SCOPE OF THE PROBLEM AND PUBLIC HEALTH IMPLICATIONS

With declining kidney function, mineral homeostasis becomes progressively dysregulated, including alterations in serum concentrations of calcium, phosphate, intact parathyroid hormone (iPTH), and fibroblast growth factor-23 (FGF-23).[1] These biochemical abnormalities are tightly associated with cardiovascular mineralization and paradoxical skeletal demineralization (Figure 62.1).[2] In 2005, Kidney Disease: Improving Global Outcomes (KDIGO), an international organization with the mission of developing clinical practice guidelines in CKD, formally classified this clinical syndrome as chronic kidney disease—mineral and bone disorder (CKD-MBD).[3] This terminology replaced "renal osteodystrophy" to better describe the broader consequences of CKD complications on mineral metabolism, the bones, and the cardiovascular system.[1] The term renal osteodystrophy is now restricted specifically to the alterations in bone morphology or pathology that can result from complications of CKD, as CKD-MBD better reflects the systemic consequences of kidney disease, beyond bone alone.[1]

CKD-MBD is a common complication in CKD, occurs early in the disease, and both persists and progresses across all stages of CKD.[1] The interactions between abnormal mineral metabolism, extraskeletal calcification, and skeletal demineralization may increase morbidity and mortality in patients with CKD.[4] Thus, management of CKD-MBD may influence important clinical outcomes in this patient population. However, much is still unknown, and there is an overall lack of large randomized controlled trials (RCTs) providing direction for clinical practice. The major basis of the recommendations in this chapter are the KDIGO CKD-MBD guidelines originally released in 2009,[1] with select updates included in the 2013 KDIGO guideline on the Evaluation and Management of Chronic Kidney Disease[4] and the 2017 CKD-MBD guidelines update.[5] The recommendations of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI), released in 2010[6] and 2017[7] to adapt the 2009 and 2017 KDIGO guidelines for use in the US, are consistent with the KDIGO guidelines, except where noted.

PATHOPHYSIOLOGY

Biochemical and hormonal abnormalities affect calcium, phosphate, vitamin D, iPTH and FGF-23 metabolism and handling, and bone and vascular calcification alterations occur in patients with CKD-MBD.

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00062-0

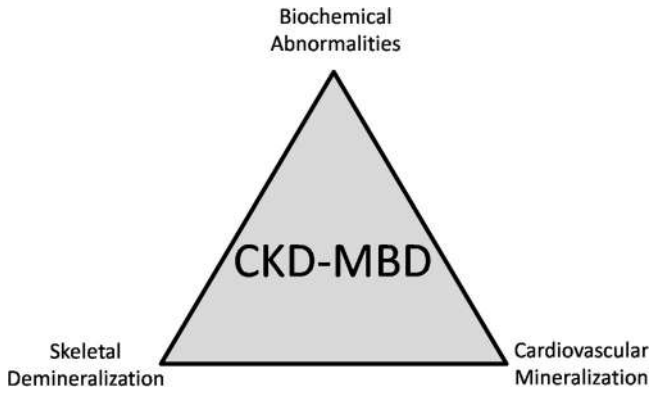


FIGURE 62.1 Components of chronic kidney disease—mineral and bone disorder (CKD-MBD). The clinical syndrome CKD-MBD was formally classified by Kidney Disease: Improving Global Outcomes in 2005 to reflect the adverse consequences of CKD complications on mineral metabolism, skeletal demineralization, and paradoxical extraskeletal cardiovascular mineralization.

Calcium

CKD is characterized by moderate hypocalcemia, although serum calcium concentration (S[Ca]) remains relatively stable in most patients with nondialysis-dependent CKD (Figure 62.2).[8,9] The mechanisms associated with the development of modest hypocalcemia in CKD patients are multifactorial but include decreased intestinal absorption and reduced 1,25 dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) levels (Figure 62.3).[10] An additional concern in patients with CKD, particularly those requiring dialysis, is increased S[Ca] resulting from pharmacological agents such as calcium-based phosphate binders. However, there are currently no data to support an increased risk of either fracture or mortality with increasing S[Ca] in patients with stage 3–5 CKD,[1] although observational studies suggest that hypercalcemia may increase the relative risk of mortality in dialysis-dependent CKD.[11–13] Based on meta-analysis in the general population, calcium supplements may increase the risk of cardiovascular events.[14] Although the applicability to patients with CKD is unclear, this is biologically plausible.

Phosphorus

In CKD stages 3–5, serum phosphate concentration (S[P]) remains normal until estimated glomerular filtration rate (eGFR) falls below 40 mL/min/1.73 m^2 and is still relatively stable until eGFR is <20 mL/min/1.73 m^2[9,15] (Figure 62.2). S[P] is maintained within the normal laboratory range until later stages of CKD mainly by FGF-23, which increases phosphate excretion to maintain normal S[P].[16] Increased S[P] is a stimulus for secondary hyperparathyroidism and a mediator of vascular calcification.[17]

Observational studies suggest that even in the normal range, increased S[P] is associated with increased risk of all-cause mortality in patients without CKD,[18,19] nondialysis-dependent CKD,[20,21] as well as consistently in patients treated with chronic dialysis.[21,22] However, the review of literature for the 2017 KDIGO guidelines update concluded that the majority of studies found this association to be consistent for S[P] above normal limits but not within the normal range. Additionally, correction of mildly elevated phosphate in the normal range with a phosphate binder in stage 3b and 4 CKD

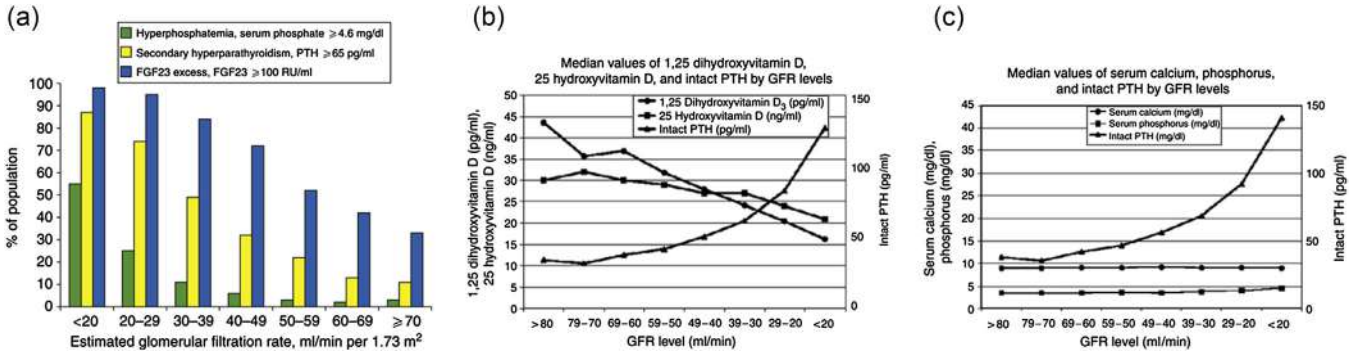


FIGURE 62.2 Alterations in biochemical and hormonal parameters with declining glomerular filtration rate (GFR) in chronic kidney disease (CKD). One of the earliest detectable changes in chronic kidney disease—mineral and bone disorder (CKD-MBD) is rising fibroblast growth factor-23 (FGF-23) levels, which increases when GFR is approximately 70 mL/min/1.73 m^2 and progressively rises further as estimated glomerular filtration rate continues to decline (Panel a, right bars. Left bars indicate hyperphosphatemia; middle bars indicate secondary hyperparathyroidism). Increasing FGF-23 contributes to a decline in calcitriol (1,25 dihydroxyvitamin D_3) levels by inhibiting 1α-hydroxylase activity and stimulating 24-hydroxylase, which is responsible for the degradation of calcitriol (Panel b). Intact parathyroid hormone (iPTH) also rises as GFR declines, although not significantly until GFR falls below 45 mL/min/1.73 m^2 (Panels b and c). In contrast, S[Ca] remains relatively stable in most patients with nondialysis-dependent CKD (Panel c). S[P] remains normal until GFR falls below 40 mL/min/1.73 m^2 and is still relatively stable until GFR is <20 mL/min/1.73 m^2 (Panels a and c). *Reprinted by permission from Macmillan Publishers Ltd: [Kidney International][6], copyright (2011) [Panel a] and Macmillan Publishers Ltd: [Kidney International][13], copyright (2007) [Panels b and c].*

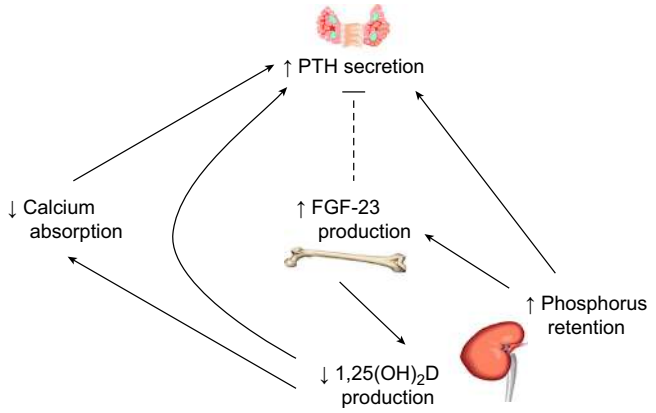


FIGURE 62.3 Biochemical and hormonal abnormalities in chronic kidney disease–mineral and bone disorder (CKD-MBD). In CKD-MBD, production of fibroblast growth factor-23 (FGF-23), the principal hormone regulating phosphorus, is elevated to counter a rise in S[P]. FGF-23 also inhibits synthesis of 1,25 dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), by decreasing renal 1α-hydroxyase expression and increasing 24-hydroxylase expression. FGF-23 also initially suppresses parathyroid hormone (PTH) release and secretion, although the parathyroid glands may become resistant and the relationship may change with advancing kidney disease. PTH release and secretion also increase in response to hypocalcemia, hyperphosphatemia, and/or decreased $1,25(OH)_2D_3$. Both decreased intestinal absorption of calcium and reduced $1,25(OH)_2D_3$ levels contribute to the development of modest hypocalcemia.

resulted in minimal decline in S[P] and increased coronary calcification score.[23]

Vitamin D

25-Hydroxyvitamin D ($25(OH)D_3$; calcidiol) is considered the best measure of vitamin D nutritional status because of its long half-life in the circulation of approximately 3 weeks. $25(OH)D_3$ is converted in the kidney by 1α-hydroxylase to $1,25(OH)_2D_3$ (calcitriol), the active form of vitamin D, although extrarenal conversion can also occur.[1] $1,25(OH)_2D_3$ is an important regulator of mineral homeostasis and musculoskeletal function, in addition to having pleiotropic extracellular effects.

Most patients with CKD have low levels of $1,25(OH)_2D_3$.[22,24] This decline occurs early in the disease, and the severity increases as CKD progresses[8,25] (Figure 62.2). Classic teaching was that the decline in $1,25(OH)_2D_3$ was the result of loss of nephron mass. It is now known that increased serum FGF-23 in the early stages of kidney disease is also an important contributor, by inhibiting 1α-hydroxylase activity and stimulating 24-hydroxylase, which is responsible for the degradation of $1,25(OH)_2D_3$[26] (Figure 62.3).

Several observational studies have shown inverse associations between vitamin D metabolites and adverse outcomes in patients with CKD, as well as in the general population. Low serum $25(OH)D_3$ level is independently associated with all-cause mortality in both nondialysis and dialysis-dependent CKD patients[27,28] and in the general population.[15,29,30] $1,25(OH)_2D_3$ levels are also inversely associated with mortality in nondialysis-dependent CKD patients. Low serum $25(OH)D_3$ and/or $1,25(OH)_2D_3$ are also independently associated with cardiovascular events and mortality in individuals with[4] and without CKD.[15,30,31] In addition, both $1,25(OH)_2D_3$[32] and $25(OH)D_3$[29] levels are inversely associated with kidney disease progression. Low $25(OH)D_3$ levels are associated with increased risk of coronary artery disease progression in the general population.[33]

Parathyroid Hormone

Under physiological circumstances, parathyroid hormone (PTH) maintains S[Ca], increases phosphate excretion, and stimulates production of $1,25(OH)_2D_3$. Production increases in response to hypocalcemia, hyperphosphatemia, and/or decreased $1,25(OH)_2D_3$ (Figure 62.3).[1] FGF-23 can also suppress PTH, although the parathyroid glands may become resistant and the relationship may change with advancing kidney disease.[26,34]

iPTH rises as GFR declines, although not in a significant way until eGFR falls below 45 mL/min/1.73 m^2 (Figure 62.2).[8] This is initially an adaptive response to maintain calcium, phosphorus, and $1,25(OH)_2D_3$ homeostasis.[1] Decreased S[Ca] was once thought to be central in the development of secondary hyperparathyroidism. It is now accepted that FGF-23 is a key player in this process, initially inhibiting PTH, although this is compromised as CKD progresses.[16]

Most observational evidence on the relationship between PTH and clinical outcomes was generated from chronic HD patients. When iPTH is elevated beyond an inflection point ranging from 480 to 600 pg/mL,[12,35,36] there is an increased mortality risk, but this finding is not consistent and the relationship may be U-shaped, inverse, or nonsignificant.[37–39] Increased iPTH may also be associated with risk of cardiovascular events in this population.[1] In general, iPTH fails to correlate with fracture risk, and the relationship of PTH levels with bone formation rates varies greatly.[1]

FGF-23

FGF-23 was first identified in 2000,[40] and the discovery has led to a reconsideration of the mechanisms driving secondary hyperparathyroidism.[16] FGF-23 is secreted by skeletal osteocytes in response to changes in bone formation and S[P] (Figure 62.3). However, the mechanisms underlying the direct regulation of

FGF-23 production are largely unknown.[41] FGF-23 is the principal-regulating hormone of phosphorus and also inhibits synthesis of $1,25(OH)_2D_3$ and suppresses PTH, at least initially.[26,34] These functions are accomplished by reducing the activity and/or expression of sodium phosphate cotransporters, possibly reducing intestinal phosphate absorption, decreasing renal 1α-hydroxylase expression, and increasing 24-hydroxylase expression.[26,34] FGF-23 acts by binding to receptors that are part of the tyrosine kinase superfamily[42] in the presence of the membrane-bound coreceptor klotho,[34] but animal studies support that FGF-23 can also act independently of klotho, at least in the heart.[43]

Increasing FGF-23 levels may be one of the earliest detectable changes in CKD-MBD. FGF-23 levels begin to increase when eGFR is approximately 70 mL/min/1.73 m^2 and progressively rise as eGFR declines further (Figure 62.2).[16,44] Small elevations in FGF-23 are initially required, as this increases renal phosphate excretion, thus maintaining S[P] within normal limits. With CKD progression, circulating FGF-23 levels continue to rise, the phosphaturic response declines, and eventually S[P] increases. It is presently unknown why FGF-23 rises early in CKD, before a rise in S[P].

In nondialysis-dependent CKD patients, FGF-23 levels are independently associated with mortality,[45,46] cardiovascular events,[45–47] CKD progression,[45,46,48] and infection-related hospitalization.[49] Very large hazard ratios support the contention that FGF-23 is a key outcome predictor. FGF-23 levels are also independently associated with left ventricular hypertrophy in nondialysis-dependent CKD patients,[43,50] chronic HD patients,[51] and in the general population.[52] Evidence in animals indicates that blocking FGF-23 can prevent the development of left ventricular hypertrophy.[43] One of the strongest working hypotheses regarding why FGF-23 predicts cardiovascular events and mortality is its causal effect on left ventricular hypertrophy.

Bone

Traditionally, renal osteodystophy has been characterized based on bone turnover and mineralization. In CKD-MBD, alterations in these parameters vary greatly. The spectrum of bone turnover ranges from abnormally low to very high, and mineralization may or may not be present.

A systematic review of bone biopsies in patients with CKD stages 3–5 showed 32% had osteitis fibrosa (increased turnover and normal mineralization), 18% adynamic (decreased turnover and acellularity), 16% were normal, 8% had osteomalacia (decreased turnover and abnormal mineralization), and 20% had mixed disease (increased turnover with abnormal mineralization).[1]

Alterations in bone are important, as this can lead to increased bone fragility and fracture. Hip fractures are two to three times more common in elderly patients with stage 3–4 CKD.[1] Although the risk in early stage CKD is unclear, chronic dialysis patients with adynamic bone disease and/or osteomalacia have an increased risk of fracture.[53,54] Dual-energy X-ray absorptiometry (DXA) bone mineral density (BMD) predicts risk of fracture across the spectrum in CKD.[55–58]

Vascular Calcification

Extraskeletal calcification of the vasculature increases progressively with declining eGFR and is more prevalent, severe, and accelerated in CKD compared to the general population.[17] Calcification can occur in both the intimal and medial layers of the vasculature, but medial calcification is considered the more common and major form of calcification in CKD.[59] Medial calcification is characterized by diffuse mineral deposition throughout the vascular tree[60] and is associated with increased large-elastic artery stiffness. This promotes increased systolic blood pressure, reduced diastolic blood pressure, increased cardiac afterload, compromised perfusion of the coronary arteries, and left ventricular remodeling.[61,62] Accordingly, vascular calcification is a major contributor to CVD in CKD patients. Observational data indicate vascular calcification predicts cardiovascular events and mortality.[17,59] However, it is presently unclear if intervening to slow progression of vascular calcification alters outcomes in CKD patients.[1]

DIAGNOSIS

The basis of these recommendations is primarily the KDIGO guidelines[1,4] (mentioning differences from KDOQI[6,7] when applicable). Traditionally, biochemical parameters have been the primary indicators for the basis of diagnosis, identifying therapeutic targets, and managing CKD-MBD. When considering biochemical values, it is recommended that all therapeutic decisions are based on serial circulating levels of calcium, phosphate, and PTH considered together, given the interdependence of these parameters and variations in levels due to food, drugs, diet, assays, and diurnal variation.[5]

Clinically significant biochemical manifestations of CKD-MBD may begin in stage 3 (a GFR of approximately 40–50 mL/min/1.73 m^2),[8] but the rate and degree of changes are highly variable. Therefore the frequency of assessment must consider the individual patient.[1]

KDIGO guidelines recommend measuring S[Ca], S[P], iPTH, and alkaline phosphatase (ALP), at least

once in all adults with an eGFR less than 45 mL/min/1.73 m^2, to establish a baseline.[4] At least one of these biochemical abnormalities must be present for the diagnosis of CKD-MBD.[1] Most observational data on these parameters were generated in HD populations. Much less is known about stage 3−5 CKD. This makes establishing diagnostic criteria as well as treatment recommendations challenging. Furthermore, there are no clear data available supporting the notion that routine measurement improves outcomes, but these are the best recommendations based on the currently available data.[1]

Calcium

KDIGO recommends monitoring S[Ca] beginning in stage 3 CKD. Although the frequency of monitoring should consider the individual patient, a reasonable monitoring schedule is every 6−12 months in stage 3, every 3−6 months in stage 4, and every 1−3 months in stage 5 (Table 62.1).[1] Ideally, ionized calcium should be used, as this is the physiologically active form. However, this is not a routinely available, practical, or cost-effective option, thus total calcium is most frequently measured.

Phosphorus

Recommendations for monitoring S[P] parallel those for S[Ca] (Table 62.1).[1] S[P] varies diurnally, although this variation is less in patients with CKD.[63]

Vitamin D

$25(OH)D_3$ is considered the best measure of vitamin D nutritional status, as it has a long half-life (approximately 3 weeks). $1,25(OH)_2D_3$ has a much shorter half-life (approximately 4−6 hours).[1] Epidemiological studies have found both $25(OH)D_3$ and $1,25(OH)_2D_3$ to be independent predictors of all-cause and cardiovascular mortality in both patients with CKD and in the general population.[27−30] Vitamin D status refers to whether or not circulating levels of $25(OH)D_3$ are considered adequate. Although there is no consensus on what are considered adequate levels, the 2013 update from KDIGO recommended using the international definition of <20 ng/mL as a cut-off for vitamin D deficiency.[4] Serum $25(OH)D_3$ levels are inversely associated with serum PTH levels in CKD[64] and non-CKD[65,66] patients, until $25(OH)D_3$ increases to 30−40 ng/mL, at which point PTH level plateaus at its nadir.[67] Such data provide the basis for the term vitamin D status, which refers generally to whether an individual has deficient, insufficient, or sufficient serum levels of $25(OH)D_3$. KDIGO recommends considering monitoring $25(OH)D_3$ in CKD stages 3−5, with repeat testing intervals commensurate with both baseline levels and current treatment (Table 62.1).[1] KDOQI also recommends periodic testing of $25(OH)D_3$ and initiating treatment if levels are low.[6] However, there is still some debate in the nephrology community regarding whether $25(OH)D_3$ levels should be measured and monitored, as there is a lack of evidence that vitamin D supplementation indeed improves clinical outcomes. The assays used to measure $25(OH)D_3$ are not well standardized. The DiaSorin assay is most commonly used in clinical practice.[1]

PTH

KDIGO recommends monitoring serum iPTH levels beginning in stage 3 and considering these levels and progression in determining repeat testing intervals. A reasonable monitoring schedule in stages 4 and 5 is every 6−12 and 3−6 months, respectively (Table 62.1). The optimal level of iPTH in stages 3−5 CKD is currently unknown, and difficult to establish, because the range of values widens as CKD progresses. In addition, there are methodological challenges to measurement associated with assay type, sample type, technique used, and variability. The second generation assay (iPTH) is most commonly used in clinical practice. There are also normally minute-to-minute oscillations in levels, although this is blunted in CKD. Thus, KDIGO does not provide a specific target recommendation, but instead recommends interpretation on the basis of the specifics of each individual laboratory. Therapy should be based on a persistent rise in levels, rather than an absolute value.[1]

FGF-23

FGF-23 is not currently considered in the diagnosis of CKD-MBD, as it is still a relatively new, but very important, component of CKD-MBD. Thus, FGF-23 is not discussed in the KDIGO or KDOQI guidelines, and FGF-23 is currently more commonly assessed in research. There are two enzyme-linked immunoassays used to measure FGF-23: the intact FGF-23 assay (primarily serum) and the C-terminal FGF-23 assay (primarily plasma). Initial studies showed a good correlation between the two, although this has been questioned.[68,69] Values for FGF-23 are skewed to the right; therefore, median levels are typically reported in research. Using the C-terminal assay, typical levels in healthy adults are 17.8−197.0 RU/mL (median 76.5 RU/mL) (Table 62.1).[70] In nondialysis-dependent CKD patients, the typical elevation is two- to fivefold higher (63.6−5592 RU/mL; median 188 RU/mL); in dialysis

TABLE 62.1 Biochemical Diagnosis of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)*

Parameter	Normal Range (Serum)	Physiological Triggers and Consequences	Changes in CKD	KDIGO Monitoring Recommendations
Calcium*	8.5–10.5 mg/dL#	Low $1,25(OH)_2D_3$, decreased intestinal absorption, and phosphate retention	Most often moderate hypocalcemia, although hypercalcemia can occur (rare)	Stage 3: every 6–12 months† Stage 4: every 3–6 months†
		Favors the development of SHP	Remains normal until eGFR <40 mL/min/1.73 m^2 and stays relatively stable until eGFR <20 mL/min/1.73 m^2	Stage 5: every 1–3 months†
Phosphorus*	2.5–4.5 mg/dL	Impaired phosphate excretion promotes a rise in S[P]	Remains normal until eGFR <40 mL/min/1.73 m^2 and stays relatively stable until eGFR <20 mL/min/1.73 m^2	Stage 3: every 6–12 months† Stage 4: every 3–6 months†
		Increased levels stimulate SHP, promote vascular calcification	Does not rise until later stages because FGF-23 initially maintains the normal range by increasing renal phosphate excretion	Stage 5: every 1–3 months†
Vitamin D*	Deficient = $25(OH)D_3$ <20 ng/mL	$1,25(OH)_2D_3$ synthesis in the kidney is compromised	Insufficiency and deficiency are highly prevalent, possibly approximately 50% of CKD patients	Baseline testing in stages 3–5, with repeat intervals commensurate with baseline levels and treatment
	Insufficient = 20–30 ng/mL	May be an underlying cause of elevated PTH		
	Sufficient >30 ng/mL			
PTH*	Abnormal if eGFR is <45 mL/min/1.73 m^2 and iPTH is persistently above upper limit of normal for the given assay and progressively rising	Increases in response to hypocalcemia, hyperphosphatemia, and/or decreased $1,25(OH)_2D_3$	Approximately 60% of patients with eGFR <60 mL/min/1.73 m^2 have elevated iPTH levels	Stage 3: based on baseline levels and CKD progression† Stage 4: every 6–12 months†
		Hypercalcemia, high $1,25(OH)_2D_3$ and FGF-23 can suppress		Stage 5: every 3–6 months†
FGF-23	In one small study: healthy adults: 17.8–197.0 RU/mL (median 76.5 RU/mL); Nondialysis-dependent CKD: 63.6–5592.0 RU/mL (median 188.0 RU/mL)	Secreted by skeletal osteocytes in response to changes in bone formation and S[P], principal regulating hormone of phosphorus	Increases very early in CKD (eGFR approximately 70 mL/min/1.73 m^2) and progressively increases as GFR declines	No recommendation given
	Maintenance HD: 150–115,000 RU/mL (median 4715.0 RU/mL)	High FGF-23 inhibits $1,25(OH)_2D_3$ and favors increased PTH		

All therapeutic decisions should be based on trends rather than a single laboratory value. *$1,25(OH)_2D_3$*, 1,25D dihydroxyvitamin D_3; *$25(OH)D_3$*, 25 hydroxyvitamin D_3; *eGFR*, estimated glomerular filtration rate; *FGF-23*, fibroblast growth factor-23; *iPTH*, intact parathyroid hormone; *S[P]*, serum phosphate concentration; *SHP*, secondary hyperparathyroidism.

* *To make a diagnosis of CKD-MBD, one of more of these laboratory abnormalities must be present.*

\# *May vary by laboratory.*

† *Frequency of monitoring should consider the presence and magnitude of abnormalities.*

patients, levels can reach an exponential 1000-fold increase (150−115,000 RU/mL; median 4175 RU/mL).[16,68,70] It is also important to consider the fractional excretion of phosphate in the interpretation of these values, as FGF-23 is the principal hormone-regulating phosphorus.

Bone

Bone biopsy−based histology is considered the gold standard technique for the diagnosis of the bone component of CKD-MBD, as it provides information regarding bone turnover, mineralization, and volume.[1] KDIGO asserts that bone biopsy is reasonable in stage 3−5 CKD if knowledge of type of renal osteodystrophy will impact treatment, but it is no longer required prior to antiresorptive therapy, based in increased experience with osteoporosis medications in CKD and growing evidence that they are effective at preventing fractures in stage 3−4 CKD.[71] DXA BMD testing is now recommended for stage 3−4 CKD with evidence of CKD-MBD and/or risk factors for osteoporosis if results will impact treatment decisions.[5] KDOQI agrees with this new recommendation, but stressed that BMD does not predict bone turnover type, which is an important determinant of pharmacological treatment and that there is a lack of data on osteoporosis medications and BMD and fracture in CKD.[7]

Vascular Calcification

Although extraskeletal calcification is a component of diagnosis of CKD-MBD, KDIGO does not recommend indiscriminate screening of all patients with CKD-MBD for vascular calcification, as it is unclear if intervention will alter outcomes.[1] KDOQI also does not recommend screening asymptomatic patients with CKD for calcification.[6] At this time, there is consensus among the nephrology community that screening for vascular calcification will increase the cost−benefit ratio, as there is a lack of potential therapeutic interventions to reverse vascular calcification. However, when vascular calcification is detected, the patient should be considered to have high cardiovascular risk.

TREATMENT

To date, the focus in the literature has been on the association between disordered mineral metabolism in CKD and adverse outcomes, including mortality, cardiovascular disease, and fractures. This has led to targeting these parameters in clinical practice to potentially improve these outcomes, but large RCTs supporting clinical practice are presently very limited.[1] Most of the available literature consists of observational data or surrogate outcomes, rather than therapeutic options associated with hard outcomes. In general, therapy has typically focused on correcting biochemical and hormonal abnormalities to limit their potentially adverse consequences. This section focuses largely on treatments targeting correction of biochemical and hormonal abnormalities.

Calcium

There is little observational or interventional evidence that targeting S[Ca] alters clinical outcomes in CKD, although calcium supplementation may increase risk of CVD in the general population.[72] KDIGO recommends avoiding hypercalcemia in stage 3−5 CKD patients,[5] based on evidence from the EVOLVE (Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events) study that mild hypocalcemia can be tolerated[73] (Table 62.2). KDOQI agrees with this recommendation, emphasizing that it allows for greater individualization of treatment strategies and use of calcimimetics to lower elevated PTH in the setting of mild hypocalcemia.[7] To avoid hypercalcemia, limiting the use of calcium-based binders, calcitriol, and/or its analogs in patients with known hypercalcemia is recommended.[5] Figure 62.4 provides an algorithmic approach to the treatment of hypercalcemia and other abnormalities of mineral metabolites in patients with CKD-MBD. An individualized approach should be used for correction of hypocalcemia, particularly for cases of severe or symptomatic hypocalcemia rather than recommending correction for all patients.[5]

Phosphorus

The data on normalizing S[P] in those patients with CKD not requiring chronic dialysis are conflicting.[23] Treatment should be aimed at lowering elevated phosphate levels in cases of overt hyperphosphatemia toward the normal range. Figure 62.4 provides a suggested approach to correcting S[P] abnormalities in nondialysis-dependent CKD patients.

Observational data suggest that phosphate binders of any type may reduce mortality in both dialysis-[74] and nondialysis-dependent CKD patients.[75] Most RCTs have been completed in chronic HD populations, with only one trial available in patients with stage 3−5 CKD.[76] The phosphate binder sevelamer slowed vascular calcification in this study, which is largely consistent with studies in dialysis patients,[22,77] although not all trials have been positive.[78,79] The efficacy of phosphate binders for reducing cardiovascular events or

TABLE 62.2 Treatment of Biochemical Abnormalities in Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)

Parameter	KDIGO/KDOQI Treatment Recommendations	Therapeutic Options
Calcium	Stage 3–5: avoid hypercalcemia	Limit calcium-based binders and/or 1,25(OH)$_2$D$_3$ or active vitamin D treatment if known hypercalcemia
Phosphorus	In stage 3–5 CKD, elevated S[P] should be lowered toward the normal range	Dietary phosphate restriction Phosphate binders
	Choice of binder should consider other components of CKD-MBD, other therapies, and side-effects In stage 3–5, lower elevated S[P] toward the normal range	• Aluminum hydroxide (not recommended) • Calcium carbonate and calcium acetate (restricted use) • Magnesium hydroxide and magnesium carbonate • Sevelamer hydrochloride and sevelamer carbonate • Lanthanum carbonate
Vitamin D	Only indicated to correct 25(OH)D$_3$ deficiency, follow recommendations for general population (1000–2000 IU/day cholecalciferol [D$_3$])	Nutritional vitamin D
	Recommend using 50,000 IU/week or per month ergocalciferol (D$_2$) to correct deficiency to >30 ng/mL	• Ergocalciferol (D$_2$) • Cholecalciferol (D$_3$)
PTH	Stages 3–5: optimal levels unknown	First evaluate for hyperphosphatemia, hypocalcemia, and vitamin D deficiency
	Suggest lowering PTH threshold in CKD stages 4–5 to prompt evaluation and possible treatment	Initial options • Limit dietary phosphate • Phosphate binders • Calcium supplements • Nutritional vitamin D (only if 25(OH)D$_3$ deficient)
		Calcitriol or vitamin D analogs should be reserved for stage 4–5 CKD with severe and progressive hyperparathyroidism
		Cinacalcet—not recommended by KDIGO in nondialysis CKD patients
		Severe HPT without response to other therapy: parathyroidectomy
FGF-23	Optimal levels unknown. KDIGO and KDOQI do not make recommendations	KDIGO does not make a recommendation
		Only therapeutic option at this time is dietary phosphate reduction
		Sevelamer and lanthanum carbonate may lower FGF-23

1,25(OH)$_2$D$_3$, 1,25D dihydroxyvitamin D; *25(OH)D$_3$*, 25 hydroxyvitamin D; *eGFR*, estimated glomerular filtration rate; *FGF-23*, fibroblast growth factor-23; *HPT*, hyperparathyroidism; *PTH*, parathyroid hormone; *S[Ca]*, serum calcium concentration; *S[P]*, serum phosphate concentration. See Figure 62.4 for an approach to treating biochemical abnormalities in patients with CKD-MBD.

mortality in nondialysis-dependent CKD is currently unknown. In dialysis patients, both an RCT[80] and secondary analysis of an open-label study[81] showed no difference in mortality based on allocation to sevelamer compared to calcium-based binders. A third study performed in incident HD patients found increased mortality in the calcium-based binder compared to the sevelamer group, although the KDIGO work group[1] raised a concern of a possibly unsuccessful randomization.[22] RCTs using phosphate binders with cardiovascular endpoints are also lacking in the chronic dialysis population. The effects of calcium-based binders compared to either sevelamer or lanthanum on bone histology are unclear, with some studies in chronic dialysis patients showing improvements and some showing worsening.[79,82,83]

Sevelamer and calcium-based binders appear to be equally effective at lowering S[P] in RCTs with stage 3–5 CKD patients.[76] However, it is suggested to restrict calcium-based phosphate binders in all hyperphosphatemic adult patients with stage 3–5 CKD.[5] Lanthanum also appears to be effective at lowering S[P] in chronic dialysis patients[84,85] and nondialysis-dependent CKD in the setting of elevated S[P].[86,87] New iron-based binders were also effective in phase 3 trials in chronic dialysis patients.[88–90]

The most recent KDIGO guidelines recommend lowering S[P] toward the normal range in stage 3–5

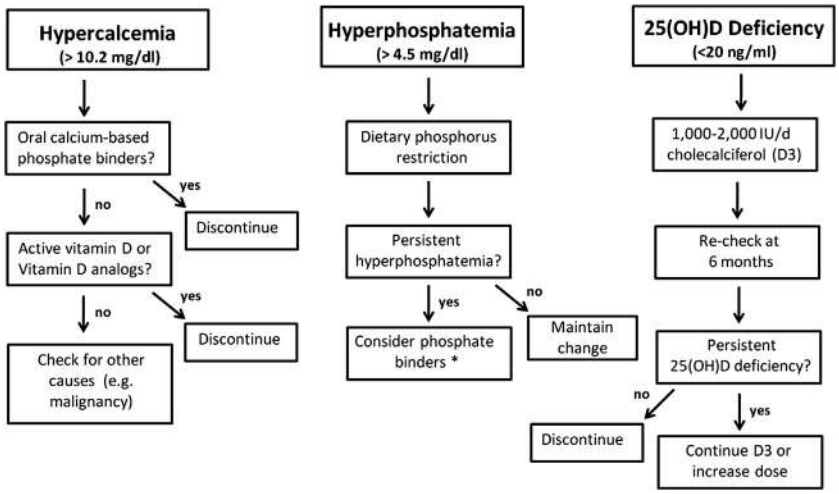


FIGURE 62.4 Algorithmic approach to treating biochemical and hormonal abnormalities in chronic kidney disease—mineral and bone disorder (CKD-MBD). The first step in the treatment of hypercalcemia is to check if the patient is taking oral calcium-based phosphate binders. If so, the binder should be discontinued. The same question should be asked regarding therapy with active vitamin D or vitamin D analogs. If neither is a potential cause of hypercalcemia, other potential causes should be evaluated, such as malignancy. To treat hyperphosphatemia, dietary phosphate restriction should first be attempted. If hyperphosphatemia persists, phosphate binders should be considered. However, phosphate binders are not FDA-approved for the treatment of hyperphosphatemia in nondialysis-dependent chronic kidney disease (indicated by *). Consistent with KDIGO recommendations, we recommend treatment of 25(OH)D_3 deficiency with 1000–2000 IU/day of cholecalciferol (D3). Serum 25(OH)D_3 should be rechecked after 6 months, with supplementation continued or increased according to repeat test levels.

CKD patients, with an emphasis on treating overt hyperphosphatemia[5] (Table 62.2). This recommendation is based on an overall lack of evidence and potential for harm in the normophosphatemic range. KDOQI recommendations noted that this recommendation could have an unintended consequence of discouraging dietary phosphorus restriction, with gradually increasing phosphorus levels in the normal range.[7] Overall, a phosphate-restricted diet combined with oral phosphate binders is a well-established recommendation for controlling hyperphosphatemia in patients with stage 3–5 CKD.[1,6] Treatment should be based on progressively or persistently elevated S[P], rather than preventive phosphate-lowering. The choice of phosphate binder should consider other components of CKD-MBD, concomitant therapies, and side effects.[5] There is currently insufficient evidence on comparative clinical efficacy to recommend a specific binder for all patients.

Dietary phosphate restriction is important in the treatment of CKD-MBD because 60–70% of ingested phosphate is absorbed.[91] Dietary phosphate intake should be limited either alone or in combination with other treatments for the treatment of hyperphosphatemia, with consideration of the source of phosphate (e.g. animal, vegetable, additives).[5] However, there are numerous challenges to achieving treatment goals, including patient compliance, issues with food labels, and the presence of abundant food additives (Table 62.3).

Phosphate binders available for the treatment of CKD-MBD have particular advantages and disadvantages (Table 62.3). Aluminum hydroxide is not recommended for use, as there is a risk of serious hematological, neurological, and skeletal adverse events as a consequence of aluminum toxicity.[91] Calcium carbonate and calcium acetate are both calcium-based phosphate binders that are inexpensive and effective at lowering S[P], but increase risk of calcium overload, which may promote vascular calcification or adynamic bone disease (although there is less calcium exposure with calcium acetate than calcium carbonate).[91] Accordingly, KDIGO suggests restricting use of calcium-based phosphate binders in stage 3–5 CKD patients.[5] Magnesium-based binders include magnesium hydroxide and magnesium carbonate. Both magnesium-based binders are associated with a lower calcium load than pure calcium-based phosphate binders. However, they have gastrointestinal side effects, are not well studied, and have lower efficacy, which may necessitate prescription of higher doses that could induce hypermagnesemia in CKD patients.[91]

Sevelamer hydrochloride is a noncalcium, nonmetal, nonabsorbable phosphate binder. Sevelamer carbonate is similar to sevelamer hydrochloride and is assumed to have equal efficacy and potentially improved acid–base balance and lower risk of acidosis.[1,92] Both have the advantages of avoiding calcium overload, metal exposure, and absorption, and have also been shown to lower

TABLE 62.3 Advantages and Disadvantages of Available Therapies to Treat Chronic Kidney Disease—Mineral and Bone Disorder (CKD-MBD)—Associated Biochemical Abnormalities

Therapeutic Options	Pros	Cons
Dietary phosphate restriction, with consideration of source	Important modulator of S[P] because 60–70% of all ingested dietary phosphate is absorbed	Challenging to adhere to (food choices, food labeling, additives, etc.)
		Not enough data available to strongly endorse as the sole therapy for treatment hyperphosphatemia
Aluminum hydroxide	Very effective phosphate binding	Not recommended due to risk of serious hematological, neurological, and skeletal adverse events resulting from aluminum toxicity
Calcium carbonate	Inexpensive, effective, and readily available	Potential of hypercalcemia-associated risks (e.g. vascular calcification, adynamic bone disease)
		KDIGO suggests restricting calcium-based phosphate binders in stage 3–4 CKD
Calcium acetate	Potentially less calcium exposure and better phosphate-binding capacity than calcium carbonate	Risk of hypercalcemia
		More costly than calcium carbonate
		KDIGO suggests restricting calcium-based phosphate binders in stage 3–4 CKD
Magnesium hydroxide and magnesium carbonate	Potentially less calcium exposure than calcium-based binders	Gastrointestinal side effects
		Lower efficacy, which may necessitate higher doses and potentially hypermagnesemia
		Not well studied
Sevelamer hydrochloride	Effective	High cost
	Avoids calcium overload	Gastrointestinal side effects
	Avoids metal exposure	High pill burden
	Not absorbed	Potential for decreased serum bicarbonate levels (acidosis)
	May have benefits beyond lowering S[P] (such as lowering LDL, slowing vascular calcification, and lowering FGF-23)	
Sevelamer carbonate	Assumed to have similar advantages to sevelamer hydrochloride with improved acid–base balance	High cost
		Gastrointestinal side effects
		High pill burden
Lanthanum carbonate	Effective	High cost
	Avoids calcium overload	Gastrointestinal side effects
	Chewable	Long-term clinical consequences unknown
	Eliminated by the liver thus metabolism not dependent on renal function	
	May have benefits beyond lowering S[P] (such as improving bone remodeling, lowering FGF-23 levels)	
Iron-based phosphate binders (ferric citrate, sucroferric oxyhydroxide)	Consistent rapid reduction in S[P]	Not yet FDA approved for phosphate lowering in nondialysis-dependent CKD
	Reduced intravenous iron and erythropoietin-stimulating agent use	Long-term clinical consequences unknown
	Lower pill burden than sevelamer	Gastrointestinal side effects
	Favorable safety profile	

TABLE 62.3 Advantages and Disadvantages of Available Therapies to Treat Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD)–Associated Biochemical Abnormalities—cont'd

Therapeutic Options	Pros	Cons
Nutritional vitamin D (D_2 and D_3)	Effective at raising $25(OH)D_3$ and $1,25(OH)_2D_3$ levels	Lack of RCTs in CKD patients
	Extra-renal conversion to $1,25(OH)_2D_3$ may confer extra-renal benefits	Less studied in CKD patients
	Can also suppress PTH	Some question as to whether it is adequate to raise $25(OH)D_3$ to sufficient levels in all CKD patients
	Inexpensive	
	Incidence of hypercalcemia and hyperphosphatemia is low	
Calcitriol (1,25D3)	Effective at raising $1,25(OH)_2D_3$ levels	May promote hypercalcemia (risk of adynamic bone disease, vascular calcification) and/or raise S[P]
	Decreases PTH production by the parathyroid glands	
Vitamin D receptor activators ($1,25(OH)_2D_3$ analogs: e.g. paricalcitol, doxercalciferol)	Effective at raising $1,25(OH)_2D_3$	May promote hypercalcemia (risk of adynamic bone disease, vascular calcification) and/or raise S[P]
	Decreases PTH production by the parathyroid glands	Failed to reduce left ventricular mass index in the PRIMO and OPERA trials
	Newer analogs are more selective for PTH suppression with fewer effects on S[Ca] and S[P]	
Cinacalcet	Effectively lowers PTH	Did not reduce mortality in EVOLVE trial
	May also lower S[P]	Gastrointestinal side effects
		Risk of hypocalcemia
		Not FDA approved for use in patients with CKD not requiring dialysis
Parathyroidectomy	Generally reduces PTH, S[Ca], and S[P]	Last choice therapy
		Lack of RCTs on the benefits and risks

$1,25(OH)_2D_3$, 1,25D dihydroxyvitamin D; *$25(OH)D_3$*, 25 hydroxyvitamin D; *FGF-23*, fibroblast growth factor-23; *PTH*, parathyroid hormone; *RCT*, randomized controlled trial; *S[Ca]*, serum calcium concentration; *S[P]*, serum phosphate concentration.

low-density lipoprotein (LDL) cholesterol.[91] Sevelamer also has potential benefits on vascular calcification and mortality,[76,80] and treatment can lower FGF-23 levels. Disadvantages of sevelamer include high cost, gastrointestinal side effects, a high pill burden, and the risk of decreased bicarbonate levels with sevelamer hydrochloride.[91]

Lanthanum carbonate is a noncalcium, naturally occurring metal-based binder first approved for use in 2004.[93] Advantages include effective phosphate lowering, avoidance of calcium overload, lesser pill requirement than sevelamer, and chewable delivery. Lanthanum is eliminated by the liver and therefore its handling is not dependent on renal function.[91] Lanthanum may also have benefits beyond lowering S[P], such as improving bone remodeling or lowering FGF-23 levels.[84,94] However, the cost of lanthanum carbonate is high, gastrointestinal side effects are common, and the long-term clinical consequences of its use are still largely unknown.[1,91,95]

Iron-based phosphate binders (ferric citrate, sucroferric oxyhydroxide) are new intestinal phosphate binders that can replete iron stores, increase hemoglobin, and reduce S[P] in phase 3 trials in chronic dialysis patients.[88–90] Advantages include reduced intravenous iron and erythropoietin-stimulating agent use, lower pill burden than sevelamer, and a favorable safety profile. However, they are not yet Food and Drug Administration (FDA)-approved for phosphate lowering in

nondialysis-dependent CKD, long-term data on clinical outcomes are lacking, and gastrointestinal side effects can occur.

Vitamin D

KDIGO recommends treating CKD patients with low circulating levels of 25(OH)D_3, with supplementation with 1000−2000 IU/day of cholecalciferol, consistent with repletion recommendations for the general population.[4] KDOQI recommends using ergocalciferol (50,000 IU weekly or monthly) to correct 25(OH)D_3 deficiency if levels are lower than 30 ng/mL.[6] Both forms of vitamin D supplementation have been shown to increase serum 25(OH)D_3 levels. However, there is a lack of data regarding the impact of these nutritional vitamin D supplements on clinical management issues, including pill burden and the cost related to treatment and monitoring. 1,25$(OH)_2D_3$ levels are usually not monitored throughout the course of CKD. Therefore, treatment should not be administered in response to low 1,25$(OH)_2D_3$. Figure 62.4 provides an algorithmic approach to treating CKD patients with low circulating levels of 25(OH)D_3, with the available evidence supporting this overall approach.

Observational data in chronic dialysis patients support increased survival with treatment with 1,25$(OH)_2D_3$ analogs,[13,27] but this finding is likely confounded by indication, and results are not consistent.[96,97] Data are limited in nondialysis-dependent CKD patients, as well as for nutritional vitamin D therapy. Observational data suggest that active vitamin D therapy is also associated with reduced risk of progression to end-stage renal disease (ESRD).[98] In a meta-analysis of trials in non-CKD patients, nutritional vitamin D supplementation was shown to decrease mortality.[99] One small observational study in chronic HD patients showed an association between cholecalciferol use and reduced left ventricular mass index.[100]

A recent trial comparing 6 months of calcitriol and cholecalciferol in participants with stage 3b and 4 CKD found no improvement in vascular endothelial function, measured by brachial artery flow-mediated dilation.[101] Similary, in an open-label randomized clinical trial in patients with secondary hyperparathyroidism receiving maintenance hemodialysis, the vitamin D receptor activator alfacalcidol failed to reduce cardiovascular events.[102] Additionally, the recently completed NIH-funded Vitamin D and Omega-3 Trial (VITAL) found no reduction in major cardiovascular events with nutritional vitamin D supplementation in the general population.[103] The PRIMO (Paricalcitol Capsule Benefits in Renal Failure-Induced Cardiac Morbidity) trial showed no change in left ventricular mass index in stage 3−4 CKD patients treated with 2 μg/day paricalcitol for 48 weeks.[104] Results were similar in the OPERA (Oral Paricalcitol in Stage 3−5 CKD) trial with 52 weeks of paricalcitol in stage 3−5 CKD patients.[105] These findings were in contrast to earlier evidence that vitamin D analogs reduce LVH in rats.[106] Both studies also demonstrated more frequent hypercalcemia with paricalcitol.

Studies on vascular calcification are inconclusive, and mouse models of CKD suggest that there is a balance needed between high and low levels of 1,25$(OH)_2D_3$ to protect against vs. induce vascular calcification.[107] It is currently unknown if vitamin D treatment reduces fracture risk in patients with CKD, and the effects on bone are inconclusive. Randomized trials have shown possible improvements in osteitis fibrosa and mineralization, but also reduced bone turnover, which could increase the risk of developing adynamic bone disease.[108,109]

In stage 3−5 CKD patients, RCTs support that calcitriol and vitamin D analogs both lower serum iPTH compared to placebo,[110−112] may increase S[Ca][110−112] or S[P],[110] or may not change either.[110] Additionally, vitamin D analogs may reduce proteinuria[113−115] and lower the inflammatory acute phase protein C-reactive protein. Nutritional vitamin D treatment may also lower iPTH in this population, and the associated incidence of hypercalcemia and hyperphosphatemia is low.[116]

KDIGO currently recommends correcting 25(OH)D_3 deficiency to >30 ng/mL using treatment strategies similar to those used in the general population (Table 62.2).[1,4] Calcitriol and vitamin D analogs should not be routinely used in stage 3−5 CKD but reserved for patients with CKD stage 4 and 5 and severe and progressive hyperparathyroidism.[5] KDOQI recommends using vitamin D2 (ergocalciferol) to correct serum 25(OH)D_3 levels that are <30 ng/mL.[6] Overall, there is no consensus regarding the optimal treatment type, dose, or target levels of 25(OH)D_3. More research is needed to help answer these questions.

Nutritional options to treat 25(OH)D_3 deficiency are ergocalciferol (D2) and cholecalciferol (D3) (Table 62.3), which must undergo conversion in the liver to 25(OH)D_3. Nutritional vitamin D is effective at raising both serum 25(OH)D_3 and 1,25$(OH)_2D_3$ levels in CKD patients in both observational studies[117,118] and RCTs.[119,120] There is currently debate regarding whether ergocalciferol or cholecalciferol is better at raising and maintaining serum 25(OH)D_3 levels.[121,122] There is overall a lack of large observational cohort studies and RCTs using nutritional vitamin D in CKD patients. However, there has been greater interest in its use in addition to or instead of active vitamin D in CKD patients more recently. There is still some question regarding whether nutritional vitamin D can adequately raise 25(OH)D_3 to sufficient levels in all CKD patients.[117,118] Nutritional vitamin D

is also effective at lowering PTH,[119,120] although the evidence is not as strong as for active vitamin D therapy.[123] An additional advantage of ergocalciferol and cholecalciferol is that they are relatively inexpensive.

Active ($1,25(OH)_2D_3$) vitamin D and $1,25(OH)_2D_3$ analogs have been more traditionally used as therapeutic options in patients with CKD. These are no longer recommended for routine use in stage 3−5 CKD, given failure to improved clinical outcomes in the PRIMO and OPERA trials and increased risk of hypercalcemia. Use should be reserved for patients with stage 4 and 5 CKD and progressive hyperparathyroidism.[5] Calcitriol ($1,25(OH)_2D_3$) is effective at raising serum $1,25(OH)_2D_3$ levels, as well as decreasing PTH production by the parathyroid glands. Calcitriol also increases S[Ca], which further suppresses PTH secretion.[124] Normalization of S[P] should occur before initiation of therapy with active vitamin D or vitamin D analogs. Observational evidence supports that calcitriol use may be associated with reduced risk of death or dialysis in patients with secondary hyperparathyroidism.[98] However, there are concerns that calcitriol use may lead to adynamic bone disease, hypercalcemia, and/or hyperphosphatemia, as well as vascular calcification.[91,124] Paricalcitol (19-nor-1α,$25(OH)_2D_2$) and doxercalciferol (1α,$25(OH)D_2$) are analogs of $1,25(OH)_2D_3$ that activate the vitamin D receptor. Vitamin D analogs are also effective at raising serum $1,25(OH)_2D_3$ levels, and newer analogs are more selective for PTH suppression with less effect on S[Ca] and S[P].[110,125] Observational evidence suggests that vitamin D analog use may improve survival in dialysis patients[13,27] and slow progression to ESRD in earlier stages.[98]

Parathyroid Hormone

The EVOLVE study raised questions regarding the utility of lowering PTH for improving cardiovascular outcomes in patients with CKD.[73] Prior to EVOLVE, observational data supported notions that lowering PTH with cinacalcet is associated with decreased all-cause and cardiovascular mortality in chronic HD patients.[11] RCTs with therapeutic agents to lower PTH (testing calcium supplementation, phosphate binders, nutritional vitamin D, $1,25(OH)_2D_3$ analogs, and calcimimetics) were mostly limited to the effects on biochemical parameters and surrogate outcomes. In a single trial in stage 3−5 CKD patients, calcium binders did not lower iPTH but increased coronary calcification score.[126] In three other clinical trials in stage 3−4 CKD, sevelamer and lanthanum also failed to lower iPTH.[23,127,128] Treatment with active vitamin D and its analogs lowers serum iPTH but may also increase S[Ca] or S[P],[110−112] as highlighted by increased risk of hypercalcemia in the PRIMO and EVOLVE studies.[104,105] Active vitamin D and vitamin D analogs have been shown to improve histological indices of bone turnover. Although most studies have been in chronic dialysis populations,[129,130] calcimimetics did lower iPTH in prospective trials of stage 3−5 CKD patients, as well as induce an asymptomatic decrease in S[Ca] and S[P].[131,132] In the ADVANCE study, a randomized trial to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in HD patients, cinacalcet, a calcimimetic, plus low-dose paricalcitol did not significantly change the primary endpoint, the Agatston coronary calcification score.[133]

The EVOLVE study was a randomized, double-blinded, placebo-controlled study in 3883 chronic HD patients with moderate to severe secondary hyperparathyroidism.[73] In the unadjusted intent to treat analysis, there was no significant change in mortality or cardiovascular events with cinacalcet, despite effective lowering of iPTH.

Optimal levels of iPTH for patients with stage 3−5 CKD are unknown, thus KDIGO does not recommend targeting a specific range (Table 62.2).[1] KDOQI suggests lowering the iPTH threshold in stage 4−5 CKD for prompting evaluation and possible treatment of hyperparathyroidism.[6] This is one of the most debated recommendations, as there is a lack of studies relating serum iPTH levels to bone disease. There is some consensus, however, that trends in iPTH levels should be considered before initiating a therapeutic intervention, as reflected by the newest KDIGO guidelines emphasizing progressively rising or persistently elevate iPTH as indications for treatment.[5] KDIGO considers any of the following to be reasonable first-line therapies for the treatment of hyperparathyroidism: reduced phosphate intake, phosphate binders, calcium supplements, and if the patient is also $25(OH)D_3$ deficient, nutritional vitamin D.[1,4] If these options are not effective, iPTH is progressively rising and remains above the upper limit of normal, and $25(OH)D_3$ deficiency is present, then treatment with $1,25(OH)_2D_3$ or $1,25(OH)_2D_3$ analogs should be considered in stage 4 and 5 CKD.

Calcimimetics are not currently recommended for treatment of hyperparathyroidism in nondialysis-dependent CKD, as the work group felt more data were still needed, nor are they approved by the FDA in this population. In circumstances of severe hyperparathyroidism that fails to respond to other therapy, parathyroidectomy is recommended.

There are advantages and disadvantages associated with calcimimetics compared to parathyroidectomy for treatment of hyperparathyroidism in CKD patients (Table 62.3). By mimicking an increase in extracellular calcium concentration, calcimimetics increase intracellular calcium levels, which decreases PTH release.[1] Cinacalcet, which acts as a positive allosteric modulator by inducing a conformational change in the calcium-sensing receptor

to increase sensitivity to extracellular calcium,[91] is the only type II calcimimetic currently available for clinical use. Although cinacalcet is effective at lowering iPTH in both chronic dialysis patients[129,130] and nondialysis CKD patients,[131,132] its use is associated with gastrointestinal side effects.[73] In the EVOLVE study, there was also an increased occurrence of hypocalcemia with use of cinacalcet, without any reduction in cardiovascular events or mortality.[73]

There is a lack of RCTs to show either the benefits or risks associated with parathyroidectomy to treat secondary or autonomous hyperparathyroidism, as well as studies specifically comparing surgical to medical therapy for treatment of secondary hyperparathroidism. However, it is generally accepted that a well-performed parathyroidectomy reduces serum iPTH concentrations, S[Ca], and S[P] in CKD patients with secondary or autonomous hyperparathyroidism. In addition to a last resort therapy when patients fail to respond to medical therapy, parathyroidectomy could also be considered if the medical management of hyperparathyroidism leads to an unacceptable rise in S[Ca] and/or S[P], or if there are other intolerable adverse events.[1]

FGF-23

The discovery of FGF-23 is relatively recent; and therefore, its role in the treatment of CKD-MBD is not yet well understood or targeted. There are some small diet manipulation studies and observational evidence that suggest that manipulating dietary phosphate intake can alter FGF-23 levels, which is dependent on the source of phosphate (animal vs. plant).[63,134,135] Several small studies have also shown that phosphate lowering with the binders sevelamer[136,137] and lanthanum (plus a low-phosphate diet)[138] can also reduce levels of FGF-23 in patients with stage 3–4 CKD. FGF-23 levels may also be reduced in stage 3–5 CKD with ferric acid treatment.[139] However, the degree of change in FGF-23 in response to phosphate binders or dietary phosphate restriction is minimal compared to the magnitude of change seen with progression of CKD. Thus manipulating phosphorus alone, either through dietary intake or with phosphate binders, may not be enough to modify FGF-23 levels in a meaningful way.

Secondary analysis of the EVOLVE study showed reductions in FGF-23 with the calcimimetic cinacalcet, which was associated with reduced rates of cardiovascular death and major cardiovascular events.[140] A recently completed phase 3 trial in stage 3b–4 CKD patients (The COMBINE [CKD Optimal Management with Binders and NicotinamidE] study) failed to demonstrate effective lowering of FGF-23 or phosphate levels with 12 months of nicotinamide, which inhibits intestinal NPT2b, with or without lanthanum carbonate.[141]

FGF-23 receptor blockers are currently being tested in animal models to suppress FGF receptor signaling.[142] An FGF-23 antibody (burosumab-twza) was recently approved by the FDA for the treatment of X-linked hypophosphatemia in adults and pediatric patients. There are also ongoing phase I/II oncology clinical trials using FGF receptor (1–4) tyrosine kinase inhibitors. This may represent a potential pharmacological target in the treatment of CKD-MBD. However, there are potential concerns regarding possible negative or unknown consequences of lowering FGF-23 that will need to be carefully considered.

Bone

KDIGO recommends that in patients with stage 1–2 CKD and osteoporosis or a high risk of fracture, and patients with stage 3 CKD with osteoporosis or a high risk of fracture and iPTH in the normal range, management should be the same as in the general population.[1] In patients with stage 3–5 CKD, biochemical abnormalities, and low BMD and/or fragility fractures, treatment options should include consideration of the magnitude and reversibility of biochemical abnormalities, as well as CKD progression; performance of bone biopsy should also be considered.[5] Bone biopsy is no longer required (although can be considered) prior to beginning an antiresorptive agent, as there is growing evidence that antiresorptive therapies are effective at preventing fractures and there is a lack of robust evidence that medications induce adynamic bone disease.[71] It is recommended that secondary hyperparathyroidism be corrected first.[1]

The risks of treatment must be weighed against potential side effects and the accuracy of the diagnosis of the underlying bone phenotype. Biphosphonates are effective at decreasing fractures in non-CKD patients with osteoporosis, and *post hoc* analyses of RCTs support they may be as effective in stage 3 CKD patients. Teriparatide is an anabolic drug that increases the formation of new bone. Teriparatide is a recombinant human 1–34 PTH, and therefore is contraindicated in patients with hyperparathyroidism.[1] Teriparatide does not appear to be contraindicated in women with stage 2–3 CKD and normal biochemistry, based on a *post hoc* analysis.[143] Desosumab is an antiresorptive agent that is a monoclonal antibody against the receptor activator of nuclear factor κB ligand. Recent studies suggest it can be safely administered in patients with CKD-associated osteoporosis, with careful monitoring for hypocalcemia, adequate calcium intake, and vitamin D supplementation.[71]

Raloxifene is a selective estrogen receptor modulator approved for the treatment of postmenopausal osteoporosis. Raloxifene reduces vertebral fracture risk in this population, although there are concerns common to

estrogen therapy, including increased risk of fatal stroke.[1] A *post hoc* analysis including participants from a trial who had mild to moderate CKD and normal biochemistry suggests raloxifene may be as safe and effective for these patients as the general population, although this cohort in not likely representative of the typical CKD population.[144]

Vascular Calcification

There is no clear evidence-based protocol established for treatment given a positive calcification test. In general, the KDIGO recommendations focus on strategies to minimize the progression of vascular calcification in patients with known calcification.[1] Noncalcium-based binders are recommended for the treatment of hyperphosphatemia in CKD patients with known vascular calcification. There is currently a lack of interventional data on the effects of calcimimetics, nutritional or active vitamin D/analogs, or parathyroidectomy on vascular calcification progression.

CONCLUSION

The pathophysiology of CKD-MBD, a common clinical syndrome in patients with CKD with consequences affecting mineral metabolism, bone mineralization, and extracellular calcification, is complex. Treatment of CKD-MBD, especially in early stages of disease, with a focus on the biochemical and hormonal factors, and calcium, phosphorus, vitamin D, iPTH and FGF-23 metabolism, as well as consideration of bone and vascular calcification, is often not evidence-based because of the lack of information from observational studies as well as RCTs performed in specific patient populations. There is great need for additional well-designed RCTs to further guide the diagnosis and complex management of patients with CKD-MBD.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl* 2009;(113):S1–130.
2. Demer L, Tintut Y. The bone-vascular axis in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2010;**19**(4):349–53.
3. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K. Definition. evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006;**69**(11): 1945–53.
4. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:19–62.
5. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl* 2017;**7**:1–59.
6. Uhlig K, Berns JS, Kestenbaum B, Kumar R, Leonard MB, Martin KJ, et al. KDOQI US commentary on the 2009 KDIGO clinical practice guideline for the diagnosis, evaluation, and treatment of CKD-mineral and bone disorder (CKD-MBD). *Am J Kidney Dis* 2010;**55**(5):773–99.
7. Isakova T, Nickolas TL, Denburg M, Yarlagadda S, Weiner DE, Gutierrez OM. KDOQI US Commentary on the 2017 KDIGO clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Am J Kidney Dis* 2017;**70**(6):737–51.
8. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int* 2007;**71**(1):31–8.
9. Gal-Moscovici A, Sprague SM. Use of vitamin D in chronic kidney disease patients. *Kidney Int* 2010;**78**(2):146–51.
10. Hruska KA, Levi M, Slatopolsky E. Disorders of phosphorus, calcium and magnesium metabolism. In: Schrier RW, editor. *Diseases of the kidney and urinary tract*. 8th ed. Philadelphia: Lippincott Williams and Wilkins; 2007.
11. Block GA, Zaun D, Smits G, Persky M, Brillhart S, Nieman K, et al. Cinacalcet hydrochloride treatment significantly improves all-cause and cardiovascular survival in a large cohort of hemodialysis patients. *Kidney Int* 2010;**78**(6):578–89.
12. Kimata N, Albert JM, Akiba T, Yamazaki S, Kawaguchi T, Fukuhara S, et al. Association of mineral metabolism factors with all-cause and cardiovascular mortality in hemodialysis patients: the Japan dialysis outcomes and practice patterns study. *Hemodial Int* 2007;**11**(3):340–8.
13. Kalantar-Zadeh K, Kuwae N, Regidor DL, Kovesdy CP, Kilpatrick RD, Shinaberger CS, et al. Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int* 2006;**70**(4):771–80.
14. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble CD, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010;**341**:c3691.
15. Ginde AA, Scragg R, Schwartz RS, Camargo Jr CA. Prospective study of serum 25-hydroxyvitamin D level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults. *J Am Geriatr Soc* 2009;**57**(9):1595–603.
16. Isakova T, Wahl P, Vargas GS, Gutierrez OM, Scialla J, Xie H, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int* 2011; **79**(12):1370–8.
17. Kendrick J, Chonchol M. The role of phosphorus in the development and progression of vascular calcification. *Am J Kidney Dis* 2011;**58**(5):826–34.
18. Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G. Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation* 2005;**112**(17):2627–33.
19. Chonchol M, Dale R, Schrier RW, Estacio R. Serum phosphorus and cardiovascular mortality in type 2 diabetes. *Am J Med* 2009; **122**(4):380–6.
20. Eddington H, Hoefield R, Sinha S, Chrysochou C, Lane B, Foley RN, et al. Serum phosphate and mortality in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2010;**5**(12):2251–7.
21. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, et al. Serum phosphate levels and mortality risk among

people with chronic kidney disease. *J Am Soc Nephrol* 2005;**16**(2): 520–8.
22. Block GA, Spiegel DM, Ehrlich J, Mehta R, Linbergh J, Dreisbach A, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int* 2005;**68**(4):1815–24.
23. Block GA, Wheeler DC, Persky MS, Kestenbaum B, Spiegel BM, Allison MA, et al. Effects of phosphate binders in moderate CKD. *J Am Soc Nephrol* 2012;**23**(8):1407–15.
24. Chonchol M, Kendrick J, Targher G. Extra-skeletal effects of vitamin D deficiency in chronic kidney disease. *Ann Med* 2011; **43**(4):273–82.
25. Levin A, Le Barbier M, Er L, Andress D, Sigrist MK, Djurdjev O. Incident isolated 1,25(OH)(2)D(3) deficiency is more common than 25(OH)D deficiency in CKD. *J Nephrol* 2012;**25**(2):204–10.
26. Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. *J Bone Miner Res* 2004;**19**(3):429–35.
27. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, et al. Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int* 2007;**72**(8):1004–13.
28. Navaneethan SD, Schold JD, Arrigain S, Jolly SE, Jain A, Schreiber Jr MJ, et al. Low 25-hydroxyvitamin D levels and mortality in non-dialysis-dependent CKD. *Am J Kidney Dis* 2011;**58**(4): 536–43.
29. Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med* 2008;**168**(15):1629–37.
30. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, et al. Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality. *Arch Intern Med* 2008;**168**(12):1340–9.
31. Kendrick J, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey. *Atherosclerosis* 2009;**205**(1):255–60.
32. Kendall JM, Thomas SE, Spurlock G, Mir MA. An active sodium transport inhibitor released from spontaneously hypertensive and normotensive rat fetal hypothalamic cells in culture. *Am J Hypertens* 1988;**1**(3 Pt 3):83S–7S.
33. Dawson-Hughes B. Serum 25-hydroxyvitamin D and functional outcomes in the elderly. *Am J Clin Nutr* 2008;**88**(2): 537S–40S.
34. Heine GH, Seiler S, Fliser D. FGF-23: the rise of a novel cardiovascular risk marker in CKD. *Nephrol Dial Transplant* 2012;**27**(8): 3072–81.
35. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 2004;**15**(8):2208–18.
36. Floege J, Kim J, Ireland E, Chazot C, Drueke T, de Francisco A, et al. Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. *Nephrol Dial Transplant* 2011;**26**(6):1948–55.
37. Avram MM, Mittman N, Myint MM, Fein P. Importance of low serum intact parathyroid hormone as a predictor of mortality in hemodialysis and peritoneal dialysis patients: 14 years of prospective observation. *Am J Kidney Dis* 2001;**38**(6):1351–7.
38. Melamed ML, Eustace JA, Plantinga L, et al. Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: a longitudinal study. *Kidney Int* 2006;**70**(2): 351–7.
39. Drechsler C, Krane V, Grootendorst DC, et al. The association between parathyroid hormone and mortality in dialysis patients is modified by wasting. *Nephrol Dial Transplant* 2009;**24**(10):3151–7.
40. Yamashita T, Yoshioka M, Itoh N. Identification of a novel fibroblast growth factor, FGF-23, preferentially expressed in the ventrolateral thalamic nucleus of the brain. *Biochem Biophys Res Commun* 2000;**277**(2):494–8.
41. Ohkido I, Yokoyama K, Kagami S, Hosoya T. The hypothesis that bone turnover influences FGF-23 secretion. *Kidney Int* 2010;**77**(8): 743–4.
42. Faul C. Fibroblast growth factor 23 and the heart. *Curr Opin Nephrol Hypertens* 2012;**21**(4):369–75.
43. Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, et al. FGF-23 induces left ventricular hypertrophy. *J Clin Investig* 2011; **121**(11):4393–408.
44. Gutierrez O, Isakova T, Rhee E, Shah A, Holmes J, Collerone G, et al. Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. *J Am Soc Nephrol* 2005;**16**(7):2205–15.
45. Kendrick J, Cheung AK, Kaufman JS, Greene T, Roberts WL, Smits G, et al. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. *J Am Soc Nephrol* 2011; **22**(10):1913–22.
46. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. *J Am Med Assoc* 2011;**305**(23):2432–9.
47. Seiler S, Reichart B, Roth D, Seibert E, Fliser D, Heine GH. FGF-23 and future cardiovascular events in patients with chronic kidney disease before initiation of dialysis treatment. *Nephrol Dial Transplant* 2010;**25**(12):3983–9.
48. Fliser D, Kollerits B, Neyer U, Ankers DP, Lhotta K, LIngenhel A, et al. Fibroblast growth factor 23 (FGF-23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. *J Am Soc Nephrol* 2007;**18**(9):2600–8.
49. Nowak KL, Bartz TM, Dalrymple L, et al. Fibroblast growth factor 23 and the risk of infection-related hospitalization in older adults. *J Am Soc Nephrol* 2017;**28**(4):1239–46.
50. Gutierrez OM, Januzzi JL, Isakova T, Laliberte K, Smith K, Collerone G, et al. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. *Circulation* 2009;**119**(19): 2545–52.
51. Kirkpantur A, Balci M, Gurbuz OA, et al. Serum fibroblast growth factor-23 (FGF-23) levels are independently associated with left ventricular mass and myocardial performance index in maintenance haemodialysis patients. *Nephrol Dial Transplant* 2011;**26**(4): 1346–54.
52. Mirza MA, Larsson A, Lind L, Larsson TE. Circulating fibroblast growth factor-23 is associated with vascular dysfunction in the community. *Atherosclerosis* 2009;**205**(2):385–90.
53. Piraino B, Chen T, Cooperstein L, Segre G, Puschett J. Fractures and vertebral bone mineral density in patients with renal osteodystrophy. *Clin Nephrol* 1988;**30**(2):57–62.
54. Gerakis A, Hadjidakis D, Kokkinakis E, Apostolou T, Raptis S, Billis A. Correlation of bone mineral density with the histological findings of renal osteodystrophy in patients on hemodialysis. *J Nephrol* 2000;**13**(6):437–43.
55. Iimori S, Mori Y, Akita W, et al. Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients–a single-center cohort study. *Nephrol Dial Transplant* 2012;**27**(1):345–51.
56. Naylor KL, Garg AX, Zou G, et al. Comparison of fracture risk prediction among individuals with reduced and normal kidney function. *Clin J Am Soc Nephrol* 2015;**10**(4):646–53.
57. West SL, Lok CE, Langsetmo L, et al. Bone mineral density predicts fractures in chronic kidney disease. *J Bone Miner Res* 2015; **30**(5):913–9.

58. Yenchek RH, Ix JH, Shlipak MG, et al. Bone mineral density and fracture risk in older individuals with CKD. *Clin J Am Soc Nephrol* 2012;**7**(7):1130–6.
59. Giachelli CM. The emerging role of phosphate in vascular calcification. *Kidney Int* 2009;**75**(9):890–7.
60. Covic A, Kanbay M, Voroneanu L, Turgut F, Serban DN, Serban IL, et al. Vascular calcification in chronic kidney disease. *Clin Sci* 2010;**119**(3):111–21.
61. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001;**103**(7): 987–92.
62. London GM. Alterations of arterial function in end-stage renal disease. *Nephron* 2000;**84**(2):111–8.
63. Moe SM, Zidehsarai MP, Chambers MA, et al. Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. *Clin J Am Soc Nephrol* 2011; **6**(2):257–64.
64. Gonzalez EA, Sachdeva A, Oliver DA, Martin KJ. Vitamin D insufficiency and deficiency in chronic kidney disease. A single center observational study. *Am J Nephrol* 2004;**24**(5):503–10.
65. Chapuy MC, Preziosi P, Maamer M, et al. Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos Int* 1997; **7**(5):439–43.
66. Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. *N Engl J Med* 1998;**338**(12):777–83.
67. Dawson-Hughes B, Harris SS, Dallal GE. Plasma calcidiol, season, and serum parathyroid hormone concentrations in healthy elderly men and women. *Am J Clin Nutr* 1997;**65**(1):67–71.
68. Shimada T, Urakawa I, Isakova T, et al. Circulating fibroblast growth factor 23 in patients with end-stage renal disease treated by peritoneal dialysis is intact and biologically active. *J Clin Endocrinol Metab* 2010;**95**(2):578–85.
69. Smith ER, Cai MM, McMahon LP, Holt SG. Biological variability of plasma intact and C-terminal FGF-23 measurements. *J Clin Endocrinol Metab* 2012;**97**(9):3357–65.
70. Imanishi Y, Inaba M, Nakatsuka K, et al. FGF-23 in patients with end-stage renal disease on hemodialysis. *Kidney Int* 2004;**65**(5): 1943–6.
71. Khairallah P, Nickolas TL. Management of osteoporosis in CKD. *Clin J Am Soc Nephrol* 2018;**13**(6):962–9.
72. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ* 2011;**342**:d2040.
73. Chertow GM, Block GA, Correa-Rotter R, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012;**367**(26):2482–94.
74. Isakova T, Gutierrez OM, Chang Y, et al. Phosphorus binders and survival on hemodialysis. *J Am Soc Nephrol* 2009;**20**(2):388–96.
75. Kovesdy CP, Kuchmak O, Lu JL, Kalantar-Zadeh K. Outcomes associated with phosphorus binders in men with non-dialysis-dependent CKD. *Am J Kidney Dis* 2010;**56**(5):842–51.
76. Russo D, Miranda I, Ruocco C, et al. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. *Kidney Int* 2007;**72**(10):1255–61.
77. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 2002;**62**(1):245–52.
78. Qunibi W, Moustafa M, Muenz LR, et al. A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. *Am J Kidney Dis* 2008;**51**(6):952–65.
79. Barreto DV, Barreto Fde C, de Carvalho AB, et al. Phosphate binder impact on bone remodeling and coronary calcification–results from the BRiC study. *Nephron Clin Pract* 2008;**110**(4): c273–83.
80. Suki WN, Zabaneh R, Cangiano JL, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int* 2007;**72**(9):1130–7.
81. St Peter WL, Liu J, Weinhandl E, Fan Q. A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: a secondary analysis of the Dialysis Clinical Outcomes Revisited (DCOR) randomized trial using claims data. *Am J Kidney Dis* 2008;**51**(3):445–54.
82. D'Haese PC, Spasovski GB, Sikole A, et al. A multicenter study on the effects of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients. *Kidney Int Suppl* 2003;(85):S73–8.
83. Ferreira A, Frazao JM, Monier-Faugere MC, et al. Effects of sevelamer hydrochloride and calcium carbonate on renal osteodystrophy in hemodialysis patients. *J Am Soc Nephrol* 2008;**19**(2):405–12.
84. Freemont AJ, Hoyland JA, Denton J. The effects of lanthanum carbonate and calcium carbonate on bone abnormalities in patients with end-stage renal disease. *Clin Nephrol* 2005;**64**(6):428–37.
85. Finn WF. Lanthanum carbonate versus standard therapy for the treatment of hyperphosphatemia: safety and efficacy in chronic maintenance hemodialysis patients. *Clin Nephrol* 2006;**65**(3): 191–202.
86. Sprague SM, Abboud H, Qiu P, Dauphin M, Zhang P, Finn W. Lanthanum carbonate reduces phosphorus burden in patients with CKD stages 3 and 4: a randomized trial. *Clin J Am Soc Nephrol* 2009;**4**(1):178–85.
87. Takahara Y, Matsuda Y, Takahashi S, Shigematsu T. Lanthanum Carbonate Study G. Efficacy and safety of lanthanum carbonate in pre-dialysis CKD patients with hyperphosphatemia: a randomized trial. *Clin Nephrol* 2014;**82**(3):181–90.
88. Floege J, Covic AC, Ketteler M, et al. A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. *Kidney Int* 2014;**86**(3):638–47.
89. Van Buren PN, Lewis JB, Dwyer JP, et al. The phosphate binder ferric citrate and mineral metabolism and inflammatory markers in maintenance dialysis patients: results from prespecified analyses of a randomized clinical trial. *Am J Kidney Dis* 2015;**66**(3): 479–88.
90. Lewis JB, Sika M, Koury MJ, et al. Ferric citrate controls phosphorus and delivers iron in patients on dialysis. *J Am Soc Nephrol* 2015;**26**(2):493–503.
91. Barreto FC, de Oliveira RA, Oliveira RB, Jorgetti V. Pharmacotherapy of chronic kidney disease and mineral bone disorder. *Expert Opin Pharmacother* 2011;**12**(17):2627–40.
92. Pai AB, Shepler BM. Comparison of sevelamer hydrochloride and sevelamer carbonate: risk of metabolic acidosis and clinical implications. *Pharmacotherapy* 2009;**29**(5):554–61.
93. Koizumi M, Komaba H, Nakanishi S, Fujimori A, Fukagawa M. Cinacalcet treatment and serum FGF-23 levels in haemodialysis patients with secondary hyperparathyroidism. *Nephrol Dial Transplant* 2012;**27**(2):784–90.
94. Gonzalez-Parra E, Gonzalez-Casaus ML, Galan A, et al. Lanthanum carbonate reduces FGF-23 in chronic kidney disease Stage 3 patients. *Nephrol Dial Transplant* 2011;**26**(8):2567–71.
95. Drueke TB. Lanthanum carbonate as a first-line phosphate binder: the "cons". *Semin Dial* 2007;**20**(4):329–32.
96. Tentori F, Albert JM, Young EW, et al. The survival advantage for haemodialysis patients taking vitamin D is questioned: findings from the Dialysis Outcomes and Practice Patterns Study. *Nephrol Dial Transplant* 2009;**24**(3):963–72.

97. St Peter WL, Li S, Liu J, Gilbertson DT, Arneson TJ, Collins AJ. Effects of monthly dose and regular dosing of intravenous active vitamin D use on mortality among patients undergoing hemodialysis. *Pharmacotherapy* 2009;**29**(2):154–64.
98. Shoben AB, Rudser KD, de Boer IH, Young B, Kestenbaum B. Association of oral calcitriol with improved survival in nondialyzed CKD. *J Am Soc Nephrol* 2008;**19**(8):1613–9.
99. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007;**167**(16):1730–7.
100. Matias PJ, Jorge C, Ferreira C, et al. Cholecalciferol supplementation in hemodialysis patients: effects on mineral metabolism, inflammation, and cardiac dimension parameters. *Clin J Am Soc Nephrol* 2010;**5**(5):905–11.
101. Kendrick J, Andrews E, You Z, et al. Cholecalciferol, calcitriol, and vascular function in CKD: a randomized, double-blind trial. *Clin J Am Soc Nephrol* 2017;**12**(9):1438–46.
102. J-DAVID Investigators, Shoji T, Inaba M, et al. Effect of oral alfacalcidol on clinical outcomes in patients without secondary hyperparathyroidism receiving maintenance hemodialysis: the J-DAVID randomized clinical trial. *J Am Med Assoc* 2018;**320**(22): 2325–34.
103. Manson JE, Cook NR, Lee IM, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med* 2019;**380**(1):33–44.
104. Thadhani R, Appelbaum E, Pritchett Y, et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. *J Am Med Assoc* 2012;**307**(7):674–84.
105. Wang AY, Fang F, Chan J, et al. Effect of paricalcitol on left ventricular mass and function in CKD–the OPERA trial. *J Am Soc Nephrol* 2014;**25**(1):175–86.
106. Kong J, Kim GH, Wei M, et al. Therapeutic effects of vitamin D analogs on cardiac hypertrophy in spontaneously hypertensive rats. *Am J Pathol* 2010;**177**(2):622–31.
107. Mathew S, Lund RJ, Chaudhary LR, Geurs T, Hruska KA. Vitamin D receptor activators can protect against vascular calcification. *J Am Soc Nephrol* 2008;**19**(8):1509–19.
108. Baker LR, Muir JW, Sharman VL, et al. Controlled trial of calcitriol in hemodialysis patients. *Clin Nephrol* 1986;**26**(4):185–91.
109. Salusky IB, Kuizon BD, Belin TR, et al. Intermittent calcitriol therapy in secondary hyperparathyroidism: a comparison between oral and intraperitoneal administration. *Kidney Int* 1998;**54**(3): 907–14.
110. Coburn JW, Maung HM, Elangovan L, et al. Doxercalciferol safely suppresses PTH levels in patients with secondary hyperparathyroidism associated with chronic kidney disease stages 3 and 4. *Am J Kidney Dis* 2004;**43**(5):877–90.
111. Coyne D, Acharya M, Qiu P, et al. Paricalcitol capsule for the treatment of secondary hyperparathyroidism in stages 3 and 4 CKD. *Am J Kidney Dis* 2006;**47**(2):263–76.
112. Nordal KP, Dahl E. Low dose calcitriol versus placebo in patients with predialysis chronic renal failure. *J Clin Endocrinol Metab* 1988; **67**(5):929–36.
113. Alborzi P, Patel NA, Peterson C, et al. Paricalcitol reduces albuminuria and inflammation in chronic kidney disease: a randomized double-blind pilot trial. *Hypertension* 2008;**52**(2):249–55.
114. Fishbane S, Chittineni H, Packman M, Dutka P, Ali N, Durie N. Oral paricalcitol in the treatment of patients with CKD and proteinuria: a randomized trial. *Am J Kidney Dis* 2009;**54**(4):647–52.
115. de Zeeuw D, Agarwal R, Amdahl M, et al. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. *Lancet* 2010;**376**(9752):1543–51.
116. Kandula P, Dobre M, Schold JD, Schreiber Jr MJ, Mehrotra R, Navaneethan SD. Vitamin D supplementation in chronic kidney disease: a systematic review and meta-analysis of observational studies and randomized controlled trials. *Clin J Am Soc Nephrol* 2011;**6**(1):50–62.
117. Al-Aly Z, Qazi RA, Gonzalez EA, Zeringue A, Martin KJ. Changes in serum 25-hydroxyvitamin D and plasma intact PTH levels following treatment with ergocalciferol in patients with CKD. *Am J Kidney Dis* 2007;**50**(1):59–68.
118. Zisman AL, Hristova M, Ho LT, Sprague SM. Impact of ergocalciferol treatment of vitamin D deficiency on serum parathyroid hormone concentrations in chronic kidney disease. *Am J Nephrol* 2007; **27**(1):36–43.
119. Dogan E, Erkoc R, Sayarlioglu H, Soyoral Y, Dulger H. Effect of depot oral cholecalciferol treatment on secondary hyperparathyroidism in stage 3 and stage 4 chronic kidney diseases patients. *Ren Fail* 2008;**30**(4):407–10.
120. Moe SM, Saifullah A, LaClair RE, Usman SA, Yu Z. A randomized trial of cholecalciferol versus doxercalciferol for lowering parathyroid hormone in chronic kidney disease. *Clin J Am Soc Nephrol* 2010;**5**(2):299–306.
121. Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. *J Clin Endocrinol Metab* 2008;**93**(3):677–81.
122. Nigwekar SU, Bhan I, Thadhani R. Ergocalciferol and cholecalciferol in CKD. *Am J Kidney Dis* 2012;**60**(1):139–56.
123. Melamed ML, Thadhani RI. Vitamin D therapy in chronic kidney disease and end stage renal disease. *Clin J Am Soc Nephrol* 2012; **7**(2):358–65.
124. Palmer SC, McGregor DO, Craig JC, Elder G, Macaskill P, Strippoli GF. Vitamin D compounds for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev* 2009;(4):CD008175.
125. Martin KJ, Gonzalez EA, Gellens M, Hamm LL, Abboud H, Lindberg J. 19-Nor-1-alpha-25-dihydroxyvitamin D2 (Paricalcitol) safely and effectively reduces the levels of intact parathyroid hormone in patients on hemodialysis. *J Am Soc Nephrol* 1998;**9**(8): 1427–32.
126. Russo D, Corrao S, Miranda I, et al. Progression of coronary artery calcification in predialysis patients. *Am J Nephrol* 2007;**27**(2): 152–8.
127. Chue CD, Townend JN, Moody WE, et al. Cardiovascular effects of sevelamer in stage 3 CKD. *J Am Soc Nephrol* 2013;**24**(5): 842–52.
128. Lemos MM, Watanabe R, Carvalho AB, et al. Effect of rosuvastatin and sevelamer on the progression of coronary artery calcification in chronic kidney disease: a pilot study. *Clin Nephrol* 2013;**80**(1): 1–8.
129. Lindberg JS, Moe SM, Goodman WG, et al. The calcimimetic AMG 073 reduces parathyroid hormone and calcium x phosphorus in secondary hyperparathyroidism. *Kidney Int* 2003; **63**(1):248–54.
130. Messa P, Macario F, Yaqoob M, et al. The OPTIMA study: assessing a new cinacalcet (Sensipar/Mimpara) treatment algorithm for secondary hyperparathyroidism. *Clin J Am Soc Nephrol* 2008;**3**(1): 36–45.
131. Chonchol M, Locatelli F, Abboud HE, et al. A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of cinacalcet HCl in participants with CKD not receiving dialysis. *Am J Kidney Dis* 2009;**53**(2):197–207.
132. Charytan C, Coburn JW, Chonchol M, et al. Cinacalcet hydrochloride is an effective treatment for secondary hyperparathyroidism in patients with CKD not receiving dialysis. *Am J Kidney Dis* 2005; **46**(1):58–67.

133. Raggi P, Chertow GM, Torres PU, et al. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrol Dial Transplant* 2011;**26**(4):1327−39.
134. Burnett SM, Gunawardene SC, Bringhurst FR, Juppner H, Lee H, Finkelstein JS. Regulation of C-terminal and intact FGF-23 by dietary phosphate in men and women. *J Bone Miner Res* 2006;**21**(8): 1187−96.
135. Gutierrez OM, Wolf M, Taylor EN. Fibroblast growth factor 23, cardiovascular disease risk factors, and phosphorus intake in the health professionals follow-up study. *Clin J Am Soc Nephrol* 2011;**6**(12):2871−8.
136. Oliveira RB, Cancela AL, Graciolli FG, et al. Early control of PTH and FGF-23 in normophosphatemic CKD patients: a new target in CKD-MBD therapy? *Clin J Am Soc Nephrol* 2010;**5**(2):286−91.
137. Yilmaz MI, Sonmez A, Saglam M, et al. Comparison of calcium acetate and sevelamer on vascular function and fibroblast growth factor 23 in CKD patients: a randomized clinical trial. *Am J Kidney Dis* 2012;**59**(2):177−85.
138. Isakova T, Barchi-Chung A, Enfield G, et al. Effects of dietary phosphate restriction and phosphate binders on FGF-23 levels in CKD. *Clin J Am Soc Nephrol* 2013;**8**(6):1009−18.
139. Fishbane S, Block GA, Loram L, et al. Effects of ferric citrate in patients with nondialysis-dependent CKD and iron deficiency anemia. *J Am Soc Nephrol* 2017;**28**(6):1851−8.
140. Moe SM, Chertow GM, Parfrey PS, et al. Cinacalcet, fibroblast growth factor-23, and cardiovascular disease in hemodialysis: the evaluation of cinacalcet HCl therapy to lower cardiovascular events (EVOLVE) trial. *Circulation* 2015;**132**(1):27−39.
141. Ix J, Isakova T, Larive B, et al. Nicotinamide and lanthanum carbonate on serum phosphate and fibroblast growth factor-23 in chronic kidney disease: the COMBINE trial. *J Am Soc Nephrol* 2019. in press.
142. Gavine PR, Mooney L, Kilgour E, et al. AZD4547: an orally bioavailable, potent, and selective inhibitor of the fibroblast growth factor receptor tyrosine kinase family. *Cancer Res* 2012; **72**(8):2045−56.
143. Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. *J Bone Miner Res* 2005;**20**(12):2105−15.
144. Ishani A, Blackwell T, Jamal SA, Cummings SR, Ensrud KE. The effect of raloxifene treatment in postmenopausal women with CKD. *J Am Soc Nephrol* 2008;**19**(7):1430−8.
145. Kendrick J, Chonchol MB. Nontraditional risk factors for cardiovascular disease in patients with chronic kidney disease. *Nat Clin Pract Nephrol* 2008;**4**(12):672−81.
146. Chonchol M, Scragg R. 25-Hydroxyvitamin D, insulin resistance, and kidney function in the Third National Health and Nutrition Examination Survey. *Kidney Int* 2007;**71**:134−9.
147. LaClair RE, Hellman RN, Karp SL, Kraus M, Ofner S, Li Q, Graves KL, Moe SM. Prevalence of calcidiol deficiency in CKD: a cross-sectional study across latitudes in the United States. *Am J Kidney Dis* 2005;**45**:1026−33.
148. Kramer H, Toto R, Peshock R, Cooper R, Victor R. Association between chronic kidney disease and coronary artery calcification: the Dallas Heart Study. *J Am Soc Nephrol* 2005;**16**:507−13.

QUESTIONS AND ANSWERS

Question 1

A 50-year-old man with stage 3b CKD (eGFR 44 mL/min per 1.73 m^2) presents for a biannual checkup. He is mildly obese (body mass index [BMI], 32 kg/m^2), with a medical history that shows a 5-year history of insulin-dependent type 2 diabetes (poorly controlled; hemoglobin A_{1c} [HbA_{1c}] 8.0%), and hypertension and hypercholesterolemia diagnosed 7 years previously. He is currently on an angiotensin converting enzyme inhibitor (ACEI) for hypertension (lisinopril 40 mg/day) and a statin (atorvastatin 40 mg/day) for hypercholesterolemia.

His BP is well controlled (120/85 mm Hg) and previous blood work shows a LDL cholesterol level of 120 mg/dL. Biochemical tests show the following: S[Ca] 8.9 mg/dL, S[P] 4.8 mg/dL, and serum iPTH 100 pg/mL. Which of the following is a nontraditional risk factor for the development of cardiovascular disease (CVD) in patients with CKD and diabetes?

A. Hypertension
B. Dyslipidemia
C. Disorders of mineral metabolism
D. Diabetes

Answer: C

Risk factors for the development of CVD in patients with CKD or ESRD may be either traditional or nontraditional. Traditional risk factors for CVD include hypertension, dyslipidemia, diabetes, and obesity, among others, all of which may or may not be present in patients with CKD. Patients with CKD are also prone to the development of vascular calcification or atherosclerosis that results from declining kidney function and disorders of mineral metabolism (a nontraditional risk factor) that may be in the causal pathway of arterial thickening and calcification. Evidence suggests that vascular calcification occurs as a result of abnormal mineral metabolism and the deposition of calcium phosphate complexes in soft tissues, blood vessels, the myocardium, and cardiac valves, which begins in early CKD. Patients with CKD are susceptible to the development of cardiovascular disease and vascular calcification, both of which can be caused by traditional and/or nontraditional risk factors. Disorders of mineral metabolism may play a major role in the development of CVD in patients with CKD.[17,145]

Question 2

According to KDIGO guidelines for the evaluation and management of patients with CKD, how often should monitoring of biochemical and blood mineralization levels be performed in stage 3 CKD patients?

A. Testing should only be performed at baseline without consideration of disease progression
B. S[Ca]/S[P] every 6–12 months and PTH based on baseline level and CKD progression
C. S[Ca] and S[P] every 3–6 months, and PTH every 6–12 months.
D. S[Ca]/S[P] every 1–3 months and PTH every 3–6 months

Answer: B

The KDIGO recommendations for monitoring biochemical and blood mineralization values, from initial injury to ESRD, reflect the recommendation for increased frequency of testing for patients whose stage of CKD progresses with declining renal function.[1] Current KDIGO guidelines recommend monitoring S[Ca], S[P], serum PTH level, and serum ALP beginning in CKD stage 3. Thereafter, for CKD stages 3–5, the frequency of monitoring S[Ca], S[P], and PTH should be based on the presence and magnitude of abnormalities and the rate of progression of CKD. In patients with stage 3 CKD, S[Ca] and S[P] should be tested every 6–12 months. Evaluation of PTH should be based on baseline level and rate of CKD progression.[1]

Question 3

A 65-year-old man with stage 4 CKD (eGFR 24 mL/min/1.73 m^2) presents to his nephrologist for a scheduled follow-up visit. The physician orders several laboratory tests to determine his S[Ca], S[P], iPTH, and 25-hydroxyvitamin D (25(OH)D) levels, and a test for bone-specific ALP. The results show some significant changes since his last visit, with his iPTH increasing from 75 pg/mL to 150 pg/mL and his S[Ca] decreasing from 9.4 mg/dL to 8.6 mg/dL. Serum vitamin D level is 15 ng/mL, S[P] is 4.6 mg/dL, and S[Cr] is 3.2 mg/dL. ALP is 152 IU/L. What mineralization test would you consider to justify intervention to normalize iPTH?

A. S[Ca]
B. 25-Hydroxy vitamin D [25(OH)D]
C. S[P]
D. S[Cr]
E. ALP

Answer: B

Sustained elevations in serum iPTH occur in response to declining renal function, impaired phosphate excretion, and an inability to activate vitamin D to calcitriol, the hormonally active form of vitamin D. Abnormalities of vitamin D metabolism play a significant role in the cascade of events leading to the development of sustained elevated levels of serum iPTH. In the body's attempt to maintain calcium homeostasis, there is an increase in the secretion of PTH to stimulate the

production of calcitriol, eventually leading to secondary hyperparathyroidism. In response to excessive levels of iPTH, there are further increases in S[P] and a vicious cycle ensues.

The goal of therapy in CKD is to reduce iPTH to normal levels, with an eventual return to homeostasis of all biochemical and blood minerals. Patients with CKD typically do not have changes in their S[Ca] and S[P], and only mild increases in serum iPTH. Therefore, testing for serum 25 (OH)D concentrations should be performed and replacement should be attempted with the objective of improving iPTH before initiating therapy with active form of vitamin D.[8,146] S[Cr] and levels of ALP are not indications for therapy.

Question 4

On a subsequent visit, the patient's S[P] has increased to 6 mg/dL. S[Ca] continues to fall, albeit slightly, and is now at 8.2 mg/dL. 25(OH)D level is 35 ng/mL after having started treatment with cholecalciferol 2000 IU/daily. Serum iPTH has also risen slightly, to 170 pg/mL. The patient remains at stage 4 CKD, with a stable GFR of 24 mL/min per 1.73 m^2.

Which of the following interventions would be an acceptable course of action in this patient based on the lab values obtained from his last two visits?

A. Decreased dietary intake of phosphorus and dietary consultation
B. Phosphate binders
C. Vitamin D sterols
D. Cinacalcet

Answer: A

Elevated S[P] levels may contribute to the development of vascular calcification through several mechanisms, which include osteochondrogenic phenotypic changes in vascular smooth muscle cells (VSMCs), phosphate-induced apoptosis of VSMC, phosphate inhibition of osteoclast differentiation, and Klotho deficiency.[17] KDIGO guidelines recommend that S[P] be maintained in the normal range in patients with CKD stages 3–5. However, the evidence that supports the use of calcium and noncalcium-based phosphate binders for the treatment of patients with elevated S[P] in patients with predialysis CKD is inconclusive.[23]

Question 5

A 66-year-old man is referred for evaluation and treatment of nephrotic syndrome. Laboratory evaluation reveals a GFR 42 mL/min/1.73 m^2, urinary protein excretion of 10 g/day, serum albumin 2 g/dL, intact parathyroid hormone level of 180 pg/mL, and a 25(OH)D level <10 ng/mL. Which one of the following statements is most accurate?

A. Vitamin D status is reflected by the serum levels of calcitriol and not 25(OH)D
B. 25(OH)D deficiency and insufficiency are highly prevalent in patients with CKD
C. Low levels of 25(OH)D are not associated with increased parathyroid hormone
D. Proteinuria does not contribute to vitamin D deficiency

Answer: B

It is being increasingly recognized that kidney disease, especially proteinuric kidney disease, is a risk factor for vitamin D insufficiency and deficiency. Increased levels of PTH are associated with the low levels of 25-hydroxyvitamin D. Current practice guidelines suggest that this should be corrected if PTH levels are elevated.[64,147]

Question 6

A 49-year-old woman is referred with stage 4 CKD that has been attributed to long-standing and poorly controlled hypertension. Her eGFR is 25 mL/min/1.73 m^2. In a previous echocardiogram, it was noted that her mitral valve was calcified. A kidney–ureter–bladder radiograph revealed aortic calcification. Which one of the following statements is most accurate?

A. Vascular calcification is always present with advanced CKD
B. Vascular calcification tends to be progressive
C. Vascular calcification is only seen in patients with diabetes and in patients who have prolonged periods of hyperphosphatemia
D. Vascular calcification would be expected to regress with control of secondary hyperparathyroidism

Answer: B

Vascular calcification in the setting of advanced CKD is virtually always progressive. In this case, the calcification is most likely medial calcification. Although common in patients with advanced CKD, it is not invariable. Vascular calcification is very common in patients with diabetic kidney disease. Efforts should be made to slow the progression of calcification by aggressive control of hyperphosphatemia, but it may occur in patients who have adequate control of S[P]. Vascular calcification typically does not regress with reduction in iPTH levels; in fact, patients with the low iPTH levels may be more prone to such calcification.[148]

CHAPTER

63

Drug Metabolism in Chronic Kidney Disease

Bradley L. Urquhart[a], *Thomas D. Nolin*[b]

[a]Department of Physiology and Pharmacology and Division of Nephrology, Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada; [b]Center for Clinical Pharmaceutical Sciences, Department of Pharmacy and Therapeutics and Department of Medicine Renal Electrolyte Division, University of Pittsburgh Schools of Pharmacy and Medicine, Pittsburgh, PA, United States

Abstract

Patients with chronic kidney disease (CKD), which is typically accompanied by several comorbid conditions, require multiple medications on a daily basis to treat their underlying disease. Decreased renal excretion of drugs is a well-documented consequence of CKD. In addition, there now is abundant evidence indicating that the function of drug metabolizing enzymes and transporters, which collectively determine net nonrenal drug clearance, is differentially altered in CKD. Basic principles of drug metabolism and transport are reviewed and discussed in the context of drug therapy in patients with CKD. Evidence is presented from preclinical to clinical studies, and important clinical examples are highlighted.

SCOPE OF THE PROBLEM

The prevalence of chronic kidney disease (CKD) in adults between 2011 and 2014 was 14.8% of the US population, and at the end of 2015 there were over 700,000 patients with end-stage renal disease (ESRD).[1] The number of patients progressing to ESRD continues to rise by approximately 20,000 cases per year, and there are now over 1 million patients globally that have ESRD and are treated with renal replacement therapies such as dialysis.[2] CKD is commonly accompanied by several comorbidities, including diabetes, hypertension, anemia, and cardiovascular disease. These comorbidities significantly increase the risk of serious events and decrease life expectancy. For example, the life expectancy at age 55 is reduced from 19.9 years with normal or slightly reduced kidney function to 5.6 years with severe CKD.[3] The increased risk of adverse events is at least partly mediated by decreased clearance of uremic toxins, molecules that accumulate in the blood of CKD patients as their kidney function declines.[4–6]

CKD patients are prescribed a disproportionately high number of medications to treat their underlying kidney disease and the large number of comorbidities. For example, ESRD patients treated with maintenance hemodialysis (HD) have a median daily pill burden of 19, with one quarter of patients exceeding 25 pills per day.[7] Collectively, HD patients take an average of 12 different medications in an attempt to control their various comorbidities.[8] A consequence of both their CKD and large pill burden is heightened risk for adverse drug events. This is highlighted by a report that indicates there is one medication-related problem for every 2.7 medication exposures in maintenance HD patients.[9] Dosing of medications in CKD continues to be a challenge, with rates of inappropriate dosing reported to be as high as 68 per 100 prescriptions for antibiotics.[10]

Changes in the pharmacokinetics of many drugs induced by kidney disease further complicates pharmacotherapy in CKD. The kidney is the primary organ responsible for drug excretion so it is not surprising that decreased kidney function decreases the excretion of many drugs. Drugs are typically designed and tested for use in healthy patients with normal kidney function with minimal to no testing in patients with impaired kidney function. Traditional strategies for prescribing drugs in CKD patients include selection of medications that exhibit minimal to no renal excretion under the premise that they may be administered in normal unadjusted doses, or using nomograms or equations to adjust the dosing of drugs that are excreted by the kidney. The revised Food and Drug Administration (FDA) guidance for industry on pharmacokinetics in patients with impaired kidney function highlights the need for

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00063-2

pharmacokinetic studies in CKD patients.[11] An additional important consideration is the impact of dialysis on drug clearance and pharmacokinetics. It is clear that dialysis does not replace the functioning kidney as several highly protein bound substrates removed *via* renal tubular secretion are inefficiently removed by dialysis, and dialytic clearance can vary substantially among drugs from within the same class.[12]

In addition to directly impacting renal drug clearance, CKD has pronounced effects on nonrenal clearance of drugs. Nonrenal drug clearance comprises hepatic and extrahepatic metabolism (collectively metabolic clearance) and drug transport. The nonrenal clearance of many drugs is altered in patients with impaired kidney function, often translating into clinically relevant changes in systemic exposure (Table 63.1). Hepatic metabolism and transport are the largest contributors to nonrenal drug clearance, although other organs such as the intestine, heart, and lung contribute to varying degrees. Changes in hepatic metabolism induced by CKD are especially important to consider because approximately 73% of drugs undergo metabolism prior to being eliminated.[13] Similarly, hepatic transporters are essential for delivering substrate drugs to the liver for subsequent metabolism and/or transporter-mediated biliary excretion. The objective of this chapter is to highlight CKD-mediated changes to drug metabolism and transport and to discuss the implications of these changes on the pharmacokinetics of drugs in CKD patients. Several excellent review articles have also addressed this area.[14–26]

TABLE 63.1 Selected Drugs With Evidence of Altered Nonrenal Clearance in Humans With Chronic Kidney Disease

Acyclovir	Ciprofloxacin	Ketorolac	Propoxyphene
Alfuzosin	Cyclophosphamide	Lanthanum	Propranolol
Aliskiren	Darifenacin	Lidocaine	Quinapril
Aprepitant	Desmethyldiazepam	Lomefloxacin	Raloxifene
Aztreonam	Dextromethorphan	Losartan	Ranolazine
Bufurolol	Diacerein	Lovastatin	Reboxetine
Bupropion	Didanosine	Metoclopromide	Repaglinide
Captopril	Dihydrocodeine	Metoprolol	Rosuvastatin
Carvedilol	Doxorubicin	Midazolam	Roxithromycin
Caspofungin	Duloxetine	Minoxidil	Sildenafil
Cefepime	Encainide	Morphine	Simvastatin
Cefmenoxime	Eprosartan	Moxalactam	Solifenacin
Cefmetazole	Erythromycin	Naltrexone	Sparfloxacin
Cefonicid	Felbamate	Nebivolol	Tacrolimus
Cefotaxime	Fexofenadine	Nefopam	Tadalafil
Cefsulodin	Fluorouracil	Nicardipine	Telithromycin
Ceftibuten	Fluvastatin	Nimodipine	Valsartan
Ceftizoxime	Guanadrel	Nitrendipine	Vancomycin
Ceftriaxone	Idarubicin	Nortriptyline	Vardenafil
Cerivastatin	Imatinib	Oxcarbazepine	Verapamil
Cibenzoline	Imipenem	Oxprenolol	Warfarin
Cilastatin	Isoniazid	Paroxetine	Zidovudine
Cimetidine	Ketoprofen	Procainamide	

Adapted in part from references 24, 26, and 90.

DRUG METABOLISM AND TRANSPORT

The majority of medications are xenobiotics, or substances foreign to the human body. Organs such as the liver, intestine, kidney, and lung have evolved a complex network of enzymes and transporters that facilitate systemic exposure and elimination of xenobiotics from the body. Drug-metabolizing enzymes are classified into phase 1 (oxidation, reduction, hydrolysis) or phase 2 (conjugation) reactions (see Figure 63.1). Drug-metabolizing enzymes usually convert lipophilic drugs into more polar metabolites to facilitate their excretion.

Drug transporters are expressed on cell membranes and mediate the uptake and efflux of drugs (Figure 63.1). The most important uptake transporters that impact drug disposition are the solute carrier (SLC) transporters. SLC transporters are typically facilitated transporters and ion-coupled secondary active transporters. There are 43 known SLC families and approximately 300 SLC transporters, many of which are determinants of drug absorption and disposition.[27] Similarly, the ATP-binding cassette (ABC) family of transporters is the most relevant efflux transporter family for drug disposition. ABC transporters are largely primary active transporters that use ATP hydrolysis as an energy source to pump substrates out of cells, often against a concentration gradient. There are 49 known ABC genes and 7 families of ABC transporters.[27]

Collectively, drug-metabolizing enzymes and transporters are key mediators of both renal and nonrenal drug clearance and act in a concerted manner to determine the pharmacokinetics of drugs. A change in the expression or activity of drug metabolizing enzymes or transporters can profoundly alter the pharmacokinetics of substrate drugs. The interplay between drug metabolizing enzymes and drug transporters is demonstrated in Figure 63.1.

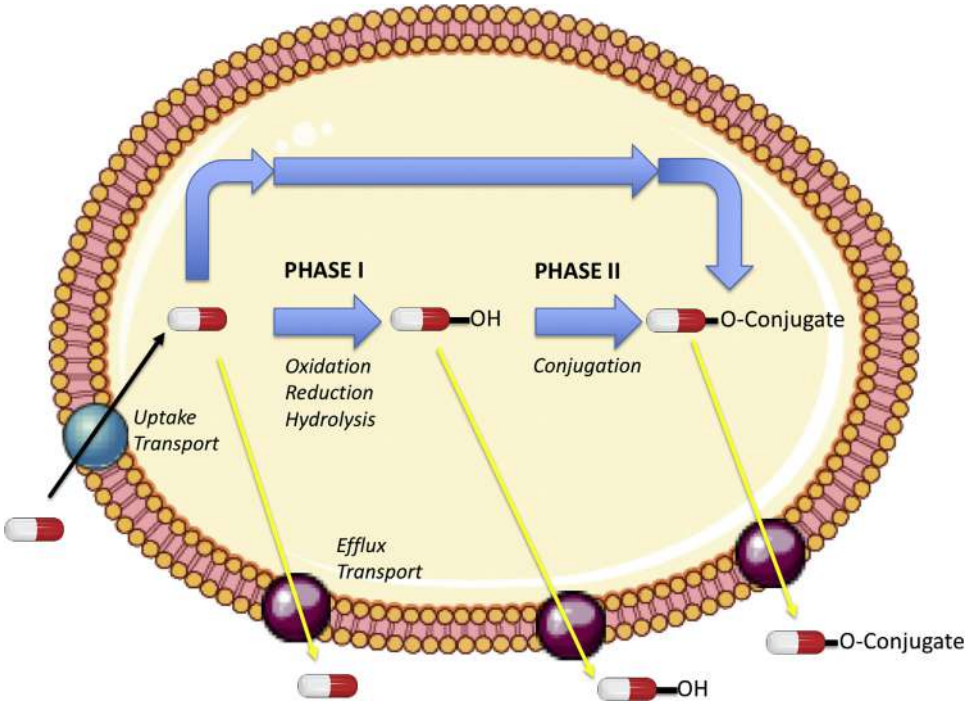


FIGURE 63.1 **The interplay between drug metabolism and transport.** Drugs may enter the cell by passive diffusion (not shown) or *via* an uptake transporter (depicted by *blue sphere*). Once inside the cell, the drug may be 1) removed from the cell by an efflux transporter (*purple sphere*) or metabolized by phase I (oxidation, reduction, hydrolysis) or phase II (conjugation) drug-metabolizing enzymes. Although drugs are typically metabolized first by phase I enzymes prior to phase II metabolism, some drugs are directly metabolized by phase II enzymes. Metabolites (phase I or II) may also be subject to efflux from the cell. *Images used to generate this figure were modified from Servier Medical Art, licensed under Creative Commons Attribution 3.0 Generic License, http://smart.servier.com/.*

DRUG METABOLISM IN PRECLINICAL MODELS OF CKD

The earliest reports of altered drug metabolism in CKD were published in the 1970s and 1980s in experimental (mostly rat) models of CKD.[28–31] These pioneering studies used probes of global cytochrome P450 activity (i.e. substrates metabolized by multiple enzymes), such as aminopyrine, acetanilide, and *p*-nitroanisol. Experimental kidney disease was typically induced in these studies by a 5/6 nephrectomy. In this procedure, 2/3 of the kidney mass is surgically resected and one week later a complete nephrectomy is performed, resulting in only 1/6 of the total kidney mass remaining. Although the remaining kidney mass undergoes hyperfiltration in an attempt to compensate for the nephron loss, the animals ultimately experience kidney disease as evidenced by increases in serum creatinine concentration (S[Cr]) and blood urea nitrogen (BUN). These early preclinical studies demonstrated a 32% reduction in total cytochrome P450 (CYP) content in CKD animals along with a 35%, 37%, and 31% decrease in the CYP-mediated metabolism of aminopyrine, *p*-nitroanisol, and acetanilide, respectively,[31] substrates that are broad probes of CYP enzymes. For example, antipyrine is metabolized by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C18, and CYP3A4 in humans.[32] Accordingly, these studies suggested that hepatic drug metabolism is decreased in CKD but provided little information on the specific pathways that are altered by kidney disease.

Subsequent research focused on delineating the specific metabolic pathways altered in CKD. Uchida and colleagues used a 5/6 nephrectomy model to evaluate the effect of CKD on hepatic drug-metabolizing enzymes.[33] A negative correlation between BUN and cytochrome P450 content as well as multiple hepatic specific activities (e.g. aminopyrine demethylase and δ-aminolevulinic acid synthetase) was observed. In addition, hepatic Cyp2c6, Cyp2c11, and Cyp3a2 were downregulated in CKD (note lower case letters in Cyps represent rodent). Leblond, Pichette, and colleagues, who systematically investigated the effect of CKD on drug metabolism in elegant studies that spanned over a decade,[34–40] demonstrated that total hepatic CYP content was negatively correlated with creatinine clearance. Although there was no change in the activity of Cyp1a or Cyp2d enzymes, a pronounced decrease in the mRNA and protein expression of Cyp2c11, Cyp3a1 (Cyp3a23), and Cyp3a2 in the 5/6

nephrectomy rat model was shown.[39] Collectively, these represent the rat orthologs of human CYP2C9 and CYP3A4, respectively. The *in vivo* relevance of these observations was also reported. Specifically, a caffeine breath test (Cyp1a probe) revealed no change in Cyp1a metabolic activity in CKD animals *in vivo* compared to controls, confirming *ex vivo* observations.[40] Similarly, *in vivo* breath tests for aminopyrine (Cyp2c11 probe) and erythromycin (Cyp3a probe) revealed a 35% decrease in the activities of Cyp2c11 and Cyp3a in CKD animals compared to controls, again confirming *ex vivo* microsomal studies.

Although this collection of work clearly indicates hepatic drug metabolism is significantly impaired in severe kidney disease induced by 5/6 nephrectomy, it raised the question of whether drug metabolism is impacted in earlier stages of disease. Velenosi and colleagues used a modified surgical/vessel ligation technique to generate a model of moderate kidney impairment[41] that demonstrated even moderate kidney disease (1.7-fold increase in S[Cr]) was able to induce a greater than 60% decrease in Cyp2c11 and Cyp3a2 mRNA and protein expression. In addition, the catalytic activity of midazolam (Cyp3a) and testosterone (Cyp2c11 and Cyp3a) were significantly decreased in both moderate and severe kidney disease. There was an exponential decline in hepatic drug metabolizing enzyme activity as kidney disease progressed, suggesting that a small change in kidney function has a profound impact on drug metabolism.[41] The dietary adenine model of CKD, which has gained popularity as it provides less variability in degree of kidney disease,[42] has also been used to study the impact of CKD on drug metabolism. Similar to the 5/6 nephrectomy model, adenine-induced CKD causes a pronounced decrease in hepatic Cyp2c11 and Cyp3a2 expression and activity in rats, but no significant differences in hepatic Cyp1a or Cyp2d.[43]

CKD also elicits changes in extra-hepatic drug metabolism. Although the liver is the body's primary metabolic organ, substantial drug metabolism occurs in both intestinal enterocytes and renal tubular cells. Expression of Cyp1a1 and Cyp3a2 mRNA and protein are significantly downregulated in rats with CKD.[44] Moreover, enzymatic activity assays using ethoxyresorufin O-dealkylation (Cyp1a) and erythromycin demethylation (Cyp3a) confirm that Cyp1a and Cyp3a activity is decreased. These changes suggest that altered intestinal drug metabolism in CKD may impact the bioavailability of drugs. Cytochrome P450 expression was also evaluated in the remnant kidney from rats that underwent 5/6 subtotal nephrectomy.[45] In contrast to liver and intestine, there was no change in renal Cyp3a2, but Cyp1a1 was significantly downregulated in CKD compared to control.[44]

Although cytochrome P450s are the most widely studied phase I drug metabolizing enzymes, hepatic reductases are also important phase I drug metabolizing enzymes relevant to drug disposition. One of the most important and widely used drugs impacted by hepatic drug reduction is the anticoagulant warfarin, which is used extensively in patients with CKD. In addition to CYP-mediated phase I metabolism, the acetonyl functional group of warfarin is reduced by hepatic reductases to form warfarin alcohols. The reduction of warfarin generates a second chiral center, such that two diastereoisomers of warfarin alcohols may be generated: warfarin alcohol 1 (*RS/SR*) and warfarin alcohol 2 (*RR/SS*). Warfarin reduction is mediated by the cytosolic enzymes carbonyl reductase 1 (CBR1) and aldo-keto reductase family 1 member C3 (AKR1C3) and by the microsomal enzyme 11 β-hydroxysteroid dehydrogenase 1 (11 β-HSD1). Alshogran and colleagues used the 5/6 nephrectomy model of CKD to evaluate the expression and activity of hepatic reductase enzymes,[46] and demonstrated that the mRNA expression of CBR1, AKR1C3, and 11 β-HSD1 were downregulated by 34%, 93%, and 35%, respectively, in CKD compared to controls. Similarly, protein expression of CBR1, AKR1C18 (encoded by the AKR1C3 gene), and 11 β-HSD1 were downregulated by 43%, 76%, and 70% in CKD compared to controls, respectively. The downregulation of these reductases resulted in a 39% decreased formation of warfarin alcohol 1 in the cytosol and a 43% decrease in microsomes from CKD rats compared to sham controls.

Phase II drug-metabolizing enzymes serve to conjugate drugs, typically by adding endogenous substances such as glutathione, sulfate, glycine, or glucuronic acid that make the parent drug more polar and/or less toxic (Figure 63.1). The predominant phase II drug-metabolizing enzymes include acetylation (by N-acetyltransferases; NAT), glucuronidation (by uridine 5′-diphospho glucuronosyltransferases; UGT), methylation (by thiopurine methyltransferases; TPMT), and conjugation with glutathione (glutathione S-transferases; GST). Although the 5/6 nephrectomy model of CKD shows no difference in expression or activity in the major UGT enzymes,[47] pronounced differences in hepatic acetylation have been described in this model.[48] Specifically, a 33% and 50% decrease in Nat1 and Nat2 expression, respectively, is apparent in CKD rats compared to controls. In addition, there is a 50% reduction in Nat2-mediated acetylation of *p*-aminobenzoic acid in CKD rat liver cytosol compared to controls.

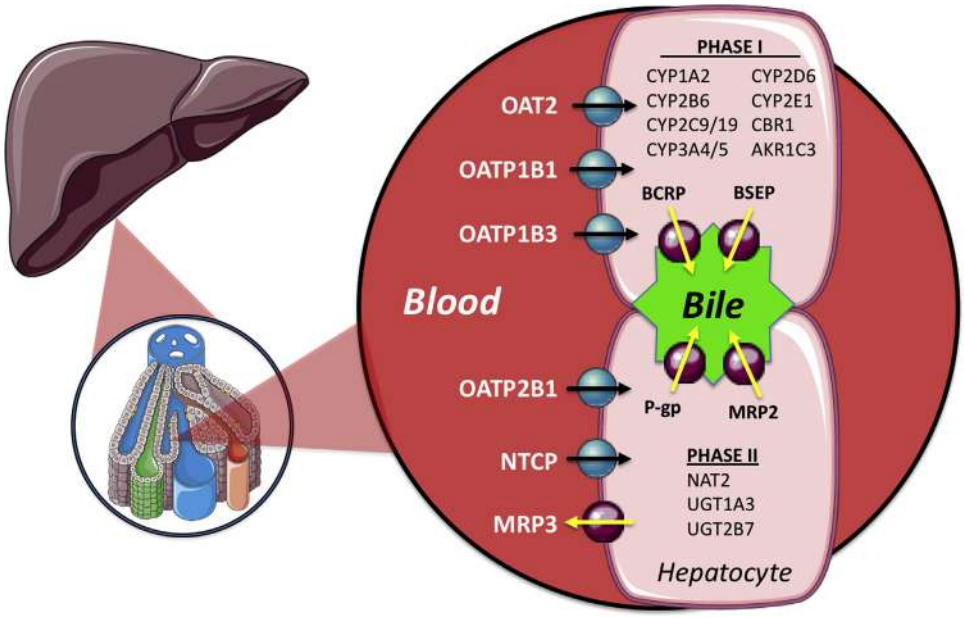


FIGURE 63.2 **Hepatic drug metabolism and transport pathways.** Hepatic sinusoids within the liver connect the portal and hepatic circulation and facilitate the formation of bile. The hepatocytes are the primary functional cells in the liver. In the context of drug therapy, drug can be taken up in hepatocytes by uptake transporters (*blue spheres*). Once within the cell, drugs can be metabolized by phase I (e.g. CYPs) or phase II drug-metabolizing enzymes. Parent drug or metabolite may be removed from the hepatocyte into the blood or excreted into the bile *via* efflux transporters (*purple sphere*). Representative transporters and enzymes are shown for reference. Note this is not a complete list. *Images used to generate this figure were modified from Servier Medical Art, licensed under Creative Commons Attribution 3.0 Generic License, http://smart.servier.com/.*

DRUG METABOLISM IN HUMANS WITH CKD

The impact of CKD on drug metabolism in humans is complex, largely owing to the multiple enzymes that metabolize drugs and the complex interplay between drug-metabolizing enzymes and drug transporters (Figure 63.1). The most common approach to assessing drug metabolism in patients with kidney disease is to evaluate the pharmacokinetic parameter clearance (CL). Clearance is the volume of blood (or plasma) from which a substance is removed per unit time. Oral drug clearance is calculated as:

$$CL_{oral} = CL/F = dose * F/AUC$$

where F = bioavailability and AUC = the area under the plasma concentration time curve. In general, oral drug clearance can be considered the sum of renal clearance, hepatic clearance, and clearance from other routes as follows:

$$CL_{oral} = CL_{renal} + CL_{hepatic} + CL_{other}$$

For highly metabolized drugs with a fractional excretion less than 10%, a change in oral clearance is typically assumed to be a change in hepatic clearance because the drug is minimally excreted in the urine and usually other clearance routes (e.g. respiratory and sweat) contribute minimally to total oral clearance. This is commonly termed nonrenal clearance (CL_{NR}) and refers to clearance by all routes other than the kidney. As described above, multiple enzymes metabolize many drugs and many are also subjected to hepatic transport (Figure 63.2). For these reasons, it is often difficult to link changes in clearance to a specific pathway (e.g. a specific cytochrome P450 isozyme). Fortunately, there are a number of fairly specific probe substrates that have been characterized that allow direct phenotypic characterization of specific metabolic pathways. These include bupropion (CYP2B6), warfarin (CYP2C9), mephenytoin (CYP2C19), sparteine (CYP2D6), midazolam (CYP3A4), and chlorzoxazone (CYP2E1). The function of several cytochrome P450 enzymes has been studied in humans with CKD using these and other probe substrates and is summarized in Table 63.2.

CYP2B6

CYP2B6 is highly expressed in human liver and metabolizes several antidepressants, anticonvulsants, and chemotherapeutic agents. The antidepressant bupropion is extensively metabolized by CYP2B6 and is the most widely used probe of this CYP isozyme. In an open-label pharmacokinetic study, healthy controls and CKD patients (mean eGFR 30.9 mL/min/1.73 m^2) were given a single 150 mg oral dose of sustained release

TABLE 63.2 Impact of Chronic Kidney Disease (CKD) on Drug Metabolizing Enzymes in Humans

Enzyme	Probe	Effect of CKD	Interpretation
CYP2B6	Bupropion	↑AUC, ↓CL/F	↓ activity in CKD
CYP2C9	Warfarin	↓*S/R* warfarin ratio	↓ activity in CKD
CYP2C19	Mephenytoin	=AUC, =CL/F	No Change in CKD
CYP2D6	Sparteine	Unclear	= or ↓ activity in CKD
	Dextromethorphan	Unclear	= or ↓ activity in CKD
	Nebivolol	↑AUC, ↓CL/F	↓ activity in CKD
CYP2E1	Chlorzoxazone	= CL	No Change in CKD
CYP3A4	Erythromycin	↓Breath test	↓ activity in CKD*
		↓CL	↓ activity in CKD*
	Midazolam		
	Oral	= AUC, CL/F	No change in CKD
	IV	↑AUC, ↓CL/F, =t1/2	No change in CKD or modest ↓
CBR1 & AKR1C3	Doxorubicin	↑AUC, ↓CL	↓ activity in CKD
	Idarubicin	↑AUC, ↓CL	↓ activity in CKD
NAT2	Isoniazid	↓CL	↓ activity in CKD
UGT1A3 & UGT2B7	Morphine	↑AUC, ↓CL	↓ activity in CKD

** Also extensively transported so unclear if changes are related to altered transport, metabolism, or both.*

bupropion. CKD patients had a 126% increase in the AUC and a 63% decrease in CL/F.[49] In a different study, patients with biopsy confirmed glomerular disease (lupus nephritis or antineutrophil associated [ANCA] vasculitis) received a single oral 150 mg dose of sustained release bupropion.[50] Patients with glomerular disease had a twofold increase in bupropion AUC and CL/F was approximately half compared to subjects without glomerular disease. Collectively, these two studies suggest that CYP2B6 activity is decreased in patients with kidney disease.

CYP2C9

CYP2C9 is highly expressed in human liver and is responsible for the metabolism of approximately 13% of the most commonly prescribed drugs.[13] Warfarin is an anticoagulant drug used to prevent blood clot formation and migration. Warfarin is a widely used medication in CKD patients for treatment of atrial fibrillation, embolism, and thrombosis and acts by inhibiting vitamin K reduction. It is a racemic mixture of two active enantiomers. The two enantiomers are differentially metabolized by hepatic CYP enzymes. Although *R*-warfarin is metabolized by multiple CYPs including CYP1A1, CYP1A2, and CYP3A4, *S*-warfarin is primarily metabolized by CYP2C9 into multiple hydroxylated metabolites. The ratio of *S*-warfarin to *R*-warfarin is used as a probe of CYP2C9 activity in patients. The *S/R*-warfarin ratio is increased by 51% in ESRD patients compared to controls, suggesting that hepatic CYP2C9 activity is decreased in kidney disease.[51] This finding is consistent with decreased hepatic expression and activity of rat CYP2C11 (generally considered the rat ortholog of human CYP2C9) in CKD.[39–41,43]

CYP2C19

Mephenytoin is a hydantoin-derivative anticonvulsant agent that is typically used to treat partial seizures in patients resistant to less-toxic drugs. It is supplied as a racemic mixture of the enantiomers *R*-mephenytoin and *S*-mephenytoin. Similar to warfarin, mephenytoin is subject to stereoselective metabolism, with *S*-mephenytoin being hydroxylated to 4-hydroxymephenytoin by CYP2C19, whereas *R*-mephenytoin is slowly demethylated. Accordingly, mephenytoin has been used as an *in vivo* probe of CYP2C19 activity by measuring the formation clearance of the CYP2C19 specific metabolite 4-hydroxymephenytoin. Mephenytoin was administered as a single oral dose to patients with varying degrees of CKD and pharmacokinetic parameters assessed.[52]

No difference in the area under the curve of *S*-mephenytoin or the formation clearance of the 4-hydroxymephenytoin metabolite suggests that CYP2C19 activity is not different in patients with CKD.

CYP2D6

CYP2D6 is one of the most abundantly expressed hepatic cytochrome P450 enzymes. It metabolizes approximately 20% of the most commonly prescribed medications.[13] The *CYP2D6* gene is highly polymorphic, and many genetic variations (e.g. single nucleotide polymorphisms, gene insertions, gene deletions) are known to affect metabolism. However, discrepant findings pertaining to the effect of CKD on CYP2D6-mediated metabolism have been reported. Sparteine is a sodium-channel blocker and class 1a antiarrhythmic agent used as an *in vivo* probe of CYP2D6. It is metabolized by CYP2D6 into the metabolites 2-dehydrosparteine and 5-dehydrosparteine. Dextromethorphan is a widely used antitussive agent that has also been used as an *in vivo* probe of CYP2D6. It is metabolized by CYP2D6 into dextrorphan, an active metabolite. CYP2D6 activity was assessed in 12 CKD patients and 12 healthy controls by administering 100 mg of sparteine and 40 mg of dextromethorphan on separate days. The initial interpretation of the study suggested that CYP2D6 activity was not altered by kidney disease.[53] These data were subsequently reanalyzed using kinetic modeling, and the authors found that CYP2D6 activity was decreased in CKD.[54] There is other support for decreased CYP2D6 in kidney disease. Other studies evaluating the effect of kidney disease have assessed the pharmacokinetics of metoprolol and paroxetine, both drugs that are highly metabolized by CYP2D6.[55–57] These studies also show an increasing trend in plasma area under the curve, suggesting CYP2D6 activity is decreased. A more recent study investigated the effect of CKD and HD on nebivolol pharmacokinetics.[58] Nebivolol is a beta blocker supplied as a racemic mixture of the enantiomers d-nebivolol and l-nebivolol and is metabolized by CYP2D6-mediated hydroxylation and glucuronidation. The area under the curve of both nebivolol enantiomers is increased in CKD patients compared to controls, and this is accompanied by a decrease in the CL/F.[58] Interestingly, ESRD patients treated with HD have no change in AUC or CL/F compared to controls. Collectively, these data suggest that CYP2D6 activity is decreased in CKD and that HD restores CYP2D6 activity, potentially by removing uremic inhibitors of metabolism. The most convincing evidence of altered CYP2D6-mediated metabolism in CKD is from an FDA analysis that systematically and quantitatively evaluated the pharmacokinetics of numerous CYP2D6 substrates reported in CKD studies.[59] This work demonstrated a decrease in CYP2D6-mediated clearance and that drug clearance decreases as kidney disease progresses.

CYP2E1

CYP2E1 metabolizes less than 5% of the most highly prescribed drugs[13] but plays an important role in determining drug toxicity. Chlorzoxazone is a centrally acting muscle relaxant with sedative properties and is hydroxylated by CYP2E1 to form 6-hydroxychlorzoxazone. The formation clearance of 6-hydroxychlorzoxazone is commonly used as a marker of CYP2E1 metabolic activity. Chlorzoxazone was administered to patients with varying levels of kidney function to assess CYP2E1 activity.[60] There was no difference in 6-hydroxychlorzoxazone formation clearance between patients, indicating that CYP2E1 activity is not affected by CKD.

CYP3A4

CYP3A4, the most abundantly expressed human CYP, metabolizes between 30% and 50% of marketed drugs.[61] Similar to CYP2D6, the effect of CKD on CYP3A4 expression and activity is unclear. Although there are many preclinical studies that demonstrate CYP3A expression and activity are decreased in experimental models of CKD, the results of clinical pharmacokinetic studies in humans are less clear and highly variable.

The macrolide antibiotic drug erythromycin has been used extensively as a probe substrate to evaluate CYP3A4 activity *in vivo*. The erythromycin breath test was developed to facilitate a relatively noninvasive method to probe CYP3A4 activity in patients. In the erythromycin breath test, patients are given ^{14}C-erythromycin, which is demethylated by CYP3A4. The demethylated carbon then appears in the breath as $^{14}CO_2$, which was presumed to be a surrogate of CYP3A4 activity. Decreased $^{14}CO_2$ excretion in breath was interpreted as a decrease in CYP3A4 and conversely, increased breath $^{14}CO_2$ was interpreted as increased CYP3A4 activity. Multiple studies used this approach to study CYP3A4 activity in CKD patients.[62,63] $^{14}CO_2$ excretion was decreased by 28% in ESRD patients compared to controls, suggesting CYP3A4 activity is decreased in this population.[62] Interestingly, $^{14}CO_2$ excretion is increased by 27% immediately following HD, suggesting that HD acutely restores CYP3A4 activity.[63] Oral and intravenous pharmacokinetics of erythromycin was simultaneously assessed in control and ESRD patients. ESRD patients exhibited decreased hepatic clearance of erythromycin.[64] Collectively, findings of these studies were interpreted on the basis of

CYP3A4 alone, and all studies reported decreased CYP3A4 activity in kidney disease, based on the premise that erythromycin clearance is primarily mediated by CYP3A4.[62–64] It is now known that erythromycin is not a specific probe of CYP3A4. In fact, the drug exhibits overlapping substrate specificity, as it is a substrate of CYP3A4 as well as organic anion transporting polypeptides (OATPs) and P-glycoprotein (P-gp) transporters.[65,66] Therefore, although erythromycin pharmacokinetics is altered in CKD, it is unlikely to be due exclusively to altered CYP3A4-mediated metabolism.

Another widely used *in vivo* probe of CYP3A4 activity is the short-acting benzodiazepine midazolam. In contrast to erythromycin, midazolam is not a substrate for any uptake (e.g. OATP) or efflux (e.g. P-gp, BCRP) transporters. Plasma concentration time curves of midazolam and the CYP3A4-mediated metabolite 1-OH midazolam are nearly superimposable in ESRD and control patients after oral administration, with no differences in AUC or CL/F, suggesting that CYP3A4 is not altered in kidney disease.[67] However, in contrast to oral midazolam, ESRD patients treated with HD who received IV midazolam had a fivefold increase in AUC and a 65% decrease in clearance compared to control.[68] This difference was not observed in ESRD patients treated with peritoneal dialysis (PD). Although this study demonstrates decreased clearance of midazolam and suggests that hepatic CYP3A4 activity is decreased in CKD, it is surprising that midazolam half-life was not different between ESRD and control patients.

The complexity of the impact of CKD on nonrenal clearance has been highlighted by FDA investigators who assessed the impact of CKD on the systemic exposure of several new drugs.[69] Some CYP3A4 substrates required dosage adjustment in CKD while others did not.[69] For example, tadalafil is extensively metabolized by CYP3A4 and minimally eliminated by the kidney (fractional excretion <0.3%). ESRD patients taking tadalafil have a twofold increase in the maximal plasma concentration and a 2.7–4.1-fold increase in the AUC compared to controls. Accordingly, a reduction in dose is recommended for ESRD patients.[69] Solifenacin has a fractional excretion of 15% and is extensively metabolized by CYP3A4. In CKD, solifenacin maximal plasma concentration, AUC, and half-life are increased by 1.2-, 2.1-, and 1.6-fold, respectively, and dose reduction is recommended in CKD.[69] Conversely, alfuzosin and vardenafil are CYP3A4 substrates and are minimally excreted in the urine but demonstrate only modest increases in maximal plasma concentration and AUC. There are no recommendations for altered dosing for alfuzosin and vardenafil in CKD.[69] Further analysis of 18 different CYP3A4/5 model drugs in 24 different studies to evaluate the systemic and quantitative effect of CKD on CYP3A4/5 provided additional insight.[59] Although CYP2D6 model drugs demonstrate a consistent decrease in clearance in CKD patients, CYP3A4/5 model drugs exhibit variable responses, with no clear relationship between kidney function and changes in drug clearance. For the CYP3A4/5 model drugs that exhibited decreased clearance, the magnitude of change was modest.

Collectively, clinical pharmacokinetic studies in humans suggest that CYP3A4/5 may be modestly decreased or not changed in CKD patients. There does not appear to be consistency among model drug substrates, which likely points to some nonspecificity of probes (e.g. substrate of multiple CYPs or transporters) and the relatively minimal impact of CKD on hepatic CYP3A4.

Hepatic Reductases

Multiple drugs that undergo hepatic reduction exhibit altered pharmacokinetics in patients with kidney disease, suggesting that this pathway of nonrenal clearance involved. Two of the best-studied examples include the anthracyclines doxorubicin and idarubicin, which undergo hepatic reduction to doxorubicinol and idarubicinol, respectively. Following a 40–60 mg IV infusion of doxorubicin, HD patients had a 71% increase in AUC and a corresponding 41% decrease in total clearance compared to controls with normal kidney function.[70] The altered doxorubicin clearance was a result of decreased doxorubicinol formation. Doxorubicin is metabolized by the hepatic reductases CBR1 and AKR1C3, so the altered pharmacokinetics is likely a result of decreased activity of these hepatic reductases. Idarubicin pharmacokinetics was studied in patients with impaired kidney function following a single 12 mg/m^2 dose.[71] Patients with a creatinine clearance less than 60 mL/min had a 38% increase in idarubicin AUC and a 30% decrease in total clearance.

Ex vivo studies using cytosolic and microsomal fractions from cadaveric liver samples obtained from ESRD and control patients have investigated the effect of CKD on hepatic reductase expression and activity.[72] Western blotting demonstrated a 65% decreased protein expression of carbonyl reductase 1 in CKD livers, and a trend toward decreased mRNA expression was observed. These data may partially explain the altered pharmacokinetics of substrate drugs such as warfarin, doxorubicin, and idarubicin in CKD patients.

NAT2

Although less commonly studied, there is evidence for altered phase II drug-metabolizing enzymes such as NAT2 in patients with kidney disease. The

prototypical probe drug for NAT2 activity *in vivo* is isoniazid, an antibacterial agent used to treat tuberculosis. Isoniazid is most commonly used to classify patients as rapid or slow acetylators based on their NAT2 genotype. NAT2 activity was determined in rapid and slow acetylator ESRD patients prior to and following kidney transplantation.[73] The nonrenal clearance of isoniazid improved by over 50% in rapid acetylators and 225% in slow acetylators following kidney transplantation. This suggests that NAT2 activity is decreased in kidney disease and that restoration of kidney function by transplantation improves NAT2 activity. A similar finding of decreased NAT2-mediated activity was found in CKD patients using the NAT substrate procainamide.[74]

UGTs

Morphine and other opioid analgesics undergo extensive glucuronidation with some of the resultant glucuronide metabolites lacking pharmacological activity (e.g. morphine 3-glucuronide), whereas others are pharmacologically active (e.g. morphine 6-glucuronide). Morphine pharmacokinetics are substantially altered in patients with CKD, as they have a significantly increased AUC and decreased clearance following standard dosing, compared to control subjects with normal kidney function.[75] Morphine is metabolized by UGT1A3 and UGT2B7. The increased AUC and decreased clearance suggest the activity of these enzymes may be impaired in CKD. Other drugs that are extensively metabolized *via* glucuronidation such as the NSAID diacerein[76] and the nucleoside reverse transcriptase inhibitor zidovudine[77] exhibit decreased nonrenal clearance in patients with CKD, supporting a decrease in UGT-mediated metabolism in kidney disease.

DRUG TRANSPORT IN PRECLINICAL MODELS OF CKD

Although the impact of drug metabolism to overall drug disposition has been known for decades, it was only recently that the importance of drug transporters to drug disposition and pharmacokinetics has been appreciated. Accordingly, our understanding of the impact of CKD on drug transporters has lagged behind that of drug-metabolizing enzymes.

The subtotal 5/6 nephrectomy used to study the impact of CKD on drug metabolism has also been employed to study drug transporters. Starting in the late 2000s, Naud, Leblond, Pichette, and colleagues used the 5/6 nephrectomy model to study the impact of CKD on transporter expression and activity.[45,78–80] At the level of the intestine, transporters play an essential role in determining the oral bioavailability of substrate drugs, with uptake transporters enhancing oral bioavailability and efflux transporters restricting drug absorption (Figure 63.3). Rats with experimental CKD (5/6 nephrectomy) had 65%, 60%, and 35% reductions in the intestinal protein expression of the efflux transporters P-gp, multidrug resistance–associated protein 2 (MRP2), and MRP3, respectively.[79] Surprisingly, the mRNA expression of these transporters was not different between CKD and control animals. Transport activity of P-gp and MRP2 transporters were assessed using everted gut sacs and the probe substrates rhodamine 123 for P-gp and 5-(and 6-) carboxy 2′,7′dichlorofluorescein for MRP2. CKD rats had a 30% reduction in P-gp activity and a 23% reduction in MRP2 activity compared to control. There were no significant differences in the expression of the uptake transporters Oatp2 or Oatp3. An additional study evaluated the effect of CKD in rats subjected to 5/6 nephrectomy. The investigators found no change in the mRNA expression of intestinal efflux transporters, but they were unable to assess protein expression or activity.[81] The likely implications of downregulated protein expression of P-gp, MRP2, and MRP3 in the setting of CKD is an increased bioavailability of substrate drugs.

Hepatic uptake and efflux transporters have also been evaluated in rats with CKD and sham control animals.[80] Protein expression of the uptake transporter Oatp2 was downregulated by 35% in CKD animals compared to control with no change in the mRNA expression. In contrast to intestinal efflux transporters, hepatic P-gp protein and mRNA expression were upregulated by 25% and 50%, respectively. Injection of the P-gp probe rhodamine 123 revealed an approximately 50% increased biliary clearance, which supports a functional increase in hepatic P-gp activity in CKD. Although surprising that CKD appears to cause opposite effects in terms of P-gp activity in intestine compared to liver, a recent study has shed light on these seemingly contrasting findings. Using a human hepatoma cell line (HepG2) and both the adenine and 5/6 nephrectomy models of CKD in mice, Machado and colleagues demonstrated that the uremic toxin indoxyl sulfate upregulates P-gp in the liver by acting as a ligand for the aryl hydrocarbon receptor (AhR).[82] Indoxyl sulfate is a gut-derived uremic toxin made from indole synthesized from gut bacteria. Although indole is made in the gut, it is oxidized and sulfated in the liver, potentially explaining hepatic P-gp specific upregulation.

Further studies have evaluated the effect of 5/6 nephrectomy in rats on kidney and brain transporters. Transporters expressed on the apical and basolateral membranes of kidney tubule cells have a profound impact on the secretion and reabsorption of drugs

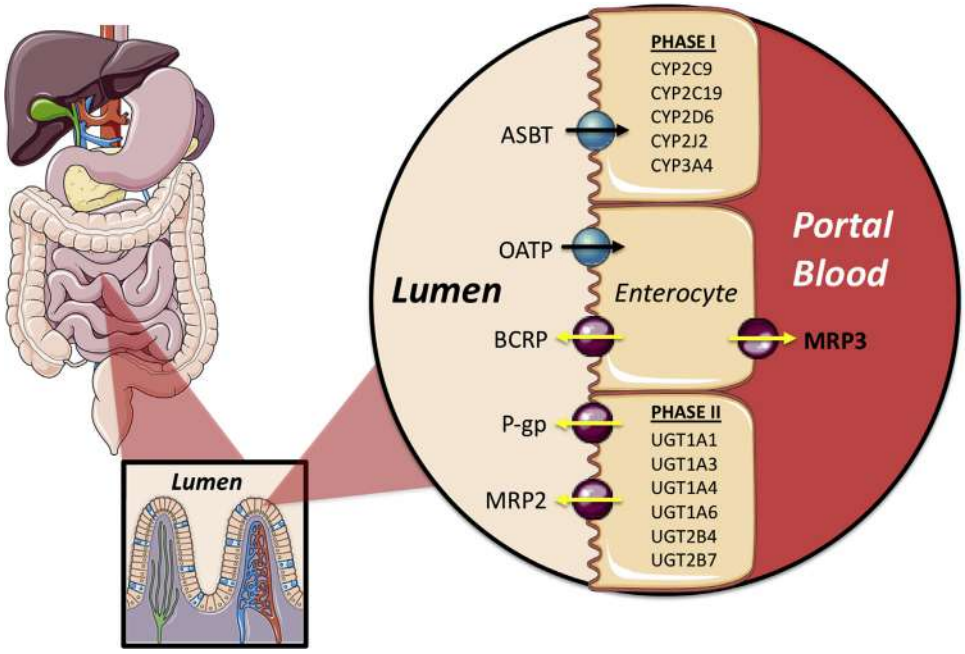


FIGURE 63.3 **Intestinal drug metabolism and transport pathways.** The majority of orally administered drugs are absorbed in the proximal intestine (duodenum and jejunum). These intestinal regions contain microvilli that increase the surface area for absorption. The apical membrane of intestinal enterocytes face the lumen of the intestine and have high expression of both uptake (*blue spheres*) and efflux (*purple spheres*) transporters. Enterocytes also express phase I and II drug-metabolizing enzymes and transporters on the basolateral membrane. Representative transporters and enzymes are shown for reference, note this is not a complete list. *Images used to generate this figure were modified from Servier Medical Art, licensed under Creative Commons Attribution 3.0 Generic License, http://smart.servier.com/.*

(Figure 63.4). In CKD rats the protein expression of several uptake transporters is downregulated, including organic anion transporter 1 (Oat1), Oat2, Oat3, organic anion transporting polypeptide (Oatp) 1, and Oatp4c1.[45] In contrast, Oatp2 and Oatp3 have increased protein expression in CKD. Efflux transporters Mrp2, Mrp3, and Mrp4 have increased protein expression in CKD. P-gp protein expression is downregulated in CKD kidneys. To assess the functional implication of CKD on transporter activity, ^{14}C-benzylpenicillin was used as a probe of Oat and Mrp transporters and ^{3}H-digoxin was used as a probe of Oatp4c1 and P-gp. The kidney/plasma ratio of ^{14}C-benzylpenicillin and ^{3}H-digoxin were increased nine-fold and four-fold, respectively, in CKD animals compared to control animals. These data suggest that CKD causes a reduction in transporter-mediated drug elimination and renal drug accumulation, which could further exacerbate kidney damage.

Endothelial cells at the blood–brain barrier help restrict drug entry into the brain. In CKD rats the protein expression of many blood–brain barrier transporters is reduced, including breast cancer resistance protein (Abcg2), Mrp2, Mrp4, P-gp, Oat3, Oatp2, and Oatp3.[78] ^{14}C-Benzylpenicillin, ^{3}H-digoxin, ^{14}C-doxorubicin, and ^{3}H-verapamil were used to assess the impact of CKD on transporter function. Surprisingly, the brain to plasma ratio was not different for ^{3}H-digoxin, ^{14}C-doxorubicin, and ^{3}H-verapamil, but it was decreased by 30% for ^{14}C-benzylpenicillin. These data suggest that a large fraction of blood–brain barrier integrity is preserved in CKD, despite significant reduction in the expression of many transporters.

DRUG TRANSPORT IN HUMANS WITH CKD

Drug transport in CKD is studied using similar approaches to drug metabolism. The pharmacokinetics of substrate drugs are evaluated, in particular the AUC and nonrenal clearance. Recent evidence suggests that several drug transporter substrates have altered pharmacokinetics in patients with kidney disease. Delineating the specific drug transporters that are affected in CKD has been difficult as many of the commonly used probe drugs are substrates of multiple transporters, and some are also metabolized.

The most consistent finding of altered drug transporter activity *in vivo* in CKD patients has been demonstrated using the transporter probe fexofenadine. Fexofenadine is useful for studying drug transporter activity in CKD because it is minimally metabolized and

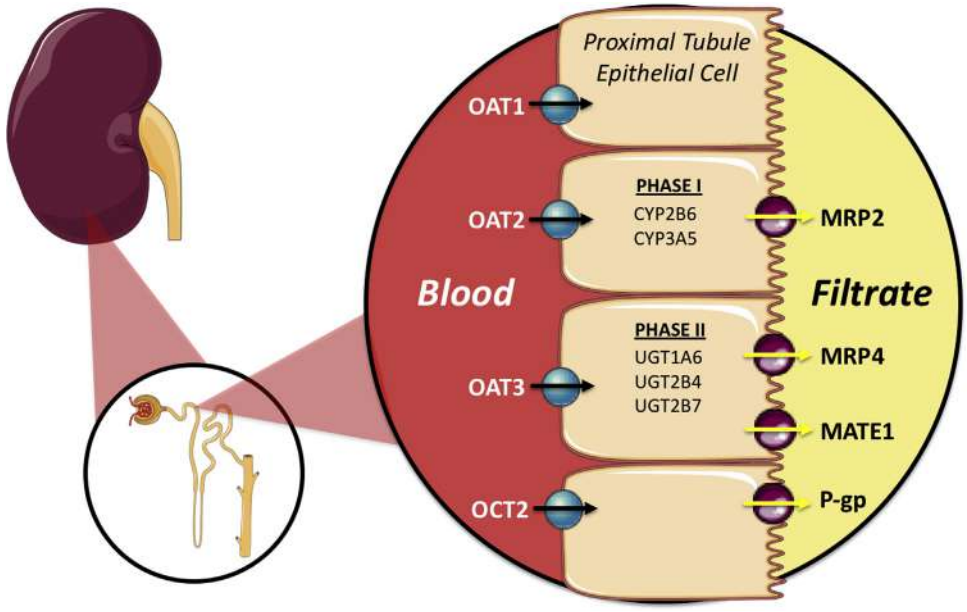


FIGURE 63.4 Kidney drug metabolism and transport pathways. The nephron is commonly thought of as the primary functional unit of the kidney. Although drug metabolism and transporter functions can be found at many regions of the nephron, the most commonly studied region are the proximal tubule cells. Uptake transporters (*blue spheres*) expressed on the basolateral membrane of proximal tubule cells carry drugs from the blood into the tubule cell. The tubule cells express several phase I (e.g. CYP) and phase II drug-metabolizing enzymes that may metabolize drugs. The apical membrane of proximal tubule cells expresses several efflux transporters (*purple spheres*) that move drugs from the tubule cell to the urinary filtrate in the lumen of the nephron to facilitate renal drug excretion. Although not shown here, there are also uptake transporters expressed at the apical membrane of proximal tubule cells that mediate drug uptake. Representative transporters and enzymes are shown for reference, note this is not a complete list. *Images used to generate this figure were modified from Servier Medical Art, licensed under Creative Commons Attribution 3.0 Generic License, http://smart.servier.com/.*

minimally excreted in the urine. Unfortunately, fexofenadine is transported by multiple uptake (e.g. OATP1B1, OATP1B3, OATP2B1) and efflux (P-gp, MRP2, MRP3) transporters, making the link between altered activity and an individual transporter very difficult to establish. Fexofenadine (120 mg oral dose) was administered to healthy controls and ESRD patients treated with maintenance HD.[67] The ESRD patients had a 2.8-fold increase in the AUC and a 63% reduction in clearance. In a similar study design, patients with biopsy-proven glomerulonephritis (systemic lupus erythematosus nephritis or small vessel vasculitis) were given 60 mg of fexofenadine.[83] The oral clearance of fexofenadine in glomerulonephritis patients was reduced by 40% compared to healthy controls. In a third study, patients with moderate to severe CKD (mean eGFR = 17 mL/min/1.73 m^2) and patients with ESRD treated by HD and PD were given 120 mg of fexofenadine.[68] The AUC in CKD, HD, and PD patients was increased by 2.9-, 2.3-, and 2.1-fold with a corresponding 61%, 56%, and 49% decrease in CL/F. Collectively, these three studies provide very strong evidence that transporter activity is altered in CKD.

Similar to fexofenadine, the HMG CoA reductase inhibitor rosuvastatin is minimally excreted in the urine (fractional excretion less than 6%) and has negligible hepatic metabolism. In addition, rosuvastatin is a substrate of multiple uptake (OATP1B1, OATP1B3, OATP2B1, OATP1A2, NTCP) and efflux (P-gp, BCRP, MRP2) transporters. Rosuvastatin plasma concentrations in patients with CKD (creatinine clearance less than 30 mL/min) are threefold higher than controls with normal kidney function, and steady state plasma concentrations are 50% higher in ESRD patients on maintenance HD.[69] Recommendations suggest that the dose of rosuvastatin in kidney disease patients should be decreased (start at 5 mg and not exceed 10 mg). Although it is difficult to delineate the pathway responsible for the altered rosuvastatin pharmacokinetics, it appears likely that OATP transporter activity is decreased in CKD, resulting in an increased accumulation of the drug in the plasma.

FDA investigators presented further evidence that OATP transporter function is impaired in humans with kidney disease[84] by evaluating 20 CKD studies of 12 different OATP substrate drugs with a fractional excretion less than 33%. The drugs included atorvastatin, bosentan, cerivastatin, erythromycin, fluvastatin, imatinib, pitavastatin, repaglinide, rosuvastatin, and torsemide. The ratio of clearance in CKD patients (mild, moderate, severe, and ESRD) to clearance in healthy controls for both total (free + protein bound) and free

drug demonstrated a clear trend of decreasing OATP substrate clearance as kidney disease progresses. Although none of the drugs are "pure" OATP substrates (they all are substrates of other transporters and/or drug-metabolizing enzymes), this clear relationship over a large number of drugs strongly suggests OATP mediated clearance is decreased in kidney disease.

MECHANISMS OF ALTERED DRUG METABOLISM AND TRANSPORT IN CKD

The mechanisms of altered drug metabolism and transport in CKD patients are somewhat controversial. Findings from preclinical models of CKD and human pharmacokinetic studies clearly indicate that kidney disease causes altered drug metabolism and transport in addition to the predictable decreases in renal excretion. The majority of reports suggest that molecules normally excreted by the functioning kidney, which are retained in CKD (uremic toxins), either 1) directly inhibit drug metabolizing enzymes and/or transporters or 2) cause up- or downregulation of expression through modification of transcriptional/translational processes. The uremic toxin hypothesis has been extensively reviewed.[14]

Direct Inhibition of Drug-Metabolizing Enzymes and Transporters

The first mechanism hypothesized for altered drug metabolism and transport in CKD is that uremic mediators directly inhibit drug metabolizing enzymes and/or transporters. For example, when microsomes from non-CKD subjects were incubated with plasma from ESRD patients, CYP2C9-mediated tolbutamide metabolism decreased by 37% and CYP3A4 midazolam metabolism decreased by 80%.[85]

Altered erythromycin pharmacokinetics have been observed in multiple human studies, and it is now well appreciated that erythromycin is a substrate of several transporters and the drug-metabolizing enzyme CYP3A4.[62,64,67] The effect of uremic toxins on erythromycin transport and metabolism was evaluated using rat hepatocytes and microsomes.[86] After incubation of multiple uremic toxins, 3-carboxy-4-methyl-5-propyl-2-furan-propanoic acid (CMPF) was demonstrated to inhibit the OATP-mediated uptake of erythromycin into hepatocytes, whereas indoxyl sulfate was shown to inhibit its CYP3A-mediated metabolism. Further evidence for the direct inhibition hypothesis comes from a human study evaluating erythromycin disposition before and after HD.[63] An improvement in erythromycin disposition (i.e. improved metabolism and/or transport) following HD was determined using the erythromycin breath test. As this was an acute study, it is likely that dialyzable uremic toxins removed during HD mediated this increase in metabolism and/or transport.

The effect of uremic toxins on OATP-mediated transport was further studied by transfecting human embryonic kidney cells (HEK293) with OATP1B1, OATP1B3, and OATP2B1.[87] The cells were then incubated with various uremic toxins and the cellular uptake of the OATP probe ^{3}H-estrone sulfate was evaluated. Uremic toxins had a profound effect on OATP-mediated transport. OATP1B1 was inhibited by indoxyl sulfate, CMPF, endothelin, quinolinic acid, indole-3-acetic acid, p-cresol, and homocysteine, whereas OATP1B3 was inhibited by indoxyl sulfate, CMPF, and p-cresol. Finally, OATP2B1 was inhibited only by CMPF. It should be noted that p-cresol is sometimes indirectly quantified as a by-product of p-cresyl sulfate, which is now known to be the circulating uremic toxin found in patients with kidney disease.

Altered Expression of Drug-Metabolizing Enzymes and Transporters

Although human pharmacokinetic studies make it difficult to determine altered expression of drug metabolism and transport in CKD, animal studies and experiments using *in vitro* cell culture techniques make it possible to interrogate mechanisms. Studies in animal models of CKD consistently demonstrate that CKD causes a decrease in enzyme and transporter mRNA and protein expression, which strongly suggests a transcriptional/translational mechanism. Several studies have taken these observations further in an attempt to delineate the mechanism. Using the 5/6 nephrectomy, chromatin immunoprecipitation (ChIP) was performed to evaluate transcription factor binding to the promoter region of the Cyp2c11 and Cyp3a2 genes in control and CKD rats.[88] Binding of RNA polymerase II to the Cyp2c11 and Cyp3a2 promoters was significantly decreased in CKD compared to controls, confirming that downregulation of these enzymes in preclinical models is mediated by decreased transcription. Further analysis demonstrated that the binding of transcription factors PXR and HNF4α to the promoter of Cyp2c11 (HNF4α) and Cyp3a2 (PXR and HNF4α) are decreased in CKD compared to controls. These nuclear receptors are primary determinants of CYP expression. The studies also indicated that CKD was associated with decreased histone acetylation, suggesting CKD induces epigenetic changes that may mediate altered expression.

Parathyroid hormone (PTH) has been proposed to be a uremic toxin that mediates the decreased expression of hepatic Cyp3a in rats with CKD. Studies that incubated

rat hepatocytes with human serum from CKD patients and healthy controls demonstrated that CKD serum downregulated the expression and activity of Cyp3a. When serum was fractionated, it was the fraction with a molecular weight between 10–15 kDa that mediated this decrease.[37] In a follow-up study, parathyroidectomy was shown to reverse the CKD-mediated decrease in Cyp3a expression and activity. Incubation with PTH dose dependently decreased Cyp3a expression in cultured rat hepatocytes.[36] Uremic mediators that downregulate CYP expression and activity appear to be dialyzable.[35] Rat hepatocytes incubated with serum obtained predialysis caused a 27% and 35% decrease in Cyp2c and Cyp3a protein expression, respectively. Serum obtained postdialysis had no effect on CYP expression.

OTHER CONSIDERATIONS IN KIDNEY DISEASE PATIENTS

Although alterations in drug metabolism and transport must be considered when prescribing drugs to patients with kidney disease, renal replacement therapy adds further complexity. The impact of dialytic clearance on plasma concentrations and, consequently, renal drug dosing must be considered. Dialytic clearance can be substantially different from renal clearance and is predominantly determined by the molecular weight, volume of distribution and protein binding of the drug, the type of dialysis membrane, and blood/dialysate flow rates.[21] There is a paucity of information currently, with data on drug dialyzability with measured clearance available for only about 10% of marketed drugs.[21] In addition, much of the information available is determined using the suboptimal arterial-venous (AV) difference method, which is known to overestimate clearance.[89]

Treating physicians can often select multiple drugs within the same class, and little information is available to determine which drug is most suitable in dialysis patients. Significant differences in drug dialyzability may exist, even among drugs within the same class.[12] For instance, atenolol and metoprolol are extensively cleared during HD, bisoprolol is moderately cleared, and the clearance of carvedilol is negligible.[12]

SUMMARY

Patients with kidney disease are prescribed numerous medications and commonly receive treatment with drugs that are predominantly cleared by nonrenal pathways. The nonrenal clearance of many drugs is altered in patients with impaired kidney function, often translating into clinically relevant changes in systemic exposure (see Table 63.1). This in turn may change the efficacy and adverse effect profile in patients if the drug dose is not adjusted. Although the precise mechanism of changes in nonrenal clearance pathways is unclear, selective modulation of activity and expression of drug-metabolizing enzymes and transport proteins has been implicated. Transcriptional, translational, and posttranslational modification, perhaps induced by uremic toxins, may play a role. Clinicians are encouraged to consider the impact of kidney disease on all aspects of safety and efficacy during the drug selection process. Although these data are limited currently, the US FDA now recommends that clinical studies be conducted for investigational compounds eliminated primarily *via* nonrenal pathways as well as those eliminated predominantly unchanged in the urine. Eventually this will generate improved data related to the impact of kidney disease on drug dosing requirements and will improve efficacy and safety in one of the most vulnerable patient populations.

References

1. USRDS. Available from: https://www.usrds.org/adrhighlights.aspx.
2. Coresh J, et al. Prevalence of chronic kidney disease in the United States. *J Am Med Assoc* 2007;**298**(17):2038–47.
3. Gansevoort RT, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013;**382**(9889):339–52.
4. Spence JD, Urquhart BL, Bang H. Effect of renal impairment on atherosclerosis: only partially mediated by homocysteine. *Nephrol Dial Transplant* 2016;**31**(6):937–44.
5. Stubbs JR, et al. Serum trimethylamine-N-oxide is elevated in CKD and correlates with coronary atherosclerosis burden. *J Am Soc Nephrol* 2016;**27**(1):305–13.
6. Bogiatzi C, et al. Metabolic products of the intestinal microbiome and extremes of atherosclerosis. *Atherosclerosis* 2018;**273**:91–7.
7. Chiu YW, et al. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. *Clin J Am Soc Nephrol* 2009;**4**(6):1089–96.
8. Manley HJ, et al. Medication prescribing patterns in ambulatory haemodialysis patients: comparisons of USRDS to a large not-for-profit dialysis provider. *Nephrol Dial Transplant* 2004;**19**(7):1842–8.
9. Manley HJ, et al. Medication-related problems in ambulatory hemodialysis patients: a pooled analysis. *Am J Kidney Dis* 2005;**46**(4):669–80.
10. Farag A, et al. Dosing errors in prescribed antibiotics for older persons with CKD: a retrospective time series analysis. *Am J Kidney Dis* 2014;**63**(3):422–8.
11. FDA. *Pharmacokinetics in patients with impaired renal function — study design, data analysis, and impact on dosing and labeling*. 2010. Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM204959.pdf.
12. Tieu A, et al. Beta-blocker dialyzability in maintenance hemodialysis patients: a randomized clinical trial. *Clin J Am Soc Nephrol* 2018;**13**(4):604–11.

13. Wienkers LC, Heath TG. Predicting in vivo drug interactions from in vitro drug discovery data. *Nat Rev Drug Discov* 2005;**4**(10):825–33.
14. Prokopienko AJ, Nolin TD. Microbiota-derived uremic retention solutes: perpetrators of altered nonrenal drug clearance in kidney disease. *Expert Rev Clin Pharmacol* 2018;**11**(1):71–82.
15. Alshogran OY, Nolin TD. Implications of kidney disease on metabolic reduction. *Curr Drug Metabol* 2016;**17**(7):663–72.
16. Schwenk MH, Pai AB. Drug transporter function–implications in CKD. *Adv Chron Kidney Dis* 2016;**23**(2):76–81.
17. Ladda MA, Goralski KB. The effects of CKD on cytochrome P450-mediated drug metabolism. *Adv Chron Kidney Dis* 2016;**23**(2):67–75.
18. Tieu A, House AA, Urquhart BL. Drug disposition issues in CKD: implications for drug discovery and regulatory approval. *Adv Chron Kidney Dis* 2016;**23**(2):63–6.
19. Naud J, et al. Drug pharmacokinetics in renal failure: what's new? *Néphrol Thérapeutique* 2015;**11**(3):144–51.
20. Nolin TD. A synopsis of clinical pharmacokinetic alterations in advanced CKD. *Semin Dial* 2015;**28**(4):325–9.
21. Velenosi TJ, Urquhart BL. Pharmacokinetic considerations in chronic kidney disease and patients requiring dialysis. *Expert Opin Drug Metabol Toxicol* 2014;**10**(8):1131–43.
22. Joy MS. Impact of glomerular kidney diseases on the clearance of drugs. *J Clin Pharmacol* 2012;**52**(1 Suppl.):23S–34S.
23. Naud J, et al. Current understanding of drug disposition in kidney disease. *J Clin Pharmacol* 2012;**52**(1 Suppl.):10S–22S.
24. Momper JD, Venkataramanan R, Nolin TD. Nonrenal drug clearance in CKD: searching for the path less traveled. *Adv Chron Kidney Dis* 2010;**17**(5):384–91.
25. Nolin TD, et al. Emerging evidence of the impact of kidney disease on drug metabolism and transport. *Clin Pharmacol Ther* 2008;**83**(6):898–903.
26. Yeung CK, et al. Effects of chronic kidney disease and uremia on hepatic drug metabolism and transport. *Kidney Int* 2014;**85**(3):522–8.
27. Giacomini KM, Sugiyama Y. In: Brunton LL, Lazo JS, K.L P, editors. *Goodman & Gilman's the pharmacological basis of therapeutics*. McGraw-Hill; 2006. p. 41–70.
28. Patterson SE, Cohn VH. Hepatic drug metabolism in rats with experimental chronic renal failure. *Biochem Pharmacol* 1984;**33**(5):711–6.
29. Leber HW, Gleumes L, Schutterle G. Enzyme induction in the uremic liver. *Kidney Int Suppl* 1978;(8):S43–8.
30. Van Peer AP, Belpaire FM. Hepatic oxidative drug metabolism in rats with experimental renal failure. *Arch Int Pharmacodyn Ther* 1977;**228**(2):180–3.
31. Leber HW, Schutterle G. Oxidative drug metabolism in liver microsomes from uremic rats. *Kidney Int* 1972;**2**(3):152–8.
32. Engel G, et al. Antipyrine as a probe for human oxidative drug metabolism: identification of the cytochrome P450 enzymes catalyzing 4-hydroxyantipyrine, 3-hydroxymethylantipyrine, and norantipyrine formation. *Clin Pharmacol Ther* 1996;**59**(6):613–23.
33. Uchida N, et al. Changes of hepatic microsomal oxidative drug metabolizing enzymes in chronic renal failure (CRF) rats by partial nephrectomy. *Jpn J Pharmacol* 1995;**68**(4):431–9.
34. Dani M, et al. Down-regulation of liver drug-metabolizing enzymes in a murine model of chronic renal failure. *Drug Metab Dispos* 2010;**38**(3):357–60.
35. Michaud J, et al. Effect of hemodialysis on hepatic cytochrome P450 functional expression. *J Pharmacol Sci* 2008;**108**(2):157–63.
36. Michaud J, et al. Role of parathyroid hormone in the downregulation of liver cytochrome P450 in chronic renal failure. *J Am Soc Nephrol* 2006;**17**(11):3041–8.
37. Michaud J, et al. Effects of serum from patients with chronic renal failure on rat hepatic cytochrome P450. *Br J Pharmacol* 2005;**144**(8):1067–77.
38. Guevin C, et al. Down-regulation of hepatic cytochrome p450 in chronic renal failure: role of uremic mediators. *Br J Pharmacol* 2002;**137**(7):1039–46.
39. Leblond F, et al. Downregulation of hepatic cytochrome P450 in chronic renal failure. *J Am Soc Nephrol* 2001;**12**(2):326–32.
40. Leblond FA, et al. Decreased in vivo metabolism of drugs in chronic renal failure. *Drug Metab Dispos* 2000;**28**(11):1317–20.
41. Velenosi TJ, et al. Down-regulation of hepatic CYP3A and CYP2C mediated metabolism in rats with moderate chronic kidney disease. *Drug Metab Dispos* 2012;**40**(8):1508–14.
42. Terai K, Mizukami K, Okada M. Comparison of chronic renal failure rats and modification of the preparation protocol as a hyperphosphataemia model. *Nephrology* 2008;**13**(2):139–46.
43. Feere DA, Velenosi TJ, Urquhart BL. Effect of erythropoietin on hepatic cytochrome P450 expression and function in an adenine-fed rat model of chronic kidney disease. *Br J Pharmacol* 2015;**172**(1):201–13.
44. Leblond FA, et al. Downregulation of intestinal cytochrome p450 in chronic renal failure. *J Am Soc Nephrol* 2002;**13**(6):1579–85.
45. Naud J, et al. Effects of chronic renal failure on kidney drug transporters and cytochrome P450 in rats. *Drug Metab Dispos* 2011;**39**(8):1363–9.
46. Alshogran OY, et al. Effect of experimental kidney disease on the functional expression of hepatic reductases. *Drug Metab Dispos* 2015;**43**(1):100–6.
47. Yu C, et al. Effect of chronic renal insufficiency on hepatic and renal udp-glucuronyltransferases in rats. *Drug Metab Dispos* 2006;**34**(4):621–7.
48. Simard E, et al. Downregulation of hepatic acetylation of drugs in chronic renal failure. *J Am Soc Nephrol* 2008;**19**(7):1352–9.
49. Turpeinen M, et al. Effect of renal impairment on the pharmacokinetics of bupropion and its metabolites. *Br J Clin Pharmacol* 2007;**64**(2):165–73.
50. Joy MS, et al. Use of enantiomeric bupropion and hydroxybupropion to assess CYP2B6 activity in glomerular kidney diseases. *J Clin Pharmacol* 2010;**50**(6):714–20.
51. Dreisbach AW, et al. Cytochrome P4502C9 activity in end-stage renal disease. *Clin Pharmacol Ther* 2003;**73**(5):475–7.
52. Nolin TD, et al. Effect of chronic kidney disease on cytochrome P450 2C19 activity and 4-hydroxymephenytoin urinary recovery. *Clin Pharmacol Ther* 2007;**81**(Suppl. 1):S56.
53. Kevorkian JP, et al. Assessment of individual CYP2D6 activity in extensive metabolizers with renal failure: comparison of sparteine and dextromethorphan. *Clin Pharmacol Ther* 1996;**59**(5):583–92.
54. Rostami-Hodjegan A, Kroemer HK, Tucker GT. In-vivo indices of enzyme activity: the effect of renal impairment on the assessment of CYP2D6 activity. *Pharmacogenetics* 1999;**9**(3):277–86.
55. Kaye CM, et al. A review of the metabolism and pharmacokinetics of paroxetine in man. *Acta Psychiatr Scand Suppl* 1989;**350**:60–75.
56. Hoffmann KJ, et al. The effect of impaired renal function on the plasma concentration and urinary excretion of metoprolol metabolites. *Clin Pharmacokinet* 1980;**5**(2):181–91.
57. Jordo L, et al. Pharmacokinetic and pharmacodynamic properties of metoprolol in patients with impaired renal function. *Clin Pharmacokinet* 1980;**5**(2):169–80.
58. Neves DV, et al. Influence of chronic kidney disease and haemodialysis treatment on pharmacokinetics of nebivolol enantiomers. *Br J Clin Pharmacol* 2016;**82**(1):83–91.
59. Yoshida K, et al. Systematic and quantitative assessment of the effect of chronic kidney disease on CYP2D6 and CYP3A4/5. *Clin Pharmacol Ther* 2016;**100**(1):75–87.

60. Nolin TD, et al. Impaired 6-hydroxychlorzoxazone elimination in patients with kidney disease: implication for cytochrome P450 2E1 pharmacogenetic studies. *Clin Pharmacol Ther* 2003;**74**(6):555–68.
61. Achour B, Barber J, Rostami-Hodjegan A. Expression of hepatic drug-metabolizing cytochrome p450 enzymes and their intercorrelations: a meta-analysis. *Drug Metab Dispos* 2014;**42**(8):1349–56.
62. Dowling TC, et al. Characterization of hepatic cytochrome p4503A activity in patients with end-stage renal disease. *Clin Pharmacol Ther* 2003;**73**(5):427–34.
63. Nolin TD, et al. Hemodialysis acutely improves hepatic CYP3A4 metabolic activity. *J Am Soc Nephrol* 2006;**17**(9):2363–7.
64. Sun H, et al. Hepatic clearance, but not gut availability, of erythromycin is altered in patients with end-stage renal disease. *Clin Pharmacol Ther* 2010;**87**(4):465–72.
65. Frassetto LA, et al. Effects of uptake and efflux transporter inhibition on erythromycin breath test results. *Clin Pharmacol Ther* 2007; **81**(6):828–32.
66. Kurnik D, Wood AJ, Wilkinson GR. The erythromycin breath test reflects P-glycoprotein function independently of cytochrome P450 3A activity. *Clin Pharmacol Ther* 2006;**80**(3):228–34.
67. Nolin TD, et al. ESRD impairs nonrenal clearance of fexofenadine but not midazolam. *J Am Soc Nephrol* 2009;**20**(10):2269–76.
68. Thomson BK, et al. Effect of CKD and dialysis modality on exposure to drugs cleared by nonrenal mechanisms. *Am J Kidney Dis* 2015;**65**(4):574–82.
69. Zhang Y, et al. Assessment of the impact of renal impairment on systemic exposure of new molecular entities: evaluation of recent new drug applications. *Clin Pharmacol Ther* 2009;**85**(3):305–11.
70. Yoshida H, et al. Pharmacokinetics of doxorubicin and its active metabolite in patients with normal renal function and in patients on hemodialysis. *Cancer Chemother Pharmacol* 1994;**33**(6):450–4.
71. Camaggi CM, et al. Idarubicin metabolism and pharmacokinetics after intravenous and oral administration in cancer patients: a crossover study. *Cancer Chemother Pharmacol* 1992;**30**(4):307–16.
72. Alshogran OY, Urquhart BL, Nolin TD. Downregulation of hepatic carbonyl reductase type 1 in end-stage renal disease. *Drug Metab Lett* 2015;**9**(2):111–8.
73. Kim YG, et al. Decreased acetylation of isoniazid in chronic renal failure. *Clin Pharmacol Ther* 1993;**54**(6):612–20.
74. Gibson TP, et al. Kinetics of procainamide and N-acetylprocainamide in renal failure. *Kidney Int* 1977;**12**(6):422–9.
75. Osborne R, et al. The pharmacokinetics of morphine and morphine glucuronides in kidney failure. *Clin Pharmacol Ther* 1993;**54**(2): 158–67.
76. Debord P, et al. Influence of renal function on the pharmacokinetics of diacerein after a single oral dose. *Eur J Drug Metab Pharmacokinet* 1994;**19**(1):13–9.
77. Singlas E, et al. Zidovudine disposition in patients with severe renal impairment: influence of hemodialysis. *Clin Pharmacol Ther* 1989;**46**(2):190–7.
78. Naud J, et al. Effects of chronic renal failure on brain drug transporters in rats. *Drug Metab Dispos* 2012;**40**(1):39–46.
79. Naud J, et al. Down-regulation of intestinal drug transporters in chronic renal failure in rats. *J Pharmacol Exp Ther* 2007;**320**(3): 978–85.
80. Naud J, et al. Effects of chronic renal failure on liver drug transporters. *Drug Metab Dispos* 2008;**36**(1):124–8.
81. Lu H, Klaassen C. Gender differences in mRNA expression of ATP-binding cassette efflux and bile acid transporters in kidney, liver, and intestine of 5/6 nephrectomized rats. *Drug Metab Dispos* 2008;**36**(1):16–23.
82. Santana Machado T, et al. Indoxyl sulfate upregulates liver P-glycoprotein expression and activity through aryl hydrocarbon receptor signaling. *J Am Soc Nephrol* 2018;**29**(3):906–18.
83. Joy MS, et al. In vivo alterations in drug metabolism and transport pathways in patients with chronic kidney diseases. *Pharmacotherapy* 2014;**34**(2):114–22.
84. Tan ML, et al. Effect of chronic kidney disease on nonrenal elimination pathways: a systematic assessment of CYP1A2, CYP2C8, CYP2C9, CYP2C19, and OATP. *Clin Pharmacol Ther* 2018;**103**(5): 854–67.
85. Taburet AM, et al. Impairment of drug biotransformation in renal disease: an in vitro model. *Clin Pharmacol Ther* 1996;**59**: 136.
86. Sun H, et al. Effects of uremic toxins on hepatic uptake and metabolism of erythromycin. *Drug Metab Dispos* 2004;**32**(11): 1239–46.
87. Reyes M, Benet LZ. Effects of uremic toxins on transport and metabolism of different biopharmaceutics drug disposition classification system xenobiotics. *J Pharm Sci* 2011;**100**(9):3831–42.
88. Velenosi TJ, et al. Decreased nuclear receptor activity and epigenetic modulation associates with down-regulation of hepatic drug-metabolizing enzymes in chronic kidney disease. *FASEB J* 2014;**28**(12):5388–97.
89. Tieu A, et al. Clearance of cardiovascular medications during hemodialysis. *Curr Opin Nephrol Hypertens* 2016;**25**(3):257–67.
90. Nolin TD. Altered nonrenal drug clearance in ESRD. *Curr Opin Nephrol Hypertens* 2008;**17**(6):555–9.

QUESTIONS AND ANSWERS

Question 1

A new drug for the treatment of hypertension is being tested in patients with CKD. It is an OATP1B1 substrate and has a fractional excretion <5%. Which of the following pharmacokinetic changes are most likely to be observed in a CKD patient compared to a control?

A. An increase in the AUC and CL/F
B. A decrease in the AUC and CL/F
C. An increase in the AUC and a decrease in the CL/F
D. A decrease in the AUC and an increase in the CL/F
E. An increase in the AUC and a decrease in the half-life

Answer: C

Hepatic OATP function is decreased in CKD. The result of decreased OATP activity is a decrease uptake of the drug into the liver, which will result in an increase in the AUC. As the drug has a very low fractional excretion, its excretion is mediated by nonrenal clearance mechanisms. The decreased OATP function will in turn result in a decrease oral clearance (CL/F) as CL/F = dose*F/AUC.

Question 2

Morphine is administered to a patient with CKD with no consideration of the impact of the patient's decreased kidney function. Which of the following is the most likely outcome?

A. The patient may experience an increased analgesic response to morphine and may also experience respiratory depression
B. The patient may have a blunted analgesic response to morphine
C. The plasma levels and AUC for morphine may be decreased compared to a patient with normal kidney function
D. The patient may need more frequent administration of morphine for analgesia
E. Increased drug transporter expression at the blood–brain barrier may restrict the entry of morphine to the brain, decreasing the analgesic response.

Answer: A

Morphine is cleared primarily by glucuronidation with a small fraction cleared unchanged in the urine. Morphine pharmacokinetics are substantially altered in kidney disease with an increased AUC and decreased CL. In addition, some morphine metabolites (e.g. morphine 6-glucuronide) have activity at opioid receptors and are renally cleared. A CKD patient that receives morphine without careful consideration of disease stage may have increased therapeutic response (analgesia) but may also be susceptible to side effects such as respiratory depression.

Question 3

Which of following statements most accurately reflects CYP3A4 activity in CKD?

A. CYP3A4 activity is markedly reduced in CKD
B. CYP3A4 activity is significantly increased in CKD
C. Increased erythromycin AUC and decreased CL/F in CKD patients indicates decreased CYP3A4 activity
D. Only select CYP3A4 substrates exhibit decreased clearance in CKD and the magnitude of change is modest
E. Vardenafil AUC is substantially increased in CKD and dose adjustment is required

Answer: D

Although studies in preclinical animal models of CKD consistently demonstrate decreased activity, clinical pharmacokinetic studies are much more variable. Although CYP3A4 substrates such as erythromycin have an increased AUC and decreased CL/F, it is unclear what role changes in drug transporter activity have on mediating the decreased clearance. The best currently available evidence suggests that only some CYP3A4 substrates have decreased clearance in CKD and the magnitude of decrease for these substrates is only modest.

Question 4

Which of the following best describes the impact of CKD on P-gp expression and activity using preclinical models?

A. Intestinal and hepatic P-gp expression and activity are increased
B. Intestinal and hepatic P-gp expression and activity are decreased
C. Intestinal P-gp expression and activity are decreased whereas hepatic P-gp expression and activity are increased
D. Intestinal P-gp expression and activity are increased whereas hepatic P-gp expression and activity are decreased
E. There is no change of intestinal or hepatic P-gp expression and activity in CKD

Answer: C

Intestinal P-gp expression is decreased in preclinical models of CKD. Studies demonstrate that this decreased expression results in a decrease in substrate (rhodamine 123) transport. Conversely, hepatic P-gp expression is

increased in preclinical models of CKD. These animals have increased biliary clearance of the P-gp substrate rhodamine 123. The opposite effects in intestine and liver may be mediated by the uremic toxin and AhR ligand indoxyl sulfate. Indoxyl sulfate is generated in the liver from indole. Accordingly, intestinal exposure is expected to be minimal in relation to hepatic.

Question 5

Substrates of which CYP enzyme most consistently exhibit decreased clearance as kidney disease progresses?

A. CYP2C19
B. CYP2D6
C. CYP2E1
D. CYP3A4
E. CYP1A2

Answer: B

Clearance of CYP1A2, CYP2C19, and CYP2E1 substrates do not appear to be decreased in CKD. Although some CYP3A4 substrates exhibit decreased clearance, others do not. There is no clear relationship between clearance and kidney disease stage. The CYP enzyme that most consistently exhibits decreased clearance is CYP2D6. In addition, there is a clear relationship between kidney disease stage and clearance for multiple CYP2D6 substrate drugs.

Question 6

Which of the following best explains the increased AUC and decreased CL of doxorubicin in patients with CKD?

A. Decreased CYP2D6-mediated metabolism in CKD
B. Decreased NAT2 activity in CKD
C. Decreased UGT2B7 activity in CKD
D. Decreased CYP3A4 activity in CKD
E. Decreased CBR1 activity in CKD

Answer: E

Doxorubicin does not undergo substantial metabolism by any CYP enzymes. Hepatic reduction by CBR1 and AKR1C3 are the primary metabolic pathways responsible for reducing doxorubicin into doxorubicinol. CBR1 expression is decreased in CKD, and this most likely causes the increased AUC and decreased clearance observed in patients.

CHAPTER

64

Use of Diuretics in Chronic Kidney Disease Patients

Arthur Greenberg

Division of Nephrology, Department of Medicine, Duke University Medical Center, Durham, NC, United States

Abstract

Diuretics are commonly prescribed to treat the sodium retention, volume expansion, and hypertension characteristic of chronic kidney disease (CKD). With reduced renal function, delivery of the drugs to their renal tubular sites of action is impaired, potentially leading to diminished potency. In addition, reduced glomerular filtration rate and alterations in sodium transport at other tubular sites can reduce the natriuretic effect of delivered drug. To use diuretics effectively in CKD, clinicians must understand these changes in diuretic pharmacokinetics and pharmacodynamics. This chapter reviews the sites and mechanisms of action of diuretics, describes how diuretic pharmacologic characteristics are affected by CKD, and details how best to overcome diuretic resistance. Much of the focus is on the loop agents, which are the most potent class of diuretics and the mainstay of treatment in CKD patients. As increasing attention is being paid to the role of thiazides and mineralocorticoid antagonists, the use of other classes of diuretics is also covered, as is the use of diuretics to treat specific subsets of CKD patients.

INTRODUCTION

The natriuretic diuretics interfere with renal tubular reabsorption of sodium, leading to loss of sodium and other solutes. This effect is beneficial in circumstances characterized by sodium accumulation with an attendant increase in total body sodium and extracellular volume. Chronic kidney disease (CKD) is one such state, and diuretics are an important therapeutic tool in CKD for treatment of volume overload, edema, and hypertension.

The delivery of diuretics to the sites at which they work and their pharmacodynamics and pharmacokinetics, relative potency, and clinical effects and utility are markedly affected by changes in renal function. A detailed understanding of the mechanism of action of diuretics is necessary to anticipate the changes in their activity in CKD and employ them effectively.[1,2] Most of this discussion focuses on the potent loop diuretics, which are the mainstay of therapy for patients with reduced renal function.

SITE AND MECHANISM OF ACTION OF DIURETICS

Diuretics act from the luminal side of the renal tubule by binding to a solute transporter or, in the case of the carbonic anhydrase inhibitors, an enzyme that indirectly promotes sodium reabsorption. Exceptions to this rule are the mineralocorticoid receptor antagonists (MRAs), which reach the nuclear aldosterone receptor from the basolateral side of collecting duct cells. Glomerular filtration of diuretics is negligible because they are highly protein bound. Acetazolamide, the loop agents, and the thiazides are weak organic anions that are secreted into the proximal tubular lumen *via* the organic acid secretory pathway in the proximal tubule. Weak acids, amiloride, and triamterene, are secreted *via* the organic base pathway. Once they reach the proximal tubular lumen, diuretics move downstream in the glomerular filtrate to their specific site of action. On binding to their receptors, diuretics block transport of sodium and accompanying anions or cations at that site (Table 64.1).

Diuretics vary in potency, which depends on the fraction of filtered sodium reabsorbed at the site where the diuretic inhibits transport, sodium delivery to the inhibited site, and the potential for sodium reabsorption distal to the site. For example, the proximal tubule diuretics have limited ability to increase overall renal sodium excretion. Although treatment with acetazolamide may cause an increase of up to 8% in sodium delivered

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00064-4

TABLE 64.1 Sites of Action of Diuretic Drugs

Drug Class	Agents	Site of Action	Maximal FE Na	Transport Site	Other
Carbonic anhydrase inhibitors	Acetazolamide	Proximal tubule	5–8%	Carbonic anhydrase, lumen, and proximal tubular cell	
Loop agents	Furosemide Bumetanide Torsemide	Thick ascending limb loop of Henle	15–20%	NKCC2	
Thiazides	Hydrochlorothiazide Chlorthalidone Chlorothiazide Numerous others	Distal convoluted tubule	10–15%	NCCT NaCl cotransporter	
ENaC blockers	Amiloride Triamterene	Collecting duct	3–5%	ENaC	
Mineralocorticoid receptor antagonists	Spironolactone Eplerenone	Collecting duct	3–5%	ENaC	Also block effect of aldosterone to stimulate basolateral Na/K ATPase

ENaC, epithelial sodium channel; *FE Na*, fractional excretion of sodium; *NCCT*, sodium chloride cotransporter; *Na/K ATPase*, sodium-potassium adenosine triphosphatase; *NKCC2*, sodium-potassium-2-chloride cotransporter.

out of the proximal tubule, distal segments of the nephron, including especially the loop of Henle and the distal convoluted tubule, can easily reabsorb the increased sodium load with which they are presented. Little net increase in sodium excretion results. In contrast, the loop agents block the Na-K-2Cl (NKCC2) transporter responsible for the reabsorption of up to 20% of the filtered sodium load, an amount that cannot ordinarily be reabsorbed at more distal sites in its entirety. The operative word here is ordinarily.

PHARMACOKINETICS

The pharmacokinetics of diuretics in health and various disease states have been extensively reviewed.[3,4] The pharmacokinetics of the loop agents in patients with normal renal function and in individuals with reduced glomerular filtration rate (GFR) are shown in Tables 64.2 and 64.3.[5–8] The bioavailability of orally administered furosemide is approximately 50%, compared with 80% for bumetanide and torsemide. However, the reported values vary widely. When switching from intravenous (IV) to oral furosemide, a doubling of the dose is a reasonable starting point for achieving a similar effect. No change in initial dose and less expected variability apply to bumetanide and torsemide. Just as results of bioavailability studies vary, so do reported diuretic renal and nonrenal clearances, protein binding, volume of distribution, and overall pharmacokinetics.[3,4,9–15] Any dosing recommendations based on pharmacokinetics should be employed with circumspection, and clinicians should anticipate the need to follow the clinical response closely and titrate the dose accordingly.

The presence of reduced renal function alters the relative potency of the three commonly used loop agents. For each drug, absolute renal excretion and hence delivery to its site of action diminishes as renal function declines. Factors that may contribute to diminished delivery include reduced GFR, reduced renal blood flow, diminished protein binding with increased apparent volume of distribution, and competition with other organic acids for tubular secretion.[4,16,17] Changed metabolism of diuretics also contributes to diminished delivery. The kidney is not the sole route of excretion of diuretics. Nonrenal excretion of bumetanide and torsemide *via* the liver is unaffected by changes in renal function. Nonrenal excretion of furosemide, in contrast, occurs *via* glucuronidation, which is accomplished in the kidney and diminished when renal function is reduced. With relatively preserved nonrenal elimination, excretion of bumetanide and torsemide is in effect shunted away from the kidney. As shown in Table 64.2, with normal renal function, roughly equivalent fractions of administered furosemide or bumetanide are excreted *via* the kidney (~60%), the site of action of these drugs. With impaired renal function (Table 64.3), the absolute fraction of all three drugs excreted by the kidneys is reduced compared with normal, but the reduction for furosemide is less. The fraction of furosemide excreted by the kidneys (9%) is approximately twice that of bumetanide (5%). Thus, the relative potency of bumetanide especially and torsemide compared with furosemide is reduced in patients with impaired kidney function.

Diuretic binding to protein falls as renal function worsens, likely due to displacement by other accumulated anions. With hypoalbuminemia, as in nephrotic syndrome, protein binding is diminished and the volume of distribution of diuretics increases, further reducing delivery.[13,17,18] In animal studies, mixing albumin with furosemide before administration reverses some of the resistance.[19] Furosemide may bind to

TABLE 64.3 Pharmacokinetics of Loop Diuretics in Patients with Impaired Renal Function

	Furosemide	Bumetanide	Torsemide
Clearance (mL/min/kg)	0.8	1.6	0.9–1.05
Fraction of dose excreted unchanged in urine, %	9.0	5.2	2.6–2.8
Plasma half-life, hours	2.6	1.6	3.8–5.2

From Voelker[7] and as summarized from published sources by Brater.[6]

TABLE 64.2 Pharmacokinetics of Loop Diuretics in Subjects with Normal Kidney Function

	Furosemide	Bumetanide	Torsemide
Bioavailability, %	11–90 (53)	58–89 (80)	79–91 (80)
Time to peak plasma concentration, hours	1–5 (1.6)	0.5–2 (1.3)	1
Clearance (mL/min/kg)	1.5–4.4 (2.2)	1.8–3.8 (2.6)	0.33–1.1 (0.6)
Fraction of dose excreted in urine unchanged, %	49–94 (60)	36–69 (65)	22–34 (27)
Plasma half-life, hours	0.3–3.4 (1.0)	0.4–1.5 (1.2)	0.8–6.0 (3.3)

Median values shown in parentheses.
Summarized from published sources by Brater.[5]

luminal albumin present due to proteinuria. Inhibition of binding of furosemide to luminal albumin by a competitive inhibitor like warfarin augmented the diuretic effect observed during *in vivo* renal tubular perfusion.[20] Studies in humans with hypoalbuminemia or nephrotic syndrome have not shown a pharmacokinetic benefit of coadministration of furosemide and albumin. However, the favorable hemodynamic effect of albumin infusion can increase sodium excretion with submaximal but not maximal doses of furosemide.[21–23] Inhibition of intraluminal furosemide binding to albumin by warfarin does not result in a significant augmentation of natriuresis in the clinical setting.[24]

PHARMACODYNAMICS

The standard way to assess the ability of a diuretic to increase urinary sodium excretion is to relate sodium excretion to urinary diuretic excretion, because the latter is a direct measure of the amount of diuretic reaching its luminal site of action. As loop diuretics bind to the electroneutral NKCC2 Na-K-2Cl cotransporter in the thick ascending limb of the loop of Henle which cotransports a sodium ion, a potassium ion, and two chloride ions across the luminal membrane, one would predict that a plot of sodium excretion as a function of diuretic excretion (Figure 64.1) would be a sigmoid curve. At low excretion rates, few diuretic receptors are occupied by bound drug and inhibited, so sodium excretion is little increased. At high diuretic excretion rates, all receptors are already saturated and increasing diuretic excretion further has little additional effect. In between, the slope of the change in sodium excretion as a function of diuretic excretion or delivery is steep.

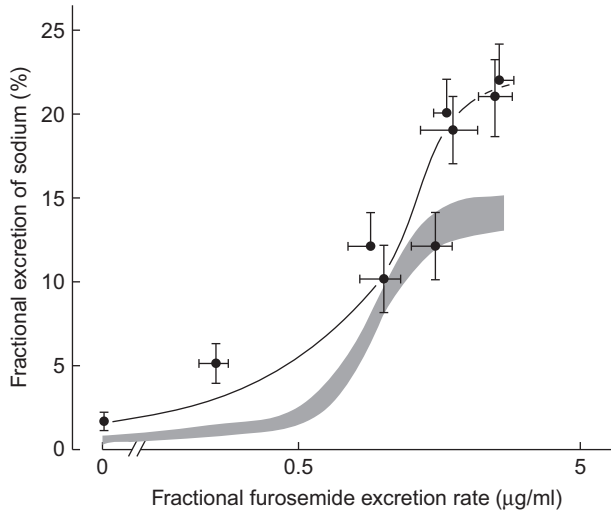


FIGURE 64.1 Relationship between fractional delivery of furosemide into urine and fractional excretion of sodium after a 2-hour furosemide infusion. Mean (±S.E.M.). Data are shown as *symbols with brackets* for patients with impaired kidney function and a *shaded curve* for normal individuals. *Reproduced with permission from reference 25.*

When expressed as fractional excretion of sodium, the response to furosemide in patients with impaired kidney function is augmented compared with normal individuals.[25] At any given rate of furosemide excretion, the fractional excretion of sodium is higher in patients with reduced GFR (Figure 64.1). This is likely a function of the adaptive mechanism for reduced GFR. To excrete the same daily load of ingested sodium, the fractional sodium excretion must be higher with reduced GFR. The curve in Figure 64.1 also provides a basis for the notion of a ceiling dose of loop diuretic. Administration of additional furosemide beyond the amount needed to reach the plateau of the sigmoid curve would not produce any additional benefit. In patients with normal renal function, the doses of loop agents required to reach maximal sodium excretion are furosemide 40 mg, bumetanide 1 mg, and torsemide 15–20 mg, hence the standard doses for these agents. With advanced renal functional impairment, only 9% of furosemide is excreted by the kidney, compared with 60% with normal renal function. The ceiling dose would therefore be expected to be five- or six-fold higher, i.e. approximately 200 mg.[25] The dose actually noted to reach saturation in the study shown in Figure 64.1 was 160 mg. Using a slightly higher value for clinical purposes leads to reasonable limits for ceiling doses of loop agents with reduced GFR in the range of 160–240 mg for furosemide, 6–10 mg for bumetanide, and 100–200 mg for torsemide.[2,6,7,26] No advantage would be expected from higher doses, although the risk of toxicity would be higher. Note the difference in equivalency ratio for impaired renal function for furosemide, bumetanide, and torsemide (20:1:20) compared with normal renal function (40:1:10–20)[6,7,27] Relative to furosemide, the potency of bumetanide especially and torsemide to some degree are diminished in patients with impaired kidney function.

DIURETIC BRAKING, TOLERANCE, AND RESISTANCE

The diuretic and natriuretic effect of a diuretic drug may decrease after the first dose and diminish further over time. Some authors reserve the term "braking" to describe the reduction in response to a diuretic that occurs after the first dose.[1,28] The principal cause is the acute reduction in intravascular volume with compensatory activation of a number of effectors including the renin–angiotensin–aldosterone system and the sympathetic nervous system, which together can reduce GFR

or alter the physical factors responsible for proximal tubular sodium and fluid reabsorption. As shown in a series of elegant studies by Wilcox et al., increased activity of these neurohumoral systems is not solely responsible for diuretic braking, because treatment with captopril and the α-adrenergic blocker prazosin does not abrogate its development.[29] A second cause of reduced diuretic efficacy is tolerance, a term used by many authors to refer to the reduction in diuretic effect seen with chronic use that develops in most patients.[1] Others employ the term tolerance to describe the first dose effect and braking to describe the subsequent effect.[30] Because these two effects predictably develop together in the setting of repeated diuretic dosing, making a precise distinction is not essential. The overall sequence is familiar to clinicians and patients alike. With first administration of an adequate dose, diuretics promote a conspicuous increase in urine output that is associated with net negative sodium balance, a reduction in weight, and lessening of edema. Over time, patients reach a steady state where the diuretic response to that same dosing regimen is less. Individual doses promote a smaller diuresis and natriuresis. Daily sodium balance may become neutral with no further weight loss occurring (Figure 64.2).

One important cause of diuretic tolerance is sequential reabsorption of solute at renal tubular sites more distal to the site of action of the administered diuretic. Loop agents are potent because they block the very large fraction of filtered sodium load reabsorbed in the loop. Under usual circumstances, transport sites

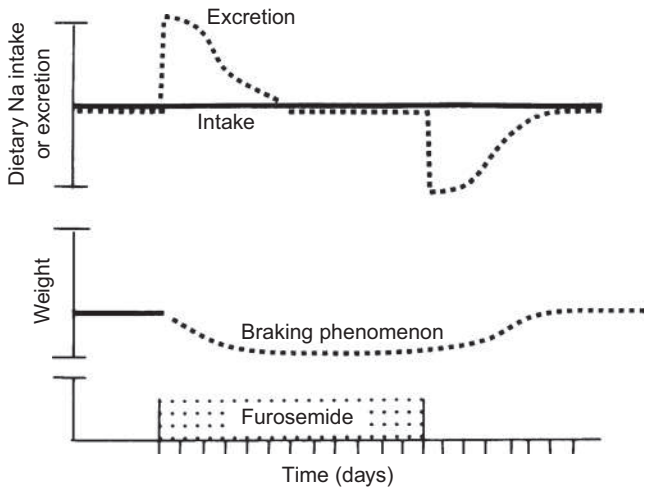


FIGURE 64.2 Diuretic tolerance or braking. Upper panel shows net sodium balance, and lower panel shows weight change in response to furosemide, which was given during the period indicated. *Reproduced with permission from reference 101 where it was redrawn with permission from Seely JF, Levy M.* Control of extracellular fluid volume. *In: Brenner BM, Rector FC, editors. The kidney. Philadelphia: WB Saunders; 1981.*

in the distal convoluted tubule and collecting duct reabsorb some but not all of the extra filtrate reaching these sites after administration of loop agents. The distal convoluted tubule can undergo structural changes that augment sodium reabsorptive capacity. Studies by Ellison et al. and by others have shown that in response to administration of furosemide, distal tubule cells undergo hypertrophy associated with increases in content of structural proteins, including the thiazide-inhibitable NaCl cotransporter (NCCT) and the Na/K ATPase that contribute to sodium transport and retention in this segment.[30–33] Over time, these adaptations increase.

Diuretic resistance is present if a dose significantly higher than the dose that produces maximal natriuresis under normal circumstances is required to produce a similar effect. Diuretic resistance can occur either on a pharmacokinetic basis due to reduced delivery of active drug to its site of action or on a pharmacodynamic basis with reduced responsiveness to drug that is delivered. The potential pharmacokinetic reasons for diuretic resistance in patients with impaired kidney function were previously discussed (see Pharmacokinetics).

The principal pharmacodynamic reason for diuretic resistance with impaired kidney function is self-evident. Despite the augmented fractional excretion of sodium that occurs with reduced kidney function (Figure 64.1), absolute sodium excretion is reduced in proportion to the reduction in filtered load and GFR.[34]

Diuretics are more effective when dietary sodium intake is restricted. A cause of apparent diuretic resistance in both patients with normal renal function and those with abnormal renal function is reabsorption of sodium at a time when the effect of a short-acting diuretic has worn off. In patients with normal renal function, the duration of action of furosemide is approximately 6 hours. Once the diuretic effect dissipates, the patient enters a compensatory sodium retentive state, i.e. diuretic braking occurs. If sodium intake is high enough, the sodium retained during that interval will reduce the net negative balance to a significant degree, leading to apparent diuretic resistance (Figure 64.3, panel A). It is clear from this figure that the administered furosemide works. It effectively increases sodium excretion during its period of activity. However, because net negative sodium balance has not been achieved, the clinically apparent effect is diuretic resistance. Imposition of a low-sodium diet (Figure 64.3, panel B) reduces the amount of sodium available for retention during the interval when the diuretic effect is absent. To some degree, this pharmacodynamic effect would be less significant with the longer acting torsemide.

Finally, augmented reabsorption of fluid due to persistence or augmentation of the factors that led to diuretic braking or tolerance can contribute to a need

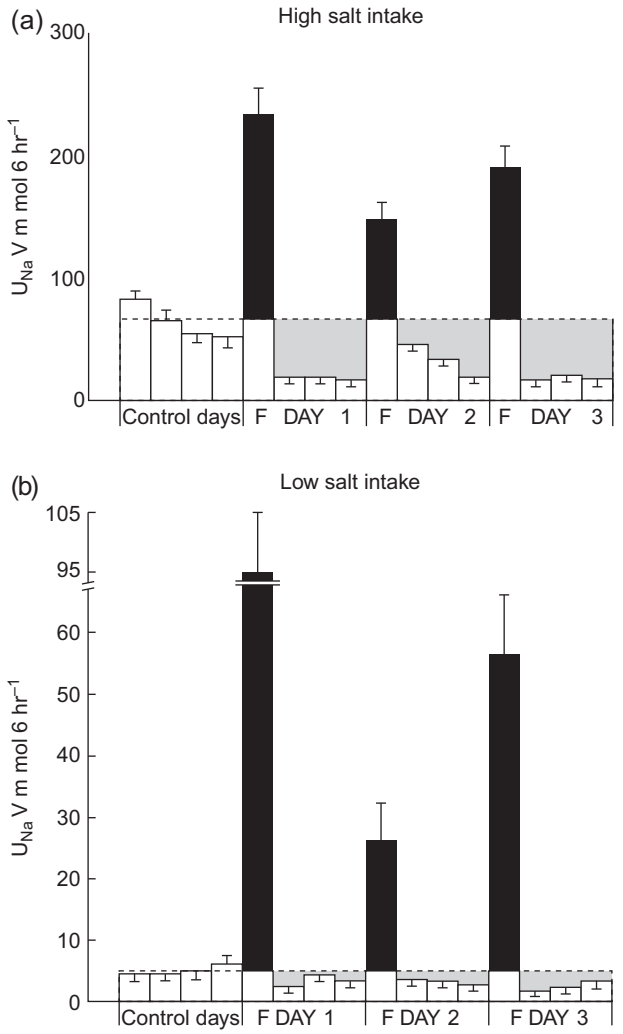


FIGURE 64.3 Apparent diuretic resistance. Effect of dietary sodium intake on overall sodium balance after administration of a single daily dose of furosemide to subjects with normal renal function. Height of bars indicates sodium excretion. *White portions* indicate excretion below ingestion rate, and *black bars* indicate excretion above ingestion rate. *Gray area* shows time period and magnitude of sodium retention during time periods when intake exceeds excretion. Note difference in scale on ordinate of each panel. In the study depicted in panel a, when subjects ingested a liberal sodium intake, the quantity of sodium retained during the intervals after the diuretic effect had dissipated (*gray areas*) was similar to the quantity of sodium excreted during the periods of diuretic action (*black bars*). The net natriuresis was thus very small. In the study depicted in panel b, dietary sodium was restricted. Little sodium was excreted during the comparable intervals after the diuretic effect dissipated. However, because there was little dietary sodium available for retention during ingestion of the restricted sodium diet, a significant net natriuresis occurred. *Reproduced with permission from reference 28.*

for higher diuretic doses. Strictly speaking, this is not diuretic resistance. The combination of mechanisms responsible for an inadequate diuretic response must be addressed simultaneously to ensure a clinically adequate diuresis (Table 64.4).

Strategies to Address Inadequate Diuretic Responsiveness due to Braking, Tolerance, or Resistance

Select an Appropriate Diuretic Dose

The dose of diuretic required to reach maximal efficacy is higher in patients with impaired kidney function than it is in individuals with normal kidney function. Using a standard 40 mg dose of furosemide in a patient with an estimated GFR (eGFR) of 20 mL/min/1.73 m^2 or a patient with hypoalbuminemia from nephrotic syndrome will predictably have limited effect. Start instead with 80 mg or 160 mg. Alternatively, start with a modest dose but plan to rapidly titrate the dose upward if no effect is observed. In the outpatient setting, patients can be counseled to observe the weight change that follows dosing and increase or decrease the dose to obtain the desired effect.

Furosemide is only 50% bioavailable, whereas the other loop agents have 80% bioavailability. Anticipate the need to double the dose of furosemide to achieve comparable activity when switching from IV to oral administration. This is especially important in patients who are discharged from the hospital coincident with the dosage and route change.

The fraction of diuretic excreted unchanged in the urine is a measure of the delivery of the diuretic to its site of action. Compared with normal renal function, with reduced kidney function, the fraction of furosemide excreted in the urine is better maintained than the comparable fractions for bumetanide and torsemide. Higher relative doses of bumetanide and torsemide will be required to treat CKD patients.

Assure that the Duration of Diuretic Effect is Adequate

As shown in Figure 64.3, reabsorption of sodium after the drug effect has dissipated may counterbalance any sodium excreted during the period of active natriuresis. Torsemide may have a longer period of action than the other loop agents, but the advantage is less in patients with reduced kidney function. Even so, a carefully conducted trial showed equivalent blood pressure lowering in CKD patients given a single daily dose of torsemide or a bioequivalent dose of furosemide in divided doses.[15] After establishing by titration a dose that is effective, repeat it on a BID or TID schedule to assure continuous inhibition of sodium reabsorption.

Limit Sodium Intake

CKD is no different than any other situation requiring diuretics. Limiting intake of sodium reduces the magnitude of natriuresis required. In addition, reducing the amount of dietary sodium available for

TABLE 64.4 Mechanisms and Possible Solutions for Diuretic Resistance in Patients with Impaired Renal Function

Observed Limitation	Possible Mechanism	Possible Solution
Overall and segmental fractional sodium excretion already increased	Limits effect of less potent diuretics	Start with a loop diuretic instead of a thiazide
Decreased proximal tubule secretion of diuretic	Competition with other organic acids for secretion	Avoid using with drugs that interfere with organic acid secretion such as cimetidine, methotrexate, sulfonamides, trimethoprim
Decreased renal elimination	Undiminished extrarenal clearance diverts drug from site of action	Note relative decrease in bumetanide and torsemide efficacy; increase dose
Enhanced sodium reabsorption in nephron segments downstream to site of action	Increased number of NCCT transporters in DCT cells, DCT hypertrophy	Use thiazide or metolazone for synergy; either effective despite reduced GFR
Diuretic is short acting	Delivery of diuretic below threshold toward the end of dosing interval	Follow diuretic response carefully and redose appropriately. Consider continuous IV infusion

NCCT, sodium chloride cotransporter; *DCT*, distal convoluted tubule; *GFR*, glomerular filtration rate.
Modified from reference 17.

retention during intervals between diuretic doses promotes the achievement of net negative balance (Figure 64.3). As patient compliance with prescribed sodium restriction is variable, measurement of 24-hour sodium excretion in the steady state can be useful to confirm adherence.

Block Reabsorption of Sodium in Sequential Nephron Segments

As discussed in diuretic braking, tolerance, and resistance, much of the tolerance seen with chronic dosing of the potent loop agents is due to augmented reabsorption in the distal convoluted tubule at the thiazide inhibitable NCCT NaCl cotransporter.[30–33] In patients with normal renal function, the addition of a thiazide or metolazone to a loop agent has a synergistic or at least additive effect on sodium excretion.[35–37] The addition of metolazone may in some circumstances produce a profound diuresis.[38] Because the effect of metolazone is protracted, it may take several days for the maximal effect to develop. Patients should be alerted to the possibility of development of an excessive response after a few days of treatment, and they should be advised to track weight loss and seek advice if urinary output exceeds the desired goal. It is often appropriate to prescribe metolazone, when used with furosemide, on an intermittent basis with dosing on alternate days or just two or three times a week. In patients limited to IV diuretics, chlorothiazide, 250 or 500 mg given intravenously twice daily, is a suitable dose for synergy. When given alone, the thiazides have reduced potency in CKD. However, several studies have documented their utility in augmenting the effect of loop agents even in patients with CKD stages 3 to 5[39,40] (Figure 64.4).

Administer the Drug via Continuous Intravenous Infusion

Continuous infusion of a loop agent may offer the advantage of maintaining a therapeutic level of diuretic over a more extended period than bolus administration. To some degree, bolus administration is inefficient. The very high blood level occurring soon after administration may be well above the plateau level of the sigmoid-shaped dose response curve. Toward the end of the dosing interval, the blood level may be below the threshold for efficacy. Although the fractional sodium excretion response to similar achieved rates of urinary furosemide excretion is the same for IV and bolus dosing, compared with bolus dosing, continuous infusion of bumetanide has been shown to produce greater sodium loss.[25,41] Furosemide bolus vs. continuous infusion was examined in a population of CKD patients given either a bolus dose or the same total dose of diuretic, with 25% given as a loading dose and 75% infused continuously over 4 hours. The continuous infusion protocol led to significantly greater absolute and fractional sodium excretion and a larger diuresis.[42] However, repeated bolus dosing can certainly be effective if urine output is monitored and the medication dose and frequency of administration is adjusted. One clinical advantage of continuous dosing is that it requires less attention compared with repeated bolus dosing on an as-needed basis. Having an effective continuous dose running "in the background" may be advantageous compared with a dosing scheme that requires active intervention and in which repeat bolus dosing may be delayed. In a different patient population, acute decompensated CHF, no efficacy difference was found with continuous compared

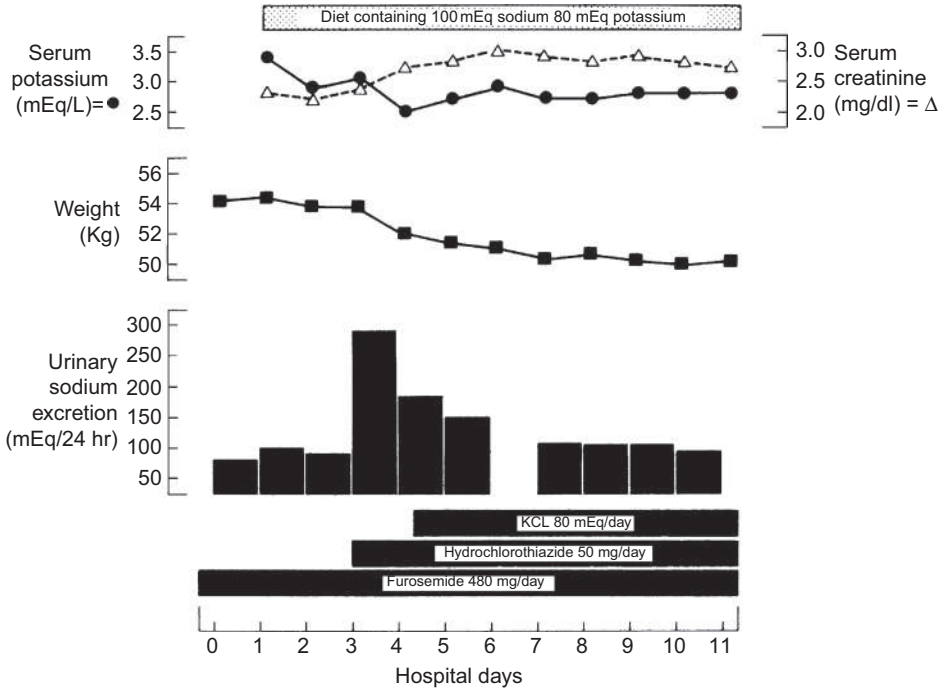


FIGURE 64.4 Additive natriuretic effect of hydrochlorothiazide to furosemide in a patient with CKD. Note that urine sodium excretion rose and weight fell coincident with addition of hydrochlorothiazide (HCTZ) to furosemide beginning on day 3. *Reproduced with permission from reference 39.*

with bolus dosing when both were given on a regular basis per protocol.[43]

The risk of diuretic ototoxicity is low with current doses of loop diuretics. Reversible ototoxicity may be noted when drug accumulates due to CKD. This is more likely with the higher peak levels achieved with bolus dosing. Continuous IV dosing may be safer in that respect.[44,45]

USE OF AGENTS OTHER THAN LOOP DIURETICS IN CKD

Carbonic Anhydrase Inhibitors

A brief course of acetazolamide may be particularly useful in patients with CKD who have developed metabolic alkalosis in clinical settings such as after receiving nasogastric suction or after a course of loop diuretics. Acetazolamide may be preferred to a thiazide when a second agent is needed to supplement a loop diuretic and metabolic alkalosis is present.

When metabolic alkalosis is absent, however, carbonic anhydrase inhibitors should be used only with great caution in CKD. Patients with impaired renal function are at increased risk for development of metabolic acidosis due to diminished ammonium production and diminished renal reserve, with an inability to compensate when acid production or bicarbonate loss is increased. Several studies have shown a high rate of development of hyperchloremic metabolic acidosis in elderly patients treated with conventional doses of acetazolamide for glaucoma.[46–48] In a study comparing 27 elderly glaucoma patients (mean age 69.1 ± 7.4 years) with age-matched controls, 4 patients (14.8%) developed mild acidosis ($7.29 < \text{pH} \leq 7.31$), 10 (37%) moderate acidosis ($7.20 < \text{pH} \leq 7.29$), and 1 (3.7%) severe acidosis (pH 7.15). Acidosis was not observed in the controls. In a second study, tCO_2 levels were inversely correlated with acetazolamide levels, which themselves correlated closely with drug dosage adjusted for creatinine clearance.

Thiazides

Conventional wisdom over many years has held that thiazides are not effective in patients with impaired kidney function. The pertinent KDIGO Guideline makes the observation that most clinicians switch from a thiazide to a loop agent in patients with CKD 4, and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure advises adding a loop agent in patients with CKD 4[1,49–52] The role of thiazides is evolving as a result of accumulating evidence that thiazides do retain efficacy in patients with CKD.[53,54] Two early studies examined this question. The first included 17 individuals with creatinine clearances ranging from 5–133 mL/min. Half had creatinine

clearances at or below 53 mL/min. Bemetizide, 25 mg, resulted in an increase in absolute sodium excretion throughout the clearance range that was proportional to the clearance value. A second study by the same investigators, also in people with a wide range of creatinine clearances, noted an increase in fractional sodium excretion after a thiazide alone. The combination of low dose HCTZ (25 mg) and 40 mg furosemide produced a significant increase in absolute sodium excretion compared with baseline. However, the difference in absolute excretion of sodium with HCTZ alone was not significant compared with placebo.[55,56] The creatinine clearances in the subset of patients with CKD ranged from 4–75 mL/min, and the absolute increment in sodium excretion was reported for the group as a whole only. This makes assessment of the efficacy at the lower GFR range difficult. Two more recent studies using diuretics in CKD compared blood pressure, fractional sodium excretion, and weights in patients with stages 3–5 CKD. Using a double-blind, placebo-controlled, randomized crossover design, patients either received placebo, 25 mg HCTZ, 40 mg furosemide, or both. Fractional sodium excretion increased and weight fell in the combination diuretic group in both studies. In one study, but not the other, fractional sodium excretion rose with HCTZ. Furosemide alone at this low dose did not result in an increase in fractional sodium excretion, but it did lower weight in one of the two studies. HCTZ alone did not result in weight reduction. Despite the lack of consistent weight reduction, mean arterial pressure fell significantly in both studies in all three diuretic groups.[40,57] An open label, parallel treatment study compared the effect of chlorthalidone 25 mg in 60 patients with impaired kidney function (mean eGFR 39, range 15–59 mL/min/1.73 m^2) to its effect in 60 patients with normal kidney function (mean eGFR 76, range 60–104 mL/min/1.73 m^2). After 8 weeks of treatment, systolic blood pressure changes were similar, decreasing 20 mm Hg (95% confidence interval −22 to −18) and 23 mm Hg (−26 to −19), respectively. The blood pressure decrement was similar in the subgroups with CKD 3b, 4, and 5[58] (Figure 64.5).

Studies have examined the effect of add-on thiazide therapy to further reduce blood pressure, proteinuria, or albuminuria in patients with CKD already receiving ACEI or ARB treatment. Some compare a thiazide with a calcium channel blocker, noting a more favorable effect on albuminuria for the thiazide but a tendency for a larger short-term fall in eGFR. Most of these studies are small. They use heterogeneous submaximal doses of different thiazides in patients at varying stages of CKD who may or may not also be receiving maximal doses of loop diuretics, ACEIs, or ARBs. The studies provide evidence that thiazides can be beneficial in this setting. However, their design does not permit separating a specific antialbuminuric effect of the thiazide itself from the blood pressure lowering effect.[59,60] One such study, a randomized crossover trial, examined addition of spironolactone 25 mg or hydrochlorothiazide 50 mg to the regimen of 21 patients with CKD stages 1–3 who were already taking enalapril. After 4 weeks of treatment, systolic blood pressure fell from 130 ± 18 to 125 ± 20 mg Hg ($p < 0.05$) with spironolactone and from 129 ± 18 to 124 ± 19 mm Hg ($p = NS$)

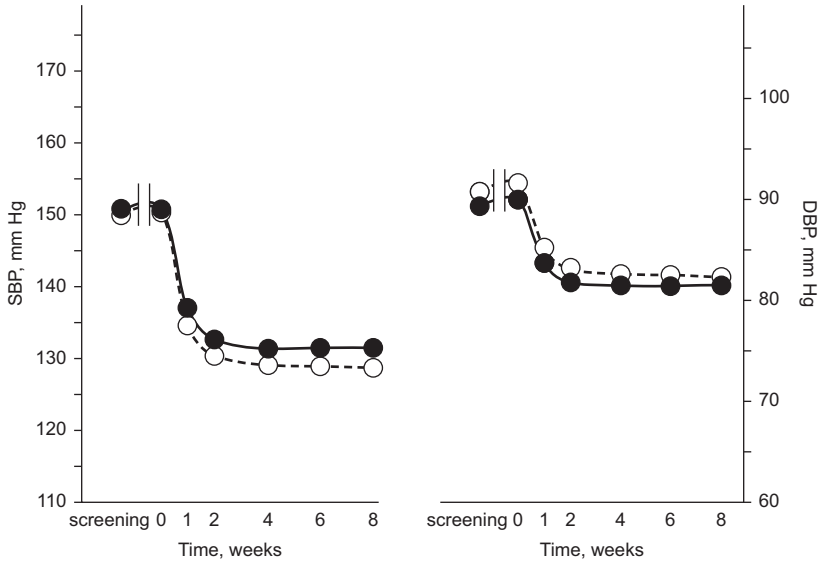


FIGURE 64.5 Means of systolic blood pressure (SBP, left) and diastolic blood pressure (DBP, right) in hypertensive individuals with eGFR<60 mL/min/1.73 m^2, *closed circles*, n = 60 and hypertensive individuals with 60 mL/min/1.73 $m^2 \leq$ eGFR $\leq$ 104 mL/min/1.73 m^2, *open circles*, n = 57 who received chlorthalidone, 25 mg daily, from week zero. Patient numbers and graphs are for per protocol groups. *Reproduced with permission from reference 58.*

with hydrochlorothiazide, as albumin excretion fell from 1600 (25–75% IQR 1047–2152) to 1125 mg/day (IQR 500–1750) ($p < 0.05$), with spironolactone and from 1417 (IQR 868–1965) to 935 mg/day (IQR 266–1603) ($p < 0.05$) with hydrochlorothiazide. In the spironolactone group, 12 patients (57%) experienced a >30% reduction in urinary albumin:creatinine ratio as did 17 (81%) of the hydrochlorothiazide-treated patients. Daily urine protein excretion fell from a mean of 1.7 (IQR 1.3–2.2) to 1.5 g (IQR 0.8–2.3) ($p < 0.05$) with spironolactone and from 1.7 (IQR 1.3–2.1) to 1.3 g (IQR 0.6–2) ($p < 0.05$) with hydrochlorothiazide. Weight fell with both regimens and the fall in albumin excretion correlated with the reduction in eGFR and blood pressure. Results were similar in a third group that received hydrochlorothiazide 50 mg plus amiloride 5 mg.[61] Taken together, these trials provide additional support for rejecting the notion that thiazides should be stopped when some arbitrary low threshold of GFR is reached, as they retain utility in lowering blood pressure and may reduce albuminuria or proteinuria.

The observed effects may be due to some other cause than a natriuresis. This is not a new observation.[62] Potential mechanisms, including diminished pressor response to catecholamines and angiotensin II, calcium desensitization of smooth muscle, nitric oxide release, and activation of potassium channels, have been reviewed.[53] Notably, intraarterial infusion of hydrochlorothiazide, but not the thiazide-like agent indapamide, causes a forearm vasodilator response both in normal individuals and those with Gitelman syndrome who lack the distal convoluted tubule NCC thiazide receptor.[63]

Results from large-scale trials also support the use of thiazides. In a *post hoc* analysis of the subgroup of patients in the ALLHAT trial with eGFR below 60 mL/min/1.73 m^2, chlorthalidone was noted to be more effective than amlodipine or lisinopril in preventing stroke and congestive heart failure, and noninferior in preventing coronary heart disease, cardiovascular disease events, or ESRD. These differences (except for a lower incidence of heart failure compared with amlodipine) did not persist at late follow-up, but patients were no longer being treated per protocol at that point. As such, this study provides evidence for efficacy of chlorthalidone in improving outcomes in CKD. Systolic blood pressure was slightly lower in the ALLHAT chlorthalidone group, although ALLHAT was not designed to assess patients with diminished renal function specifically, and patients with serum creatinine (S[Cr]) above 2.0 mg/dL or proteinuria were excluded.[64,65] Considerable support for the use of thiazide-type diuretics was provided by the SPRINT trial, which, in contrast to ALLHAT, was specifically designed to examine cardiovascular outcomes in patients with impaired kidney function. Its study protocol recommended that thiazide diuretics be chosen as initial antihypertensive therapy. Fully 46.8% of the 1330 intensively treated CKD patients and 30.1% of the 1316 CKD patients that received standard therapy were receiving a thiazide-type diuretic at last visit, although no breakdown between the two formulary agents, chlorthalidone and hydrochlorothiazide/amiloride, was provided. The study demonstrated reduced rates of major cardiovascular events and all-cause death in its intensive blood pressure control group, a large plurality of whom were receiving thiazides to achieve the blood pressure goal.[66]

A potential role of thiazide therapy compared with loop diuretic therapy to lessen the risk of development of secondary hyperparathyroidism in CKD has been suggested by an analysis of the Chronic Renal Insufficiency Cohort. In this patient population, eGFR ranged from 20 to 70 mL/min/1.73 m^2. In the subset of patients receiving diuretics, the adjusted daily calcium excretion was 39.6 mg/24 h (37.2–42.2, 95% CI). In the subset receiving loop diuretics alone, it was 55.0 mg/24 h (50.8–59.5, $p < 0.05$ vs. no diuretic). In the subset receiving thiazides alone, it was 25.5 mg/24 h (23.3–27.8, $p < 0.05$ vs. no diuretic). In the subset receiving both, it was 30.3 mg/24 h (26.6–34.5, $p < 0.05$).[67] PTH levels were higher in the loop diuretic-treated patients compared with patients who received no diuretics, but there was no difference between thiazide-treated patients and the controls. The adjusted odds ratio for secondary hyperparathyroidism, defined as a PTH≥65 pg/mL, was higher for participants treated with loop diuretics than for those with no diuretics. The odds of developing secondary hyperparathyroidism were not increased in patients receiving thiazides or in patients receiving both diuretics. The reduction in odds in the latter group was seen only in patients with stage 2 or 3 CKD. Thiazides were not protective in patients with stage 4 CKD. As the accompanying editorial pointed out, however, whether these biochemical differences mean that an improvement in clinical outcomes such as reduced cardiovascular morbidity or mortality or reduced fracture rate will result from addition or substitution of a thiazide is far from established.[68]

Little guidance is available on the choice of thiazide or thiazide-type diuretic to use in patients with CKD. Drug potency varies between agents. In normal individuals, the amount of drug estimated to produce a 10 mm Hg reduction in systolic BP is 1.4 mg for bendroflumethiazide, 8.6 mg for chlorthalidone, and 26.4 mg for hydrochlorothiazide.[69] Chlorthalidone is often recommended because of its longer duration of action, and the large-scale trials cited above used it exclusively or favored it over hydrochlorothiazide, but its longer

duration of action may predispose to a higher risk of complications.[64,66,70] Formal comparisons in patients with CKD are lacking.

Mineralocorticoid Receptor Antagonists

Two MRAs are currently approved for use by the US FDA, spironolactone and eplerenone. The former is nonspecific, with lesser but still significant affinity for progesterone and androgen receptors, a characteristic responsible for its endocrine side effects, including gynecomastia, diminished libido, and menstrual irregularities. Eplerenone is a more specific MRA. It has fewer off-target effects but is also less potent and more expensive. The pharmacokinetics of neither agent is significantly affected by renal functional impairment. Both these agents have steroid chemical structures. New, nonsteroidal agents, including finerenone, which has a dihydropyridine structure, are under development.[71–74] MRAs are highly effective in lowering blood pressure in patients with normal renal function and resistant hypertension. They have long been used as add on therapy in that setting.[75] However, any benefit of lowering blood pressure in CKD patients, particularly individuals already receiving an ACEI or ARB, has to be considered in the context of the risk of hyperkalemia.

Studies in patients with CKD document similar efficacy of MRAs for blood pressure control and provide reassurance that if used with care, the risk of hyperkalemia is not prohibitive. One such study retrospectively examined 88 patients with resistant hypertension who were begun on spironolactone. The baseline drug regimen included an ACEI or ARB in 90% of patients. Thirty-four patients had CKD, defined as an eGFR <60 mL/min/1.73 m^2. Mean systolic blood pressure fell from 153 ± 18 to 143 ± 20 mm Hg ($p = 0.006$), from baseline to first clinic visit after starting spironolactone in the CKD patients, and from 150 ± 17 to 135 ± 17 mm Hg ($p < 0.001$), in the patients without CKD. In both groups, about half of patients responded with a blood pressure drop, but half were nonresponders. Serum potassium (S[K]) increased by 0.5 ± 0.6 mEq/L in the CKD group vs. 0.3 ± 0.5 mEq/L in the patients without CKD, a difference that was not statistically significant. Hyperkalemia, defined as S[K] $>5.5\%$, occurred in 5.7% of CKD patients compared with none of the non-CKD patients ($p = 0.07$). In a multivariable model, only eGFR <45 mL/min/1.73 m^2 was associated with a higher risk of hyperkalemia. The dose of spironolactone was less than 25 mg in 93% of individuals. Length of follow-up beyond one return visit was not specified, and whether more patients would have responded with longer follow-up or developed hyperkalemia is unknown.[76] In a retrospective study of 36 patients with resistant hypertension, all with stage 3 CKD, in whom spironolactone (mean dose 23.6 ± 10.5 mg) or eplerenone (mean dose 60.4 ± 33.9 mg) was added to a preexisting drug regimen that included an ACEI or ARB, systolic blood pressure after a median of 312 days dropped from 162 ± 22 to 138 ± 14 mm Hg, $p < 0.0001$, and diastolic blood pressure from 87 ± 17 to 74 ± 12 mm Hg, $p < 0.0001$. The eGFR decreased from 48.6 ± 8.7 to 41.2 ± 11.5 mL/min/1.73 m^2 ($p = 0.002$). S[K] increased from 4.0 ± 0.5 to 4.4 ± 0.5 mEq/L ($p = 0.0001$), with 8 (22%) patients developing hyperkalemia (S[K] >5 mEq/L) at any time, including 3 (8%) with a value of S[K] above 5.5 mEq/L.[77] In a study of patients with mild to moderate CKD (eGFR 30–89 mL/min/1.73 m^2) spironolactone, 25 mg, or placebo was used as an add on to maximal ACEI or ARB therapy over a 40 week period. Patients who developed hyperkalemia during a one-month open label spironolactone run in period were dropped from the study before randomization. Of the 112 patients who went forward, fewer than 1% developed S[K] $\geq$6.0 mEq/L. Eleven patients (9 on spironolactone) developed hyperkalemia in the S[K] 5.5–5.9 mEq/L range. At 40 weeks, the drop in ambulatory systolic blood pressure was -6 mg Hg (95% CI -8 to -1) in the spironolactone treated group vs. 1 mm Hg (-3 to -1) in the placebo group ($p < 0.01$). In this group of patients who were already receiving maximal ACEI or ARB therapy, the only predictor of hyperkalemia was baseline S[K] > 5.0 mEq/L[78] Another study noted eGFR<45 mL/min/1.73 m^2 and treatment-induced drop in systolic blood pressure >15 mm Hg as risk factors for hyperkalemia.[79]

An influential population-based study showed an increased rate of hyperkalemia morbidity and mortality following publication of the RALES study, and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure cautions against initiating aldosterone receptor antagonists in patients with a basal S[K] exceeding 5 mEq/L.[50,80] Even so, these small but granular studies provide reassurance that MRAs can be used safely in patients with mild to moderate reductions in GFR. Eplerenone has a shorter half-life than spironolactone. Its use has been suggested as an alternative to spironolactone in CKD because its effect will dissipate sooner if hyperkalemia develops. Conventional strategies to permit use of MRAs in CKD include restriction of potassium intake, supplementation with bicarbonate to provide a nonreabsorbable anion (excretion of which may enhance potassium excretion), and concomitant use of kaliuretic loop diuretics. Patiromer and sodium zirconium cyclosilicate have recently been approved as potassium lowering agents.[81,82] Published data specifically addressing hyperkalemia risk in patients with CKD stages 3b, 4, and 5 are lacking; no studies systematically address the effect of concurrently prescribed

kaliuretic loop or thiazide diuretics or bicarbonate on hyperkalemia risk.[83]

In summary, MRAs effectively lower blood pressure in patients with reduced GFR, including those receiving ACEIs or ARBs, but their safe use requires ongoing vigilance regarding the possible development of hyperkalemia.

Mineralocorticoid receptors are now known to be present not only in principal cells of the collecting duct but also in a variety of other cells or tissues, among them the heart, brain, vascular smooth muscle, and glomerular podocytes. At these sites, activation of the mineralocorticoid receptor has pleiotropic effects to increase the release or activation of vasoconstrictors and inflammatory or profibrotic cytokines, promote cardiac and kidney fibrosis, contribute to insulin insensitivity, and cause glomerular podocyte damage with worsened proteinuria. As a result, increasing attention has been drawn to the use of MRAs in patients with CKD to reduce proteinuria, reduce risk of ESRD, and improve cardiovascular outcomes.[84,85] As aldosterone levels increase in 30–50% of patients after initiation of ACEI or ARB therapy, a phenomenon called aldosterone escape or breakthrough, adding MRA therapy to the regimen of CKD patients already receiving ACEI or ARB therapy could be especially attractive.[72] Addition of spironolactone or eplerenone has been demonstrated to reduce proteinuria by 38–61% in such patients or to reduce albuminuria by 33–48%.[86–90] This practice has been the subject of several systematic reviews or meta-analyses. Although they confirm that added MRAs reduce blood pressure and proteinuria or albuminuria, increase the rate of development of hyperkalemia, and modestly lower GFR over the short term, none of the small studies that form the basis of this conclusion was designed or powered to assess hard, patient-centered outcomes such as cardiovascular events, mortality, or development of ESRD. Thus, neither individual studies nor the comprehensive reviews provide compelling evidence to date regarding whether MRAs have an indication in CKD beyond management of refractory hypertension.[84,91–93] Large-scale trials with the potential to provide more definitive data are underway[83] (https://clinicaltrials.gov/ct2/show/NCT02540993).

USE OF DIURETICS FOR TREATMENT OF HYPERTENSION IN CKD

Extracellular volume overload is an important contributor to hypertension in CKD patients, and correction of volume overload with diuretics is a key part of treatment. When appropriately dosed, loop diuretics are plainly effective in reducing extracellular volume and lowering blood pressure in CKD patients.[15,94] Although this principle is generally accepted, diuretics appear to be underutilized in CKD patients, perhaps because of prescriber concerns about the tendency of these agents to lower eGFR if clinical or subclinical volume depletion is induced. A large study evaluating treatment of hypertension in 26 Italian CKD clinics observed furosemide use (the loop diuretic prescribed virtually exclusively) in only 27% of stage 3, 42% of stage 4, and 51% of stage 5 patients. In more than half of the patients who were receiving a loop diuretic, the dose was deemed inadequate. A fixed dose combination of losartan 50 mg/hydrochlorothiazide 12.5 mg was found to be inferior to losartan 50 mg plus nifedipine 20–40 mg for lowering blood pressure in CKD patients, highlighting the need to choose an appropriate diuretic in an adequate dosage.

DIURETIC COMPLICATIONS

Diuretic complications have been extensively reviewed.[45,95] Metabolic derangements resulting from use of thiazide or loop diuretics include hyponatremia, hypokalemia, hypomagnesemia, hyperuricemia, hyperglycemia, and metabolic alkalosis. Hypokalemia and metabolic alkalosis become less of a problem as renal function worsens. In addition, concomitant use of ACEIs or ARBs as well as MRAs in this population may mitigate hypokalemia or result in frank hyperkalemia. Spironolactone may contribute to the development of metabolic acidosis.[96] When present, hypokalemia is readily managed with potassium supplementation or addition of a potassium-sparing agent. Hyponatremia carries an adverse prognosis in CKD patients, as it does in the general population.[97,98] Hyponatremia is much more common with the thiazides, which block sodium transport in the distal convoluted tubule diluting sites. Recently, a genetic risk factor for thiazide-induced hyponatremia related to altered prostaglandin transport and diminished water excretion has been identified.[99] In any event, thiazide diuretics should be stopped and a loop agent substituted if continued diuretic therapy is required in CKD patients with hyponatremia. Hyperuricemia can be a relative contraindication for diuretic use. Gout combined with the unsuitability of NSAID treatment in CKD patients may also be responsible for the reluctance of some clinicians to prescribe diuretics. However, hyperuricemia is amenable to therapy with allopurinol. Hypomagnesemia may be a particular problem in renal transplant patients with CKD who receive both diuretics and tacrolimus. Clinicians should be vigilant for this complication, supplement magnesium, and stop proton pump inhibitors, if coprescribed, as required. Finally, diuretics may exacerbate urinary incontinence. Reported diminished adherence to diuretics is 3–4 times more prevalent among patients with urinary incontinence, a factor that may contribute to apparent refractoriness to diuretics.[100]

CONCLUSION

As CKD is commonly associated with sodium retention, which contributes importantly to hypertension, diuretics are often prescribed to CKD patients. The potent loop agents remain the mainstay of diuretic therapy, but their proper use requires an understanding of their altered pharmacokinetics and pharmacodynamics in CKD. Repeating an inadequate dose is futile; it is essential to use upward dosage titration to identify an effective dose, which can then be repeated. Short-acting agents, such as furosemide and bumetanide, should be given more than once per day to assure that the antinatriuresis characteristic of the diuretic-free interval does not negate the natriuresis achieved while active drug is present. Recent data, confirmed by the SPRINT trial, suggest that thiazides have persistent benefit with improved outcomes even in advanced CKD. They need not be abandoned at some arbitrary level of GFR.[66] Mineralocorticoid antagonists are particularly useful add-on agents both for blood pressure control and to reduce proteinuria and slow disease progression in CKD, although clinicians should maintain vigilance for hyperkalemia when an agent of this class is used.

References

1. Brater DC. Diuretic therapy. *N Engl J Med* 1998;**339**:387–95.
2. Sica DA. Diuretic use in renal disease. *Nat Rev Nephrol* 2012;**8**: 100–9.
3. Brater DC. Diuretics. In: Williams RL, Brater DC, Mordenti J, editors. *Rational therapeutics. A clinical pharmacologic guide for the health professional*. New York: Marcel Dekker, Inc.; 1990. p. 269–314.
4. Sica DA, Gehr TW. Diuretic use in stage 5 chronic kidney disease and end-stage renal disease. *Curr Opin Nephrol Hypertens* 2003;**12**: 483–90.
5. Brater DC. Clinical pharmacology of loop diuretics. *Drugs* 1991; **41**(Suppl. 3):14–22.
6. Brater DC. Diuretic resistance: mechanisms and therapeutic strategies. *Cardiology* 1994;**84**(Suppl. 2):57–67.
7. Voelker JR, Cartwright-Brown D, Anderson S, Leinfelder J, Sica DA, Kokko JP, Brater DC. Comparison of loop diuretics in patients with chronic renal insufficiency. *Kidney Int* 1987;**32**:572–8.
8. Beermann B, Groschinsky-Grind M. Clinical pharmacokinetics of diuretics. *Clin Pharmacokinet* 1980;**5**:221–45.
9. Benet LZ. Pharmacokinetics/pharmacodynamics of furosemide in man: a review. *J Pharmacokinet Biopharm* 1979;**7**:1–27.
10. Tilstone WJ, Fine A. Furosemide kinetics in renal failure. *Clin Pharmacol Ther* 1978;**23**:644–50.
11. Beermann B, Dalen E, Lindstrom B. Elimination of furosemide in healthy subjects and in those with renal failure. *Clin Pharmacol Ther* 1977;**22**:70–8.
12. Cutler RE, Forrey AW, Christopher TG, Kimpel BM. Pharmacokinetics of furosemide in normal subjects and functionally anephric patients. *Clin Pharmacol Ther* 1974;**15**:588–96.
13. Andreasen F, Hansen HE, Mikkelsen E. Pharmacokinetics of furosemide in anephric patients and in normal subjects. *Eur J Clin Pharmacol* 1978;**13**:41–8.
14. Goto S, Yoshitomi H, Miyamoto A, Inoue K, Nakano M. Binding of several loop diuretics to serum albumin and human serum from patients with renal failure and liver disease. *J Pharmacobio-Dyn* 1980;**3**:667–76.
15. Vasavada N, Agarwal R. Role of excess volume in the pathophysiology of hypertension in chronic kidney disease. *Kidney Int* 2003; **64**:1772–9.
16. Brater DC. Resistance to loop diuretics. Why it happens and what to do about it. *Drugs* 1985;**30**:427–43.
17. Wilcox CS. New insights into diuretic use in patients with chronic renal disease. *J Am Soc Nephrol* 2002;**13**:798–805.
18. Rane A, Villeneuve JP, Stone WJ, Nies AS, Wilkinson GR, Branch RA. Plasma binding and disposition of furosemide in the nephrotic syndrome and in uremia. *Clin Pharmacol Ther* 1978;**24**:199–207.
19. Pichette V, Geadah D, du SP. Role of plasma protein binding on renal metabolism and dynamics of furosemide in the rabbit. *Drug Metab Dispos* 1999;**27**:81–5.
20. Kirchner KA, Voelker JR, Brater DC. Binding inhibitors restore furosemide potency in tubule fluid containing albumin. *Kidney Int* 1991;**40**:418–24.
21. Fliser D, Zurbruggen I, Mutschler E, Bischoff I, Nussberger J, Franek E, Ritz E. Coadministration of albumin and furosemide in patients with the nephrotic syndrome. *Kidney Int* 1999;**55**:629–34.
22. Akcicek F, Yalniz T, Basci A, Ok E, Mees EJ. Diuretic effect of frusemide in patients with nephrotic syndrome: is it potentiated by intravenous albumin? *BMJ* 1995;**310**:162–3.
23. Phakdeekitcharoen B, Boonyawat K. The added-up albumin enhances the diuretic effect of furosemide in patients with hypoalbuminemic chronic kidney disease: a randomized controlled study. *BMC Nephrol* 2012;**13**:92.
24. Agarwal R, Gorski JC, Sundblad K, Brater DC. Urinary protein binding does not affect response to furosemide in patients with nephrotic syndrome. *J Am Soc Nephrol* 2000;**11**:1100–5.
25. Brater DC, Anderson SA, Brown-Cartwright D. Response to furosemide in chronic renal insufficiency: rationale for limited doses. *Clin Pharmacol Ther* 1986;**40**:134–9.
26. Rudy DW, Gehr TW, Matzke GR, Kramer WG, Sica DA, Brater DC. The pharmacodynamics of intravenous and oral torsemide in patients with chronic renal insufficiency. *Clin Pharmacol Ther* 1994;**56**:39–47.
27. Allison ME, Lindsay MK, Kennedy AC. Oral bumetanide in chronic renal failure. *Postgrad Med J* 1975;**51**(Suppl. 6):47–50.
28. Wilcox CS, Mitch WE, Kelly RA, Skorecki K, Meyer TW, Friedman PA, Souney PF. Response of the kidney to furosemide. I. Effects of salt intake and renal compensation. *J Lab Clin Med* 1983;**102**:450–8.
29. Wilcox CS, Guzman NJ, Mitch WE, Kelly RA, Maroni BJ, Souney PF, Rayment CM, Braun L, Colucci R, Loon NR. Na+, K+, and BP homeostasis in man during furosemide: effects of prazosin and captopril. *Kidney Int* 1987;**31**:135–41.
30. Ellison DH. Diuretic drugs and the treatment of edema: from clinic to bench and back again. *Am J Kidney Dis* 1994;**23**:623–43.
31. Ellison DH, Velazquez H, Wright FS. Adaptation of the distal convoluted tubule of the rat. Structural and functional effects of dietary salt intake and chronic diuretic infusion. *J Clin Investig* 1989; **83**:113–26.
32. Chen ZF, Vaughn DA, Beaumont K, Fanestil DD. Effects of diuretic treatment and of dietary sodium on renal binding of 3H-metolazone. *J Am Soc Nephrol* 1990;**1**:91–8.
33. Kaissling B, Stanton BA. Adaptation of distal tubule and collecting duct to increased sodium delivery. I. Ultrastructure. *Am J Physiol* 1988;**255**:F1256–68.
34. Ellison DH. Treatment of disorders of sodium balance in chronic kidney disease. *Adv Chron Kidney Dis* 2017;**24**:332–41.

35. Brater DC, Pressley RH, Anderson SA. Mechanisms of the synergistic combination of metolazone and bumetanide. *J Pharmacol Exp Ther* 1985;**233**:70–4.
36. Marone C, Muggli F, Lahn W, Frey FJ. Pharmacokinetic and pharmacodynamic interaction between furosemide and metolazone in man. *Eur J Clin Investig* 1985;**15**:253–7.
37. Greenberg A, Wallia R, Puschett JB. Combined effect of bumetanide and metolazone in normal volunteers. *J Clin Pharmacol* 1985;**25**:369–73.
38. Gunstone RF, Wing AJ, Shani HG, Njemo D, Sabuka EM. Clinical experience with metolazone in fifty-two African patients: synergy with frusemide. *Postgrad Med J* 1971;**47**:789–93.
39. Wollam GL, Tarazi RC, Bravo EL, Dustan HP. Diuretic potency of combined hydrochlorothiazide and furosemide therapy in patients with azotemia. *Am J Med* 1982;**72**:929–38.
40. Dussol B, Moussi-Frances J, Morange S, Somma-Delpero C, Mundler O, Berland Y. A pilot study comparing furosemide and hydrochlorothiazide in patients with hypertension and stage 4 or 5 chronic kidney disease. *J Clin Hypertens* 2012;**14**:32–7.
41. Rudy DW, Voelker JR, Greene PK, Esparza FA, Brater DC. Loop diuretics for chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. *Ann Intern Med* 1991;**115**:360–6.
42. Sanjay S, Annigeri RA, Seshadri R, Rao BS, Prakash KC, Mani MK. The comparison of the diuretic and natriuretic efficacy of continuous and bolus intravenous furosemide in patients with chronic kidney disease. *Nephrology* 2008;**13**:247–50.
43. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011;**364**:797–805.
44. Gerlag PG, van Meijel JJ. High-dose furosemide in the treatment of refractory congestive heart failure. *Arch Intern Med* 1988;**148**:286–91.
45. Greenberg A. Diuretic complications. *Am J Med Sci* 2000;**319**:10–24.
46. Chapron DJ, Gomolin IH, Sweeney KR. Acetazolamide blood concentrations are excessive in the elderly: propensity for acidosis and relationship to renal function. *J Clin Pharmacol* 1989;**29**:348–53.
47. Maisey DN, Brown RD. Acetazolamide and symptomatic metabolic acidosis in mild renal failure. *Br Med J* 1981;**283**:1527–8.
48. Heller I, Halevy J, Cohen S, Theodor E. Significant metabolic acidosis induced by acetazolamide. Not a rare complication. *Arch Intern Med* 1985;**145**:1815–7.
49. Reubi FC, Cottier PT. Effects of reduced glomerular filtration rate on responsiveness to chlorothiazide and mercurial diuretics. *Circulation* 1961;**23**:200–10.
50. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, Roccella EJ. National heart LaBIJNCoP, national high blood pressure education program coordinating committee: the seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *J Am Med Assoc* 2003;**289**:2560–72.
51. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004;**43**:S1–290.
52. Chapter 2: lifestyle and pharmacological treatments for lowering blood pressure in CKD ND patients. *Kidney Int Suppl* 2012;**2**:347–56.
53. Karadsheh F, Weir MR. Thiazide and thiazide-like diuretics: an opportunity to reduce blood pressure in patients with advanced kidney disease. *Curr Hypertens Rep* 2012;**14**:416–20.
54. Sinha AD, Agarwal R. Thiazide diuretics in chronic kidney disease. *Curr Hypertens Rep* 2015;**17**:13.
55. Knauf H, Cawello W, Schmidt G, Mutschler E. The saluretic effect of the thiazide diuretic bemetizide in relation to the glomerular filtration rate. *Eur J Clin Pharmacol* 1994;**46**:9–13.
56. Knauf H, Mutschler E. Diuretic effectiveness of hydrochlorothiazide and furosemide alone and in combination in chronic renal failure. *J Cardiovasc Pharmacol* 1995;**26**:394–400.
57. Dussol B, Moussi-Frances J, Morange S, Somma-Delpero C, Mundler O, Berland Y. A randomized trial of furosemide vs hydrochlorothiazide in patients with chronic renal failure and hypertension. *Nephrol Dial Transplant* 2005;**20**:349–53.
58. Cirillo M, Marcarelli F, Mele AA, Romano M, Lombardi C, Bilancio G. Parallel-group 8-week study on chlorthalidone effects in hypertensives with low kidney function. *Hypertension* 2014;**63**:692–7.
59. Hoshino T, Ookawara S, Miyazawa H, Ito K, Ueda Y, Kaku Y, Hirai K, Mori H, Yoshida I, Tabei K. Renoprotective effects of thiazides combined with loop diuretics in patients with type 2 diabetic kidney disease. *Clin Exp Nephrol* 2015;**19**:247–53.
60. Ishimitsu T, Ohno E, Nakano N, Furukata S, Akashiba A, Minami J, Numabe A, Matsuoka H. Combination of angiotensin II receptor antagonist with calcium channel blocker or diuretic as antihypertensive therapy for patients with chronic kidney disease. *Clin Exp Hypertens* 2011;**33**:366–72.
61. Morales E, Caro J, Gutierrez E, Sevillano A, Aunon P, Fernandez C, Praga M. Diverse diuretics regimens differentially enhance the antialbuminuric effect of renin-angiotensin blockers in patients with chronic kidney disease. *Kidney Int* 2015;**88**:1434–41.
62. Jones B, Nanra RS. Double-blind trial of antihypertensive effect of chlorothiazide in severe renal failure. *Lancet* 1979;**2**:1258–60.
63. Pickkers P, Hughes AD, Russel FG, Thien T, Smits P. Thiazide-induced vasodilation in humans is mediated by potassium channel activation. *Hypertension* 1998;**32**:1071–6.
64. Rahman M, Pressel S, Davis BR, Nwachuku C, Wright Jr JT, Whelton PK, Barzilay J, Batuman V, Eckfeldt JH, Farber MA, Franklin S, Henriquez M, Kopyt N, Louis GT, Saklayen M, Stanford C, Walworth C, Ward H, Wiegmann T. Cardiovascular outcomes in high-risk hypertensive patients stratified by baseline glomerular filtration rate. *Ann Intern Med* 2006;**144**:172–80.
65. Rahman M, Ford CE, Cutler JA, Davis BR, Piller LB, Whelton PK, Wright Jr JT, Barzilay JI, Brown CD, Colon Sr PJ, Fine LJ, Grimm Jr RH, Gupta AK, Baimbridge C, Haywood LJ, Henriquez MA, Ilamaythi E, Oparil S, Preston R. Long-term renal and cardiovascular outcomes in antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) participants by baseline estimated GFR. *Clin J Am Soc Nephrol* 2012;**7**:989–1002.
66. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, Cushman WC, Hawfield AT, Johnson KC, Lewis CE, Oparil S, Rocco MV, Sink KM, Whelton PK, Wright Jr JT, Basile J, Beddhu S, Bhatt U, Chang TI, Chertow GM, Chonchol M, Freedman BI, Haley W, Ix JH, Katz LA, Killeen AA, Papademetriou V, Ricardo AC, Servilla K, Wall B, Wolfgram D, Yee J. Effects of intensive BP control in CKD. *J Am Soc Nephrol* 2017;**28**:2812–23.
67. Isakova T, Anderson CA, Leonard MB, Xie D, Gutierrez OM, Rosen LK, Theurer J, Bellovich K, Steigerwalt SP, Tang I, Anderson AH, Townsend RR, He J, Feldman HI, Wolf M. Chronic renal insufficiency cohort (CRIC) study group: diuretics, calciuria and secondary hyperparathyroidism in the chronic renal insufficiency cohort. *Nephrol Dial Transplant* 2011;**26**:1258–65.
68. Kovesdy CP, Kalantar-Zadeh K. Diuretics and secondary hyperparathyroidism in chronic kidney disease. *Nephrol Dial Transplant* 2011;**26**:1122–5.

69. Peterzan MA, Hardy R, Chaturvedi N, Hughes AD. Meta-analysis of dose-response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. *Hypertension* 2012;**59**:1104–9.
70. Ernst ME, Carter BL, Goerdt CJ, Steffensmeier JJ, Phillips BB, Zimmerman MB, Bergus GR. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension* 2006;**47**:352–8.
71. Yang P, Huang T, Xu G. The novel mineralocorticoid receptor antagonist finerenone in diabetic kidney disease: progress and challenges. *Metabolism* 2016;**65**:1342–9.
72. Schwenk MH, Hirsch JS, Bomback AS. Aldosterone blockade in CKD: emphasis on pharmacology. *Adv Chron Kidney Dis* 2015;**22**: 123–32.
73. Filippatos G, Anker SD, Bohm M, Gheorghiade M, Kober L, Krum H, Maggioni AP, Ponikowski P, Voors AA, Zannad F, Kim SY, Nowack C, Palombo G, Kolkhof P, Kimmeskamp-Kirschbaum N, Pieper A, Pitt B. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. *Eur Heart J* 2016;**37**:2105–14.
74. Bakris GL, Agarwal R, Chan JC, Cooper ME, Gansevoort RT, Haller H, Remuzzi G, Rossing P, Schmieder RE, Nowack C, Kolkhof P, Joseph A, Pieper A, Kimmeskamp-Kirschbaum N, Ruilope LM. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. *J Am Med Assoc* 2015;**314**:884–94.
75. Nishizaka MK, Zaman MA, Calhoun DA. Efficacy of low-dose spironolactone in subjects with resistant hypertension. *Am J Hypertens* 2003;**16**:925–30.
76. Heshka J, Ruzicka M, Hiremath S, McCormick BB. Spironolactone for difficult to control hypertension in chronic kidney disease: an analysis of safety and efficacy. *J Am Soc Hypertens* 2010;**4**:295–301.
77. Pisoni R, Acelajado MC, Cartmill FR, Dudenbostel T, Dell'Italia LJ, Cofield SS, Oparil S, Calhoun DA. Long-term effects of aldosterone blockade in resistant hypertension associated with chronic kidney disease. *J Hum Hypertens* 2012;**26**:502–6.
78. Edwards NC, Steeds RP, Chue CD, Stewart PM, Ferro CJ, Townend JN. The safety and tolerability of spironolactone in patients with mild to moderate chronic kidney disease. *Br J Clin Pharmacol* 2012;**73**:447–54.
79. Khosla N, Kalaitzidis R, Bakris GL. Predictors of hyperkalemia risk following hypertension control with aldosterone blockade. *Am J Nephrol* 2009;**30**:418–24.
80. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. *N Engl J Med* 2004;**351**:543–51.
81. Weir MR, Mayo MR, Garza D, Arthur SA, Berman L, Bushinsky D, Wilson DJ, Epstein M. Effectiveness of patiromer in the treatment of hyperkalemia in chronic kidney disease patients with hypertension on diuretics. *J Hypertens* 2017;**35**(Suppl. 1):S57–63.
82. Packham DK, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G, Qunibi W, Pergola P, Singh B. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med* 2015;**372**:222–31.
83. Hill NR, Lasserson D, Thompson B, Perera-Salazar R, Wolstenholme J, Bower P, Blakeman T, Fitzmaurice D, Little P, Feder G, Qureshi N, Taal M, Townend J, Ferro C, McManus R, Hobbs FR. Benefits of Aldosterone Receptor Antagonism in Chronic Kidney Disease (BARACK D) trial-a multi-centre, prospective, randomised, open, blinded end-point, 36-month study of 2,616 patients within primary care with stage 3b chronic kidney disease to compare the efficacy of spironolactone 25 mg once daily in addition to routine care on mortality and cardiovascular outcomes versus routine care alone: study protocol for a randomized controlled trial. *Trials* 2014;**15**:160.
84. Shavit L, Lifschitz MD, Epstein M. Aldosterone blockade and the mineralocorticoid receptor in the management of chronic kidney disease: current concepts and emerging treatment paradigms. *Kidney Int* 2012;**81**:955–68.
85. Hirsch JS, Drexler Y, Bomback AS. Aldosterone blockade in chronic kidney disease. *Semin Nephrol* 2014;**34**:307–22.
86. Tsuboi N, Kawamura T, Okonogi H, Ishii T, Hosoya T. The long-term antiproteinuric effect of eplerenone, a selective aldosterone blocker, in patients with non-diabetic chronic kidney disease. *J Renin Angiotensin Aldosterone Syst* 2012;**13**:113–7.
87. Morales E, Millet VG, Rojas-Rivera J, Huerta A, Gutierrez E, Gutierrez-Solis E, Egido J, Praga M. Renoprotective effects of mineralocorticoid receptor blockers in patients with proteinuric kidney diseases. *Nephrol Dial Transplant* 2013;**28**:405–12.
88. Rossing K, Schjoedt KJ, Smidt UM, Boomsma F, Parving HH. Beneficial effects of adding spironolactone to recommended antihypertensive treatment in diabetic nephropathy: a randomized, double-masked, cross-over study. *Diabetes Care* 2005;**28**:2106–12.
89. Epstein M, Williams GH, Weinberger M, Lewin A, Krause S, Mukherjee R, Patni R, Beckerman B. Selective aldosterone blockade with eplerenone reduces albuminuria in patients with type 2 diabetes. *Clin J Am Soc Nephrol* 2006;**1**:940–51.
90. Mehdi UF, Adams-Huet B, Raskin P, Vega GL, Toto RD. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. *J Am Soc Nephrol* 2009;**20**:2641–50.
91. Bomback AS, Kshirsagar AV, Amamoo MA, Klemmer PJ. Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. *Am J Kidney Dis* 2008;**51**:199–211.
92. Bolignano D, Palmer SC, Navaneethan SD, Strippoli GF. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev* 2014:CD007004.
93. Currie G, Taylor AH, Fujita T, Ohtsu H, Lindhardt M, Rossing P, Boesby L, Edwards NC, Ferro CJ, Townend JN, van den Meiracker AH, Saklayen MG, Oveisi S, Jardine AG, Delles C, Preiss DJ, Mark PB. Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: a systematic review and meta-analysis. *BMC Nephrol* 2016;**17**:127.
94. Vasavada N, Saha C, Agarwal R. A double-blind randomized crossover trial of two loop diuretics in chronic kidney disease. *Kidney Int* 2003;**64**:632–40.
95. Sica DA. Hypertension, renal disease, and drug considerations. *J Clin Hypertens* 2004;**6**:24–30.
96. Gabow PA, Moore S, Schrier RW. Spironolactone-induced hyperchloremic acidosis in cirrhosis. *Ann Intern Med* 1979;**90**:338–40.
97. Kovesdy CP, Lott EH, Lu JL, Malakauskas SM, Ma JZ, Molnar MZ, Kalantar-Zadeh K. Hyponatremia, hypernatremia, and mortality in patients with chronic kidney disease with and without congestive heart failure. *Circulation* 2012;**125**:677–84.
98. Hoorn EJ, Zietse R. Hyponatremia and mortality: moving beyond associations. *Am J Kidney Dis* 2013;**62**:139–49.
99. Ware JS, Wain LV, Channavajjhala SK, Jackson VE, Edwards E, Lu R, Siew K, Jia W, Shrine N, Kinnear S, Jalland M, Henry AP, Clayton J, O'Shaughnessy KM, Tobin MD, Schuster VL, Cook S, Hall IP, Glover M. Phenotypic and pharmacogenetic evaluation of patients with thiazide-induced hyponatremia. *J Clin Investig* 2017;**127**:3367–74.
100. Patel M, Vellanki K, Leehey DJ, Bansal VK, Brubaker L, Flanigan R, Koval J, Wadhwa A, Balasubramanian N, Sandhu J, Kramer H. Urinary incontinence and diuretic avoidance among adults with chronic kidney disease. *Int Urol Nephrol* 2016;**48**: 1321–6.
101. Quamme GA. Loop diuretics. In: Dirks JH, Sutton RAL, editors. *Diuretics. Physiology pharmacology & clinical use*. Philadelphia: W. B. Saunders Company; 1986. p. 86–116.

QUESTIONS AND ANSWERS

Question 1

A 63-year-old man with IgA nephropathy returns to CKD clinic for follow-up. He has no complaints and reports good compliance with his sodium and potassium restricted diet. Current medications include ramipril 10 mg, amlodipine 10 mg, and chlorthalidone 25 mg. Blood pressure is 128/78 mm Hg. Physical examination is unremarkable. No edema is present.

Laboratory values: BUN 17, S[Cr] 1.9, eGFR 36 mL/min/1.73 m^2, S[Na] 138 mmol/L, S[K] 5.2 mmol/L, S[Cl] 105 mmol/L, and tCO_2 23 mmol/L. Urine protein: creatinine ratio (UPCR) 1.1 g/g.

Which one of the following is the best course of action now?

A. Stop ramipril
B. Add sodium bicarbonate 650 mg BID
C. Stop chlorthalidone, substitute furosemide
D. Continue current regimen
E. Add sodium polystyrene sulfonate resin in sorbitol three times weekly

Answer: D

The patient is doing well, with excellent blood pressure control. Although renal function is worse than the level at which conventional wisdom holds that thiazides are effective, several recent papers suggest that thiazides do lower blood pressure at this level of renal function, perhaps through a mechanism other than diuresis. Thus, Answer C is incorrect. The potassium level is not high enough to warrant other measures (A, B, or E) to lower it.

Question 2

A 45-year-old woman with polycystic kidney disease presents for follow-up. She has noted difficulty focusing on intellectual tasks and mild memory impairment. Although she had significant difficulty with depression a year ago before sertraline was begun, in the interval, her insomnia and depressed mood have not recurred. Having read on a website that vasopressin may promote cyst growth, she has increased fluid intake to at least 3 L per day. She has smoked one pack of cigarettes per day since age 22. Medications include hydrochlorothiazide 25 mg, lisinopril 10 mg daily, sertraline 50 mg, and extended release metoprolol 25 mg daily. Physical examination discloses a well-appearing woman with blood pressure 131/82 mm Hg. The kidneys are not palpable. No edema is present.

Laboratory values: BUN 13 mg/dL, S[Cr] 1.6 mmol/L, eGFR 37 mL/min/1.73 m^2, S[Na] 128 mmol/L, S[K] 3.9 mmol/L, S[Cl] 103 mmol/L, tCO2 22 mmol/L, and glucose 98 mg/dL. Urine osmolality 205 mOsm/kg and urine sodium concentration 55 mmol/dL.

Which one of the following is the best approach now?

A. Urge the patient to drink only when thirsty
B. Stop hydrochlorothiazide, begin furosemide
C. Stop hydrochlorothiazide and sertraline
D. Obtain chest CT
E. Stop lisinopril

Answer: B

The patient's symptomatic hyponatremia may potentially be caused by several factors. Hydrochlorothiazide blocks sodium transport at the distal convoluted tubule diluting site and interferes with urinary dilution. Sertraline and other SSRIs are common causes of the syndrome of inappropriate anti-diuretic hormone secretion (SIADH). Ingestion of water in excess of thirst is unlikely to be a cause of hyponatremia on its own at this level of renal function, but it will lead to hyponatremia if renal diluting ability is impaired by hydrochlorothiazide or SIADH. ACEIs have rarely been reported to cause SIADH, but lisinopril is much less likely to contribute to the hyponatremia than sertraline or hydrochlorothiazide, so Answer E is wrong. It might be possible to correct the hyponatremia simply by urging the patient to reduce water intake, but she would still likely be at risk, so A is wrong. Furosemide blocks urinary concentration and is much less likely to cause hyponatremia; most cases of loop diuretic-induced hyponatremia occur in the setting of congestive heart failure, which itself may have been the cause. The patient benefitted significantly from the sertraline, so it would make sense to try to maintain her on this therapy by stopping the hydrochlorothiazide alone (B) rather than both drugs (C). As an initial step, one would observe the response to stopping hydrochlorothiazide before looking for a lung tumor as a cause of SIADH, so D is wrong.

Question 3

A 72-year-old man with ischemic cardiomyopathy (ejection fraction 35%) and presumed hypertensive nephrosclerosis returns for follow-up. He reports worsening dyspnea and edema despite following a low-salt diet. Specific questions about his dietary choices indicate that his salt intake is likely quite high. Current medications include furosemide 120 mg BID, carvedilol 25 mg BID, lisinopril 20 mg daily, ASA 81 mg daily, and diltiazem 240 mg daily. Pulse is 58 bpm with blood pressure 150/90 mm Hg. The jugular veins are seen 2 cm above the sternal angle and the chest is clear. No gallop is present. One plus edema is present bilaterally.

Laboratory values: BUN 33 mg/dL, S[Cr] 2.8 mg/dL, eGFR 31 mL/min/1.73 m^2, and S[K] 4.4 mg/dL.

In addition to recounseling the patient on a reduced sodium diet, which one of these changes in his therapeutic regimen is most appropriate now?

A. Add metolazone 2.5 mg three days per week
B. Stop furosemide, substitute torsemide
C. Increase diltiazem
D. Increase furosemide to 160 mg BID
E. Add spironolactone 25 mg

Answer: A

The patient demonstrates diuretic resistance. Despite being on a high dose of furosemide, volume overload and blood pressure are not controlled. There is no major advantage of torsemide over twice daily furosemide in this setting, and changing to a new loop agent would require dose finding, so B is incorrect. Simply increasing furosemide (D) is unlikely to be effective. Spironolactone is useful for refractory hypertension, but it is unlikely to provide enough diuretic effect in this case (E). Increasing diltiazem may be unwise at this pulse rate and will not improve sodium balance. Although it requires the addition of another medicine, adding metolazone is likely to have a pronounced additive or synergistic effect to furosemide on sodium excretion.

Question 4

A 53-year-old woman with long-standing type II diabetes mellitus is referred by her primary care physician for management of recent onset hypertension and edema. She is presently managed with insulin glargine 30 U HS and insulin aspart 5 U tid with meals, plus sliding scale, as well as losartan 100 mg. At presentation, her weight is 90 kg with height 61 inches, BMI 37.5 kg/m^2, and blood pressure 150/92 mm Hg. The balance of the physical examination is remarkable only for obesity and trace bilateral ankle edema.

Laboratory values: S[Cr] 1.8 mg/dL with eGFR 31 mL/min/1.73 m^2, serum albumin (S[Alb]) 3.2 g/dL. UPCR is 3.2 g/g.

You begin furosemide 40 mg daily, counsel her on a 4 g sodium diet, and arrange follow-up in a month.

On her return, the patient reports that the furosemide is working well. She has a brisk urine output right after she takes the drug. On examination, her weight is 90.3 kg, blood pressure 148/92 mm Hg, and trace bilateral ankle edema persists.

Which of the following is the best course of action now?

A. Counsel on 500 mg sodium diet
B. Add hydrochlorothiazide 25 mg
C. Add spironolactone 25 mg
D. Change furosemide to 40 mg BID
E. Switch to bumetanide 2 mg daily

Answer: D

From the patient's description, the furosemide is having its desired effect as a diuretic, but the patient has not lost weight or experienced an improvement in blood pressure or fluid overload. Reducing sodium intake would help (see Figure 64.3), but a 500 mg sodium diet (A) is unlikely to be achievable. Switching to another short-acting loop agent even at a higher dose (E) would not solve the problem of having diuretic activity of too brief a duration. The correct strategy is to add a second dose of furosemide to prolong its activity. Adding additional agents (B and C) would help, at the cost of more polypharmacy.

Question 5

A 26-year-old man with frequently relapsing minimal change nephropathy presents to the emergency room. He developed leg swelling over the several preceding days. Before that, he had been well. He was taking no medications and had normal renal function and no proteinuria. His last relapse was 18 months ago. His blood pressure was 105/68 mm Hg and the balance of the examination was remarkable only for 2+ bilateral leg edema.

Laboratory values: BUN 8 mg/dL, S[Cr] 0.9 mg/dL, and S[Alb] 2.4 g/dL.

The emergency room physician prescribes 40 mg furosemide IV to little effect.

The reason for this patient's poor response to furosemide is most likely which one of the following?

A. Diuretic braking
B. Diuretic tolerance
C. Reduced bioavailability
D. Diminished protein binding
E. Hypertrophy of distal convoluted tubule sodium reabsorptive sites

Answer: D

Diuretic braking refers to the reduced diuretic effect that occurs *after* the first or just a few doses of diuretic and tolerance to the reduced effect that occurs later and which is sometimes due to the hypertrophy of distal tubule sodium reabsorptive sites that occurs in response to the increased load of sodium passing that site after a loop agent is administered. This patient has not required diuretic therapy in some time and is thus diuretic naïve. So, the failure of the first dose of furosemide to act cannot be attributed to A, B, or E. Bioavailability of orally administered drugs may be reduced by gut edema, but the furosemide was given IV, bypassing the gut. Therefore, C is not relevant. Loop diuretics are highly protein bound in plasma. When hypoalbuminemia is present, the apparent volume of distribution increases, and delivery to the proximal tubule site where

furosemide is secreted into the lumen is diminished. Hence, D is the reason why a dose of furosemide that would have been expected to work at this level of renal function did not.

Question 6

A 63-year-old man with CKD due to diabetic nephropathy is admitted to the CCU after the sudden onset of chest pain and dyspnea. Home medications include aspirin, losartan, insulin, and furosemide 40 mg daily. Blood pressure is 140/95 mm Hg. Physical examination discloses rales midway up the chest and trace bilateral ankle edema is present. The chest radiograph shows mild pulmonary edema. Cardiac enzyme studies and ECG disclose a non-ST segment elevation myocardial infarction. Kidney function is at baseline.

Laboratory values: BUN 42 mg/dL, S[Cr]1.5 mg/dL, and eGFR 50 mL/min/1.73 m^2.

The patient is treated with supplemental oxygen, heparin, and a β-blocker, and aspirin and losartan are continued. You advise that furosemide be given with a goal of net negative fluid balance of 2 L over the course of the day. The CCU staff administers furosemide, 80 mg, intravenously.

The next morning, you note that in response to the furosemide, the urine output was 1200 mL over the ensuing 4 hours. However, overall fluid balance for the first 24 hours in the hospital was positive, with intake 2200 mL in and output 1800 mL (all urine). The patient continues to require supplemental oxygen. Renal function is unchanged.

At this point, you reiterate the goal of establishing net negative fluid balance and recommend which one of the following?

A. Furosemide 160 mg IV
B. Furosemide 80 mg followed by a continuous infusion
C. Stop losartan
D. Bumetanide 4 mg IV
E. Add chlorothiazide 250 mg IV BID

Answer: B

Furosemide 80 mg was effective in increasing urine output, but net negative fluid balance was not achieved because the diuretic effect was not sustained throughout the day. The patient could be managed effectively with repeated boluses of furosemide 80 mg if they are given. However, that option was available the day before but not utilized. It would thus make sense to switch to a continuous infusion titrated to a dose that will achieve negative balance. A single larger dose of furosemide or comparable dose of bumetanide would not solve the problem so A and D are incorrect. There is no evidence of diuretic tolerance as yet, so chlorothiazide is not indicated. Renal function is stable, so there is no reason to believe stopping losartan would improve the diuresis.

CHAPTER

65

Nonsteroidal Antiinflammatory Drugs and Opioids in Chronic Kidney Disease

David M. Clive[a], *Pia H. Clive*[b]

[a]University of Massachusetts Medical School, Department of Medicine, Division of Renal Medicine, Worcester, MA, United States; [b]UMass Memorial Medical Center, Worcester, MA, United States

Abstract

Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit the synthesis of prostaglandins, which comprise an important compensatory mechanism for maintaining renal blood flow, glomerular filtration, and water and electrolyte homeostasis in the setting of a number of pathophysiologic states including chronic kidney disease (CKD). CKD patients are, therefore, at risk for adverse renal side effects of NSAIDs, including acutely worsened renal function, hyperkalemia, hyponatremia, sodium retention, and exacerbation of hypertension. Although these effects are generally reversible on discontinuation of the drugs, patients with CKD must be monitored closely while taking NSAIDs.

Evidence suggests that heavy cumulative NSAID consumption is capable of causing chronic kidney injury with manifestations similar to those seen in classic analgesic nephropathy, including chronic interstitial nephritis and papillary necrosis. The pathogenesis of this disorder is probably renal medullary ischemia resulting from diversion of blood flow to the cortex that occurs with suppression of prostaglandin synthesis. CKD due to NSAIDs is probably rare.

Extra caution is indicated when (1) committing patients to high-dose, long-term NSAID therapy or (2) recommending NSAID therapy of any duration to patients with CKD or other risk factors for adverse renal side effects including advanced age, use of diuretics, congestive heart failure, cirrhosis, and hypertension.

As with NSAIDs, opioid analgesics must be considered from two standpoints: their ability to cause chronic kidney injury, which appears rare if it occurs at all, and the susceptibility of patients with chronically impaired renal function to the hemodynamic and neurotoxic effects of opioids, a problem commonly confronted in the clinic.

INTRODUCTION

Because pain is the most common symptom for which people consult their physicians, it is hardly surprising that the consumption of analgesic medications in the US is enormous. It is estimated that 19% of the population regularly use aspirin, albeit not exclusively for pain. Another 12.8% use nonaspirin NSAIDs regularly. These numbers appear to be on the rise.[1] Excessive use of opioids is now pervasive due to the prevalence of addiction, as well as profligate overprescription. At the time of this writing, opioid use represents one of the nation's greatest public health crises. Recent estimates of the prevalence of CKD in this country average around 15%. One may extrapolate from these numbers that the relationship between CKD and analgesic medications is a topic of potentially major clinical significance.

In examining this relationship, we will first explore the propensity of these agents to exert adverse effects on the kidney. Next, we will consider the extent to which CKD patients, by virtue of their reduced renal function, have a reduced tolerance for them. We will apply this approach to both the NSAIDs and opiates.

NSAIDS AND CKD

The potential for harmful interactions between nonsteroidal antiinflammatory drugs (NSAIDS) and the kidney has been known for 60 years. The earliest reports were of a fulminant form of acute kidney injury (AKI) known as "phenylbutazone anuria." Although phenylbutazone has virtually disappeared from clinical use in humans, the number of NSAID products available for administration to humans has exploded in the years since. Several different classes of NSAIDs have been marketed (Table 65.1), most recently the coxibs, or selective cyclooxygenase-2 antagonists. NSAIDs may be the

https://doi.org/10.1016/B978-0-12-815876-0.00065-6

TABLE 65.1 Nonsteroidal Antiinflammatory Drugs

Class	Examples
Indoleacetic acid derivatives	Indomethacin, sulindac, ketorolac
Propionic acid derivatives	Ibuprofen, naproxen
Coxibs	Celecoxib, valdecoxib
Salicylates	Aspirin, salsalate
Fenamic acid derivatives	Meclofenamate
Oxicams	Meloxicam, piroxicam
Pyrazolidines	Phenylbutazone

most widely used of all drugs, with over 70 million prescriptions written annually in the US.[2] Aspirin, the first and most familiar NSAID, was developed in the late 19th century. In the decades since, newer and more potent agents have been introduced, some of which became available as over-the-counter formulations in the late 1980s. Two of these, ibuprofen and naproxen, can produce adverse renal effects. Both are widely advertised and consumed. The proliferation of NSAID products has not been confined to the introduction of new compounds. Newer formulations and delivery systems have also appeared. Adverse renal effects have recently been reported in association with topical NSAID formulations.[3,4]

The explosion in NSAID consumption in the US has occurred in parallel with a sharp increase in the prevalence of chronic kidney disease (CKD). Although the current epidemiologic trends of CKD doubtless reflect the influence of many factors, it is logical to ask whether NSAID use may be one of them. This is the first of two key issues to be examined in this chapter.

PHARMACOLOGY OF NSAIDS

The principal pharmacologic action of all NSAIDs is to alter the metabolism of arachidonic acid. This 20-carbon fatty acid, present in all cells, is the precursor of the eicosanoids, a family of physiologically active compounds comprising the prostaglandins and leukotrienes (Figure 65.1). These substances are *autocoids*, meaning their effects are exerted primarily on the tissue in which they are synthesized. Different cell types have differing proclivities for producing specific eicosanoid end-products. The paradigmatic illustration of this phenomenon is the abundant production by platelets of thromboxane A_2, a prostaglandin that induces platelet aggregation and vasoconstriction. In endothelial cells, the predominant eicosanoid product is prostaglandin I_2 (prostacyclin), a vasodilator and inhibitor of platelet aggregation. The opposing effects of these substances lend protective balance to the interaction between blood vessels and thrombocytes. Variability of eicosanoid production is seen among the renal cell types as well.

The primary step in the metabolism of arachidonic acid is catalyzed by cyclooxygenase (COX). It is this step that is inhibited by NSAIDs. Mammalian cells express two isoforms of cyclooxygenase, COX-1 and COX-2. COX-1 predominates in gastric mucosa, where prostaglandins confer protection against acid-peptic assault. For this reason, the specific COX-2 inhibiting NSAIDs are felt to be safer for patients at risk for gastric bleeding and ulceration. COX-2 is the predominant cyclooxygenase isoenzyme in the kidney. It is, therefore, not surprising that COX-2 inhibitors are reported to cause renal effects similar to those of the traditional, nonspecific NSAIDs.

PROSTAGLANDINS AND THE KIDNEY: AN OVERVIEW

Both COX-1 and COX-2 are present in kidney tissue. COX-1 is constitutively expressed in the distal nephron. Its chief product is prostaglandin E_2 (PGE_2). COX-2 is more widely distributed throughout the kidney. Like COX-1, it is constitutively expressed, but it is also inducible under conditions of physiologic stress. The inducible expression of COX-2 in the renal cortex and medulla appear to be under independent control.[5] The physiologic stresses that lead to enhanced cortical COX-2 activity are those associated with increased activity of the renin–angiotensin–aldosterone system (RAAS), such as sodium depletion and reduced renal perfusion. A bidirectional stimulatory relationship exists between the two hormonal systems: angiotensin II stimulates production of COX-2 eicosanoid products, and those products, in turn, stimulate renin release.

Several generalizations may be made regarding the actions of renal prostaglandins, which are listed in Table 65.2.

(1) As *autocoids*, prostaglandins synthesized in the kidney act on the kidney. Prostaglandins and prostaglandin metabolites excreted in the urine represent mostly those that were produced in the kidney.

(2) The importance of prostaglandins affecting compensatory mechanisms in pathophysiologic states exceeds that of their role in normal renal physiology. This assertion is based on two

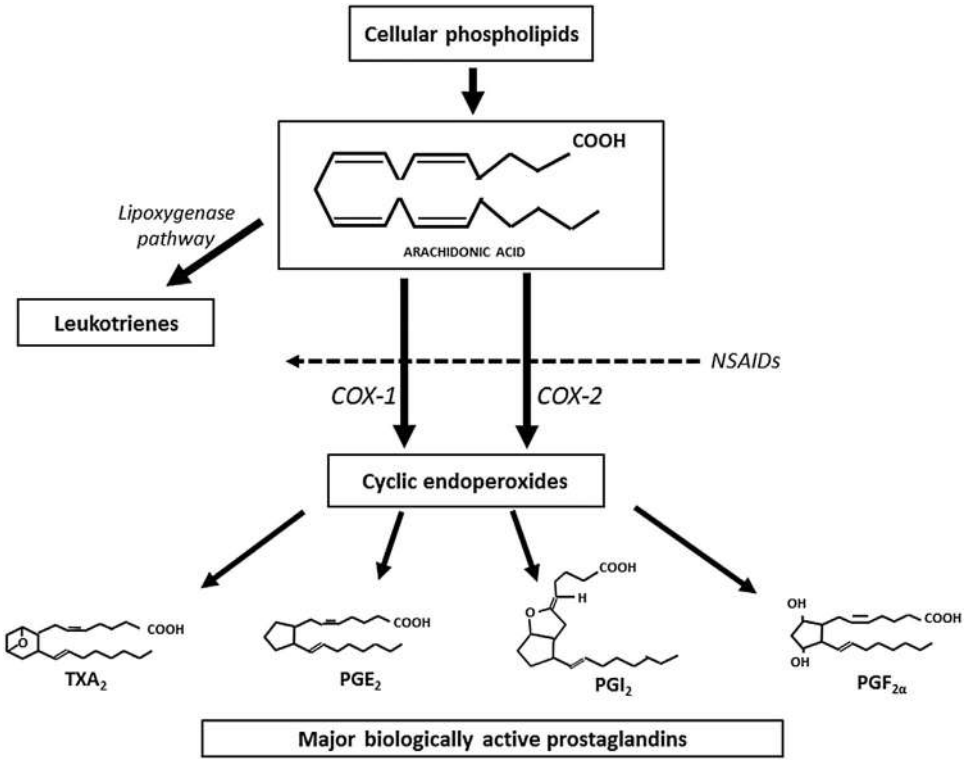


FIGURE 65.1 Biosynthetic pathway of eicosanoids. The eicosanoid precursor molecule is arachidonic acid, derived from substrate in the cell membrane phospholipid pool. Arachidonic acid may be metabolized by either of two enzymatic pathways. The lipoxygenase pathway produces a family of inflammatory mediators and cytokines known as leukotrienes. The cyclooxygenase (COX) system produces prostaglandins. Cyclooxygenase catalyzes the conversion of arachidonic acid to cyclic endoperoxides, which are short-lived prostaglandin precursors with no intrinsic biologic role other than as parent molecules for the biologically active prostaglandins. There are two isoforms of cyclooxygenase, COX-1 and COX-2; their relative importance varies among different tissues. NSAIDs inhibit cyclooxygenase activity. PGI_2 is prostacyclin. *PG*, prostaglandin; *Tx*, thromboxane.

TABLE 65.2 Major Roles of Prostaglandins in Renal Physiology and Clinical Consequences of Inhibition of Prostaglandin Synthesis

Role	Action	Consequences of Inhibition
Maintenance of renal blood flow	Counterregulate the action of vasoconstrictor hormones	Acute kidney injury (vasomotor nephropathy)
Potassium homeostasis	Promote potassium excretion through stimulation of renin secretion	**1)** Hyperkalemia **2)** Hyporeninemic hypoaldosteronism (type IV renal tubular acidosis)
Water balance	Counterregulate the action of antidiuretic hormone on medullary collecting tubule	Hyponatremia
Sodium homeostasis	Modulate sodium reabsorption at multiple nephron sites	**1)** Edema **2)** Exacerbation of congestive heart failure **3)** Exacerbation of cirrhotic ascites and edema **4)** Exacerbation of hypertension

observations. First, under normal physiologic conditions, people are rarely subject to adverse renal consequences of inhibition of prostaglandin synthesis by NSAIDS. Second, under many of the conditions associated with renal sensitivity to NSAIDs (Table 65.3), urinary excretion of prostaglandin metabolites is above normal, indicating a high level of renal cyclooxygenase activity.

(3) As already noted in relation to the RAAS, prostaglandins serve to counterregulate the actions of other hormones on the kidney. A similar check-and-balance relationship exists between antidiuretic hormone and prostaglandins.

TABLE 65.3 Predisposing Factors for Adverse Renal Effects of NSAIDs

Reduced renal blood flow
Volume depletion
Congestive heart failure
Cirrhosis
Chronic kidney disease
Hypertension
Medications (triamterene, calcineurin inhibitors, ACE inhibitors, ARBs, diuretics)
Older age

Table 65.4 lists the various renal abnormalities that have been reported in patients taking drugs that inhibit prostaglandin synthesis. Most of these are predictable given the information in Table 65.2.

NSAIDS AS A CAUSE OF CHRONIC KIDNEY DISEASE

Mechanism

NSAID nephropathy is thought to be an ischemic, rather than toxic, process. In contrast to phenacetin, implicated in the pathogenesis of classic analgesic nephropathy, NSAIDs and their metabolites are not inherently nephrotoxic. In animal studies, suppression of prostaglandin synthesis by NSAIDs induces regional changes in intrarenal blood flow with marked reduction in medullary perfusion.[6] Prolonged medullary ischemia can lead to atrophy and fibrosis of deep nephron structures and ultimately papillary necrosis.

TABLE 65.4 Renal Syndromes Attributed to NSAIDs

ACUTE KIDNEY INJURY
• Prerenal azotemia
• Vasomotor nephropathy
• Crystal nephropathy
• Acute tubular necrosis
• Acute interstitial nephritis and proteinuria
FLUID, ELECTROLYTE, AND ACID–BASE IMBALANCES
• Sodium retention
• Hyperkalemia
• Hyponatremia
• Type IV renal tubular acidosis
Exacerbation of hypertension
Chronic kidney disease

Importance of NSAID Use as a Causative Factor in CKD

The collective evidence that NSAIDs are capable of causing irreversible renal damage is less robust than that supporting their role in AKI. In the past three decades, isolated reports have imputed such a relationship, but in none of these is the case for direct causality beyond question.[7–14]

Clinical investigators have attempted to solidify this case. Segasothy and coworkers evaluated renal function and morphology in 94 chronic arthritis patients with a history of relatively heavy NSAID exposure. Of 82 patients who completed the assessment, 12% had radiographic evidence of papillary necrosis and 24% higher than expected serum creatinine concentration (S[Cr]) levels. These findings were distributed among patients with several unrelated forms of arthritis, strengthening the authors' conclusion that heavy NSAID use, and not the disease process being treated, was culpable in the pathogenesis of their CKD.[15]

Sandler et al. conducted telephone interviews of 554 North Carolinians with newly diagnosed chronic renal disease to assess their prior intake of NSAIDs, and compared it with that of 516 control subjects. Heavy NSAID use was associated with a twofold risk of renal disease, although the effect was limited to male subjects over the age of 65.[16] In another survey, 716 end-stage renal disease (ESRD) patients and 316 control subjects were queried regarding their pattern of use of three types of analgesics: acetaminophen, aspirin, and nonaspirin NSAIDs. The ESRD patients were stratified into three groups according to the etiology of their renal disease: diabetes mellitus, hypertension, and all others. A very strong cumulative dose-dependent interaction was found between NSAID use and prevalence of ESRD. A weaker relationship was found for acetaminophen. It is interesting that no such risk enhancement was seen with aspirin.[17] A retrospective analysis of incident Taiwanese dialysis patients between 1998 and 2009 found that use of NSAIDs within the preceding 14 days raised the relative risk for initiation of chronic dialysis by a factor of 2 to 3.[18]

Renal function was followed over an 11-year period in a cohort of 1697 women enrolled in the national Nurses' Health Study. These women were asked about their use of aspirin, acetaminophen, and nonaspirin NSAIDs. Their change in renal function over time was

compared with that of non-NSAID users. The only significant interaction between analgesic intake and abnormally rapid decline in renal function was seen with acetaminophen.[19] Slightly different results emanated from a similar investigation looking at a healthy male cohort of participants in the national Physicians' Health Study. Here, a modestly increased risk of reduced renal function was demonstrated among especially heavy users of nonaspirin NSAIDs or acetaminophen, while a possibly protective, albeit minimal, effect was seen with aspirin.[20] More conventional usage patterns were not associated with risk enhancement.[21]

Further attempts have been made to identify an epidemiologic link between NSAID consumption and CKD.[22–27] As is often the case with retrospective, case-control, and cross-sectional studies, caution is warranted in interpreting these data. Many of these studies relied on estimates and recollections by patients of their pill consumption over many years. The variability of the collective data precludes any meaningful estimate of actual risk. In some studies, interactions of NSAIDs with renal failure were limited to small subsets of subjects. Even in those studies showing an association between NSAID use and CKD, the causal sequence remains unproven, because increased use of NSAIDs may occur as a consequence of musculoskeletal complications of CKD, such as metabolic bone disease and crystal arthropathies. Whether NSAID use is heavier among persons with CKD than in demographically comparable subjects with normal kidney function is unclear.[28]

One group has attempted to clarify the role of NSAIDs in the pathogenesis of CKD by prospectively examining the incidence of papillary necrosis among 259 people receiving long-term, high-dose NSAIDs for treatment of arthritis.[29] Over the 11-year study period, 69 new cases of papillary necrosis were diagnosed and confirmed radiographically. This study, while prospective, poses several impediments to interpretation. First, the population was demographically limited; the subjects were all Malaysian. Second, in addition to nonaspirin NSAIDs, some of the affected patients received other analgesics, including aspirin, phenacetin, paracetamol, and herbal supplements. Third, of the 29 patients who took nonaspirin NSAIDs alone, some received phenylbutazone. Fourth, no longitudinally studied control group of age-matched arthritis patients not receiving NSAIDs was available for comparison. These shortcomings notwithstanding, the incidence of papillary necrosis documented in this study is concerning, particularly in light of the fact that papillary necrosis is not a highly sensitive finding for diagnosing analgesic nephropathy radiographically.[30]

Relationship between NSAID-Induced CKD and Analgesic Nephropathy

The term *analgesic nephropathy* is traditionally reserved for a syndrome of progressive renal atrophy and failure resulting from long-term use of phenacetin or related compounds, alone or in combination with other drugs. Because NSAIDs have analgesic properties, NSAID-induced CKD is often classified under the same heading. Although classic analgesic nephropathy and chronic NSAID-induced interstitial disease are both characterized by chronic tubulointerstitial nephritis and papillary necrosis, it is unlikely that they share the same pathogenesis. The mechanism by which phenacetin injures kidneys involves accumulation in the medulla of nephrotoxic metabolites and generation of reactive oxygen species (its relative acetaminophen has similar, albeit milder, effects). NSAIDs have minimal cytotoxicity in renal tissue *per se*. Their damage appears mediated through the previously discussed ischemic mechanism. Despite these differences, the two drug etiologies are closely linked epidemiologically, because patients commonly use both forms of analgesics. It is likely that their respective mechanisms are synergistic in the pathogenesis of CKD in patients taking NSAIDs and acetaminophen or phenacetin in combination.[31] Although phenacetin-induced analgesic nephropathy predisposes to the development of renal and urologic neoplasms, this association has not been described with NSAIDs.[32,33]

Conclusions

Although the accrued evidence that NSAID use can induce chronic kidney injury is not ironclad, it is strong enough to support the following conclusions: (a) NSAIDs appear capable of causing a morphologic pattern of renal injury similar to that of classic analgesic nephropathy, with interstitial fibrosis and papillary necrosis; (b) this form of injury appears limited to patients with very high cumulative NSAID exposure; and (c) the toxicity of NSAIDs may be magnified when taken in combination, or in conjunction with other medications such as acetaminophen and caffeine. The possibility that men may be more susceptible than women to NSAID-related CKD, as suggested by two of the individual studies cited, bears further study. Clinicians should be mindful of the likelihood of a causal link between NSAIDs and CKD when committing patients to long-term NSAID therapy. Blood pressure, blood chemistries, and urinalysis should be monitored routinely during treatment. At the earliest sign of change in any of these

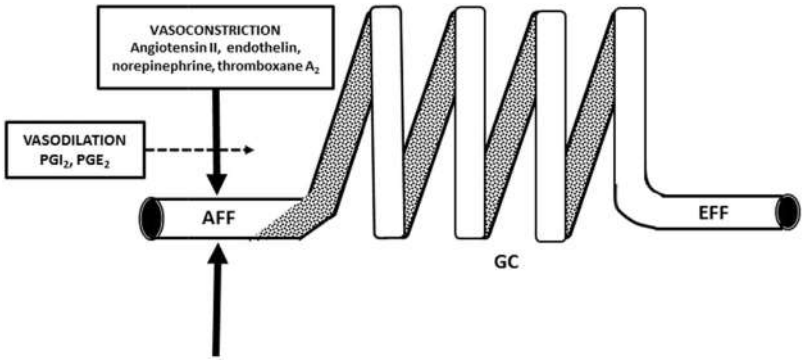


FIGURE 65.2 **Prostaglandin dependence of renal function.** Vasodilatory prostaglandins such as PGI_2 and PGE_2 offset the actions of circulating and locally produced vasoconstrictors at the afferent arteriole. This modulation of afferent resistance is particularly important in conditions of high vasoconstrictor activity. NSAID use under such conditions can lead to unopposed vasoconstriction and reduction of glomerular perfusion. *AFF*, afferent arteriole; *EFF*, efferent arteriole; *GC*, glomerular capillary.

parameters, alternatives to NSAID therapy should be considered, some of which may be found later in this chapter.

ADVERSE CONSEQUENCES OF NSAID THERAPY IN PATIENTS WITH CKD

Are patients with CKD at enhanced risk for adverse renal effects and, if so, which ones? What is known about the pathogenesis of such effects, and how can they be avoided in CKD patients for whom NSAID therapy is indicated?

Indeed, an array of renal abnormalities attributable to NSAIDs have been described. These have been reviewed extensively[34–41] and are shown in Table 65.4. In normal individuals, NSAIDs rarely evoke significant changes in blood pressure, renal function, water, or electrolyte balance. NSAID-related renal syndromes occur almost exclusively in pathophysiologic settings, an observation that is consistent with the primarily compensatory role of renal prostaglandins. Of these predisposing conditions, which are listed in Table 65.3, CKD was among the first to be reported.

Acute and Acute-On-Chronic Kidney Injury Due to NSAIDs

To maintain glomerular blood flow in the face of an activated renin–angiotensin system, as occurs in congestive heart failure, cirrhosis, and sodium deprivation, modulation of afferent arteriolar resistance by vasodilatory prostaglandins (PGs) is essential. The prostaglandin dependence of renal function in patients with these conditions is evidenced by their elevated urinary excretion of prostaglandin metabolites, and the observation that NSAIDs can cause AKI in these conditions. This form of AKI has been variously termed vasomotor nephropathy, autoregulatory failure, functional acute renal failure, or decompensated prerenal azotemia (Figure 65.2). As is characteristic of hemodynamically mediated forms of AKI, the syndrome will usually reverse readily when the offending agent is withdrawn, although if renal perfusion has been sufficiently compromised by the NSAID, frank acute tubular necrosis (ATN) may develop.[29]

Recent reports have suggested a particularly heightened risk for AKI when NSAIDs are added to the medication regimens of patients already receiving diuretics and ACE inhibitors or ARBs.[41–46] This would seem straightforward from a pathophysiologic perspective as this combination of agents could impair autoregulation of vascular tone in both the pre- and postglomerular arterioles.

The prevailing hemodynamic adaptations that occur in CKD kidneys are less predictable. Patients with CKD typically have chronic volume expansion and suppression of their renin–angiotensin system, yet are still prone to NSAID-induced vasomotor nephropathy. In 1978, Kimberly and Plotz reported several patients with systemic lupus erythematosus who developed reversible AKI while receiving aspirin.[47] They subsequently reported the same phenomenon in association with other NSAIDs.[48] The best explanation for these findings is that while these patients ostensibly had good baseline renal function, their glomerular filtration rate (GFR) was probably maintained by glomerular hyperfiltration, and that this process is prostaglandin-dependent. Evidence exists to support this hypothesis. It is known from micropuncture studies in rats that subnormal afferent arteriolar resistance permits hyperfiltration in remnant glomeruli.[49,50] In a rodent kidney ablation model, the renal functional changes associated with uninephrectomy were blunted in rats treated with either indomethacin or a selective COX-2 inhibitor.[51] In

humans, the hyperfiltration observed in a group of subjects with sickle cell nephropathy was blunted by both indomethacin and sulindac,[52] by celecoxib in euglycemic patients with early type 1 diabetic nephropathy,[53] and by aspirin in children with chronic obstructive uropathy.[54]

The observations of Kimberly and Plotz notwithstanding, review of the literature on NSAID-related AKI suggests that this phenomenon occurs much less frequently with salicylates than with other classes of NSAIDs. Early literature suggested that sulindac, too, was less often associated with such cases.[55,56] However, a recent meta-analysis of this literature suggests that the relative nephrotoxicity of different NSAIDs, including the selective COX-2 inhibitors, is still not well established.[57]

The exact risk of acute renal decompensation in a CKD patient at the outset of NSAID exposure is unknown because prospective data from randomized, controlled trials are lacking, and because this risk may be further influenced by multiple factors. In a general population survey among residents of Saskatchewan, current NSAID use was found to raise the risk of hospitalization for AKI fourfold. Age >65 years was likewise an independent risk factor with an associated hazard ratio of 3.5. Unfortunately, baseline level of renal function was not examined as a risk factor in this analysis.[58] However, other epidemiologic surveys as well as clinical investigation provide evidence that renal senescence is a risk factor (see below).

In patients with glomerular diseases, the sensitivity of renal function to cyclooxygenase-inhibiting drugs was noted by Patrono and colleagues to correlate with basal excretion of 6-keto-$PGF_{1\alpha}$, the chief metabolite of prostacyclin, suggesting dependence of renal function on prostacyclin. This group found that patients with active lupus nephritis excrete large amounts of not only 6-keto-$PGF_{1\alpha}$, but thromboxane B_2, the main metabolite of the vasoconstrictor prostanoid thromboxane A_2, as well. Their experience is that renal function in lupus nephritis is less severely affected by NSAIDs than in other glomerular diseases. They posit that, at baseline, lupus patients produce excessive thromboxane A_2 which causes chronic afferent vasoconstriction, thus limiting glomerular filtration. When these patients take NSAIDs, the decremental effect on GFR that would be expected from reduced prostacyclin production is offset by the concomitant reduction in thromboxane. Patrono has suggested that the clinical consequences of cyclooxygenase inhibition in the intrarenal microcirculation depend on the net change in the balance between prostaglandins that are vasodilatory and inhibitory of platelet function vs. those that are vasoconstrictive and prothrombotic.[59] Further support for this hypothesis comes from their finding that thromboxane-specific inhibitors raise GFR in SLE.[60]

In summary, the CKD patient's renal response to an NSAID may be influenced by several factors:

1) *The etiology of the underlying renal disease.*
2) *The change in the specific pattern of eicosanoid synthesis engendered by cyclooxygenase inhibition.*
3) *The nature of the NSAID, its pharmacokinetics, and COX-specificity.*

The pharmacologic effects of NSAIDs vary markedly among specific agents. Sulindac, despite its chemical kinship to indomethacin, is much less nephrotoxic, although probably not totally innocuous as originally thought.[50,51] NSAIDs in the salicylate class are the least frequently identified in reports of adverse renal effects, but tend to have lower antiinflammatory potency than other NSAIDs.

The interest in COX-2-specific inhibitors derives from the fact that COX-1-generated PGE_2 is integral to the protection of the gastric mucosa. The selective COX-2 inhibitors have been implicated in numerous reports of adverse renal side effects, as might be expected given the abundant expression of cyclooxygenase-2 in the kidney.[38,61–64] *They should be considered no less potentially nephrotoxic than traditional cyclooxygenase inhibitors*. This heterogeneity of effects between NSAIDs is well exemplified in the coronary circulation. Aspirin is a pure COX-1 antagonist that binds irreversibly to the membranes of platelets and blocks the synthesis of their principal eicosanoid product, thromboxane A_2. This specificity confers on aspirin its balance of antithrombotic and antiinflammatory potency that is unique among NSAIDs and has made aspirin the clinical mainstay in prophylaxis against coronary events.[65] A meta-analysis of the effects of other NSAIDs on the risk of atherothrombotic events (chiefly myocardial infarction and stroke) showed a substantially increased risk with rofecoxib, diclofenac, and ibuprofen, but not naproxen or celecoxib.[66] The association between rofecoxib and coronary events was sufficiently serious to force the withdrawal of this agent from the market.[67,68]

Pharmacokinetics may also influence risk. In a German study comparing renal function in NSAID users compared with nonusers undergoing elective orthopedic surgery, the prevalence of renal dysfunction was highest among patients using longer half-life (>4 hours) drugs. This study was a cross-sectional, interview-driven analysis looking at prevalence, not incidence, and thus limited in its ability to establish causality or to differentiate between CKD and AKI.[69] A randomized, prospective,

drug challenge study in an elderly cohort demonstrated that the negative effect on GFR of the longer acting NSAIDs sulindac and celecoxib is more sustained than that induced by ibuprofen.[70] Similar findings were reported by other investigators.[71]

4) *Timing of drug exposure.* The acute renal response to NSAIDs may differ from the chronic response. In the study referenced immediately above, which was designed to delineate the acute and chronic effects of various NSAIDs on renal function in an elderly cohort, while most subjects demonstrated a decline in GFR within an hour of drug challenge, no effects were seen following one-month of sustained exposure to the same agents.[72]
5) *"Host" factors, including patient age.* The response of renal function to NSAIDs has been studied extensively in the elderly population, because the prevalence of both CKD and age-related decline in renal function without evidence of discrete renal disease is high. The results have varied from study to study. Caution has been recommended in committing elderly patients to sustained courses of long-acting NSAIDs.[73,74] In another drug challenge study with a crossover design comparing the effects of celecoxib vs. naproxen in healthy elderly subjects over periods of up to 10 days, both agents engendered negative changes in GFR and sodium excretion, albeit of minimal magnitude.[62] Although the risk of AKI from NSAIDs in the truly healthy elderly is probably very small, the prevalence of comorbidities including unrecognized CKD among the aged warrants close monitoring when prescribing NSAIDs, especially in the very elderly (age >85 years).[74]

Nonhemodynamically Mediated Acute Kidney Injury Due to NSAIDs

A*cute interstitial nephritis* (AIN) due to NSAIDs is relatively unusual. It differs from typical drug-induced AIN in lacking hypersensitivity features such as eosinophilia, eosinophiluria, or rash and is often accompanied by nephrotic-range proteinuria. It is the most idiosyncratic of NSAID-related renal syndromes. Antecedent CKD is not, as far as is known, a risk factor. Tubulointerstitial nephritis was been reported in patients receiving aminosalicylates for inflammatory bowel disease.[75,76]

Medications with solubility characteristics conducive to intratubular crystallization can cause microobstructive AKI. This phenomenon is rare with NSAIDs, but has been reported with sulindac, and was partly responsible for the removal of zomepirac from the marketplace in the 1980s. As with AIN, there is no evidence that CKD places the patient at increased risk.

Effect of NSAIDs on the Progression of Established CKD

Concern has been expressed in the medical literature that long-term NSAID use may exacerbate the course, or accelerate the progression, of chronic renal parenchymal disease. Gooch et al. evaluated the effects of NSAIDs on kidney function in a large population of older (>66 years) patients with preexisting CKD. Patients in the highest decile of self-reported cumulative NSAID use had a 26% increase in risk of experiencing a mean decline in eGFR of >15 mL/min/1.73 m^2 over a two-year study period compared with nonusers.[77] A cross-sectional study of over 19,000 CKD patients in a random sampling of Taiwanese National Health Insurance enrollees found that use of aspirin, nonaspirin NSAIDs, and acetaminophen all were associated with markedly increased risk of ESRD in a cumulative dose-dependent manner. Again, the order of causality cannot be strictly established due to limitations inherent to this type of the study and the question raised by the observed interaction with acetaminophen.[78]

Exactly how serious a threat NSAIDs pose for accelerated progression of CKD, and whether certain etiologies of CKD may be more prone than others, are as yet unknown. From a mechanistic standpoint, it is entirely plausible that NSAIDs could accelerate CKD progression by superimposing an ischemic insult on that of the primary renal disease. However, this same reduction in perfusion might be expected to afford the glomeruli protection from hyperfiltration injury. These effects of NSAIDs on glomerular hemodynamics were the basis for their use years ago in patients with severe and refractory nephrotic syndrome for palliation of proteinuria. Despite sporadic reports of success, this approach has been largely abandoned due to the availability of more reliable alternatives. Consequently, little has been learned about the impact of prolonged, deliberate NSAID exposure on the course of CKD. NSAIDs have also been employed as antithrombotic therapeutic adjuncts in chronic glomerulonephritis, but this experience, too, has added little to our understanding of the net effect of long-term NSAID use on chronic renal disease outcomes. At this time, there is no solid evidence on which to base the use of NSAIDs as a nephroprotective measure in CKD. In fact, based on available data, the clinician is well advised to act on the assumption

that NSAIDs can speed the progression of renal injury and to minimize exposure of CKD patients to them. A recent meta-analysis of the global literature linking NSAIDs and CKD reached similar conclusions.[79]

Hyperkalemia

The overall risk of hyperkalemia among patients taking NSAIDs is unknown and is clearly subject to ancillary host susceptibility factors, many of them the same as those for other renal complications of NSAIDs. In a large, Veterans Administration case-control study, the effect of NSAIDs as a sole, independent risk factor for hyperkalemia was negligible.[80] A 1985 Israeli study analyzed changes in renal function and serum electrolytes in 50 elderly inpatients receiving indomethacin for a variety of indications. A minority (≈30%) of these patients had underlying renal insufficiency. In all patients, potassium concentration rose steadily until discontinuation of the drug. In 13 patients, the increment in serum potassium concentration (S[K]) exceeded 3.6 mMol/L, and in 23 the peak potassium concentration exceeded 5.0 mMol/L. Not surprisingly, older age and the presence of predrug azotemia correlated with the magnitude of rise in S[K] level. The authors did not report which other medications these patients might have received.[81]

Although the patients at greatest risk for hyperkalemia are those who sustain AKI from NSAIDs, hyperkalemia can occur even in the absence of a substantial fall in GFR. The pathogenesis of NSAID-related hyperkalemia is felt chiefly to reflect the suppressive effect on the renin–angiotensin–aldosterone axis of inhibiting prostaglandin synthesis and may present as type IV renal tubular acidosis. In one such case, the patient's underlying rheumatologic condition necessitated continuation of the NSAID, but the manifestations of type IV RTA were controlled with the addition of fludrocortisone to his therapeutic regimen.[82] An identical pattern of hyperkalemic acidosis occurs in congenital hypoprostaglandism.[83] Because, in normal subjects, indomethacin impairs neither the disposal of nor the aldosterone response to an acute potassium load,[84] one must assume that reduced availability of prostaglandins is somehow deleterious to adrenocortical function in those individuals who develop NSAID-induced hyporeninemic hypoaldosteronism.

Other pathogenetic mechanisms of hyperkalemia from NSAIDs have been posited. There is evidence suggesting that function of potassium secretory channels in the distal nephron may be dependent on prostaglandins.[85] It has also been speculated, albeit never proved, that prostaglandins may facilitate transcellular disposition of potassium.

NSAID therapy should be approached cautiously in patients with baseline renal insufficiency or other medical conditions that may reduce potassium tolerance. Extreme caution is warranted when adding NSAIDs to regimens that include other medications associated with hyperkalemia, notably ACE inhibitors, ARBs, aliskiren, spironolactone, trimethoprim, and potassium-sparing diuretics.

Hyponatremia

Prostaglandins oppose the effects of ADH on the collecting tubule epithelium, thus providing a counterregulatory balance to ADH-induced water reabsorption. It is not surprising that NSAIDs may render patients prone to hyponatremia. At highest risk are patients with preexisting conditions known to limit their water excretion, particularly those characterized by a reduction of effective circulating volume, such as congestive heart failure.[86] Even with normal systemic hemodynamics, however, CKD can predispose to NSAID-induced hyponatremia. Clinicians must exercise caution when considering persons with CKD for a course of NSAID therapy, particularly those patients with a prior history of hyponatremia. Blood chemistries should be monitored frequently (about every two weeks or until the stability of blood chemistries has been ascertained) with the expectation of determining the possible need for daily water restriction. Although a synergistic effect of NSAIDs and thiazide diuretics in promoting hyponatremia has not yet been demonstrated, it would seem prudent to avoid this drug combination.

Sodium Retention

Antinatriuresis is the most common renal side effect of NSAIDs. In large trials of nonspecific and COX-2-specific NSAIDs in patients with osteoarthritis, the incidence of edema, generally mild, ranged from approximately 2–6%.[87] Again, the most vulnerable patients are those with sodium retentive conditions such as cirrhosis and congestive heart failure, disorders in which optimization of renal hemodynamics is prostaglandin-dependent. Cyclooxygenase inhibition in these situations lessens glomerular perfusion and filtration, resulting in both a reduction of the filtered load and increased tubular reabsorption of sodium. In addition to altered hemodynamics, sodium retention also reflects the elimination of the natriuretic effects of prostaglandins, which inhibit tubular sodium transport in the normal kidney. This more direct antinatriuretic action of NSAIDs can occasionally have significant impact even in normal individuals. In one investigation in which 36 normal subjects were challenged with

indomethacin or a COX-2-selective NSAID, the antinatriuretic effects of each agent were shown to persist only through the first 72 hours of treatment.[88] How this escape natriuresis occurs is unknown nor is it known why it presumably fails to occur in those occasional seemingly normal individuals who develop edema on NSAIDs.

Studies have demonstrated NSAIDs are capable of mitigating the natriuretic effects of loop and thiazide diuretics.[89–94] Sodium retention, like most other renal side effects of NSAIDS, is reversible. Natriuresis generally occurs on discontinuation of the drug, with restoration of pretreatment sodium balance.

Exacerbation of Hypertension

The intimate relationship between hypertension and CKD is familiar to all clinicians and detailed elsewhere in this text. Hypertension is a common primary cause of CKD. Conversely, hypertension is the nearly inevitable result of declining GFR in patients with CKD of most etiologies. Regardless of whether hypertension represents a primary or secondary phenomenon in a given patient with CKD, it can accelerate the course of progressive renal injury. Besides blunting the action of diuretics, NSAIDs can reduce the efficacy of other antihypertensive agents including calcium channel blockers,[95] vasodilators,[87] and, possibly, beta blockers.[96,97] In a randomized controlled trial in which celecoxib was given to 178 participants already receiving an ACE inhibitor for hypertension, no effect of the NSAID on blood pressure was seen.[98] The ability of NSAIDs to mitigate action of some antihypertensive drugs is understandable, given the vasodilatory and natriuretic properties of the predominant renal eicosanoids. In the Success VI trial comparing the vascular effects of rofecoxib and celecoxib, the tendency to cause edema paralleled their tendency to cause increased systolic blood pressure, with rofecoxib exerting greater effects than celecoxib.[99] The significance of these observations is threefold. First, they strengthen the contention that antinatriuresis plays a role in NSAID-related exacerbation of hypertension. Second, they illustrate that cyclooxygenase-2 specificity may actually enhance the harmfulness of NSAIDs to the kidneys. Third, they underscore the disproportionate morbidity of rofecoxib compared with the closely related compound, celecoxib. This last point was upheld in another similar study comparing the vascular actions of several NSAIDs in type 2 diabetic hypertensive patients receiving NSAIDs for osteoarthritis, which found rofecoxib more apt to exacerbate hypertension than either naproxen or celecoxib.[100]

Because CKD is so prevalent and so likely to go unrecognized in our population, and because antiinflammatory self-medication use is so abundant, physicians should alert their patients to the potential for untoward interactions.[26] The significance of NSAIDs in clinical hypertension resides in their ability to exacerbate preexisting hypertension or to vitiate the actions of antihypertensive drugs. However, evidence from several sources, including the national Nurses Health Study, raises concern about an increased risk of incident hypertension among otherwise healthy persons who use NSAIDs heavily.[101–103] In any event, blood pressure, like other parameters of renal function, should be monitored closely throughout the course of NSAID therapy in patients with known hypertension or CKD or both, and appropriate adjustments in antihypertensive regimens made when necessary.

NONRENAL SIDE EFFECTS OF NSAID USE IN PATIENTS WITH CKD

NSAIDs can increase the risk of cardiovascular events in patients with atherosclerosis. Given the enormous prevalence of atherosclerosis at all stages of CKD, such patients should be considered at particularly high risk for cardiovascular morbidity when taking NSAIDs. It is important to inform patients of this risk and advise them to seek immediate medical attention if any symptoms suggestive of coronary or cerebrovascular ischemia should arise. The risk of atherothrombotic complications in these patients is another reason why stringent attention must be paid to blood pressure control.

Of all NSAID side effects, the most familiar to physicians and patients alike, and the most concerning epidemiologically, are those involving the gastrointestinal tract: dyspepsia, gastritis, peptic ulceration, and upper gastrointestinal hemorrhage. Gastritis and peptic ulcer disease were formerly thought to be more prevalent in CKD patients than in the population at large. Although current consensus challenges this contention, recent evidence suggests that CKD patients with peptic ulcer disease are more prone to complications such as recurrent bleeding.[104] Given this, and the clinical observation that peptic ulcer disease tends to be less symptomatic in CKD patients than in others, it is prudent to consider these patients at increased risk of gastrointestinal morbidity from NSAIDs. Although COX-2 inhibitors are safer from the gastrointestinal standpoint, they are no safer for the kidneys than traditional NSAIDs and may pose a higher risk of cardiovascular complications. It is thus impossible to specify a particular NSAID of choice for CKD patients. Agents of either group should be used with extreme caution, and patients should be monitored for the appearance of gastrointestinal

complications. CKD patients receiving NSAIDs should receive proton-pump inhibitors concomitantly for gastrointestinal prophylaxis.

NSAIDS AND CKD: RECOMMENDATIONS FOR THE CLINICIAN

The combined prevalence of NSAID use and CKD throughout the modern world represents a substantial hazard for untoward interactions. Fortunately, most adverse renal effects of NSAIDs are reversible, and patients at highest risk are readily identifiable. The presence of risk factors does not categorically preclude the use of NSAIDs when indications arise, as long as careful physician oversight of NSAID therapy is provided. An algorithm illustrating an approach we recommend is shown in Figure 65.3. When NSAID therapy is indicated for a patient with renal risk factors, it may be worth starting with one of the better tolerated agents such as a nonacetylated salicylate. While less often associated with renal side effects, these agents lack the antiinflammatory potency of most other NSAIDs. They are unlikely to be of benefit in a highly active inflammatory state such as acute gouty arthritis or a flare of systemic lupus. If they are tried, and fail to engender the desired therapeutic response, a trial of a more potent NSAID such as naproxen, indomethacin, or ibuprofen may be considered, provided the patient is closely monitored.

NSAIDs are extremely effective in the treatment of a wide variety of inflammatory conditions and have an established role in the palliation of pain. What alternatives are available for patients who cannot tolerate them? The answer to this question clearly depends on the indication for treatment. Corticosteroids offer an alternative option for treating inflammatory disorders. The risks associated with systemic steroid therapy must be weighed if this option is under consideration. A localized inflammatory condition, such as a monoarthritis or bursitis, may respond to direct injection, which lessens systemic exposure. CKD patients with gout or pseudogout can be safely treated with colchicine provided the clinician titrates the dose carefully to minimize gastrointestinal symptoms. If colchicine therapy is to last longer than a week, the white blood cell count should be monitored.

Acetaminophen is a good alternative to NSAIDs for management of mild to moderate pain. Although

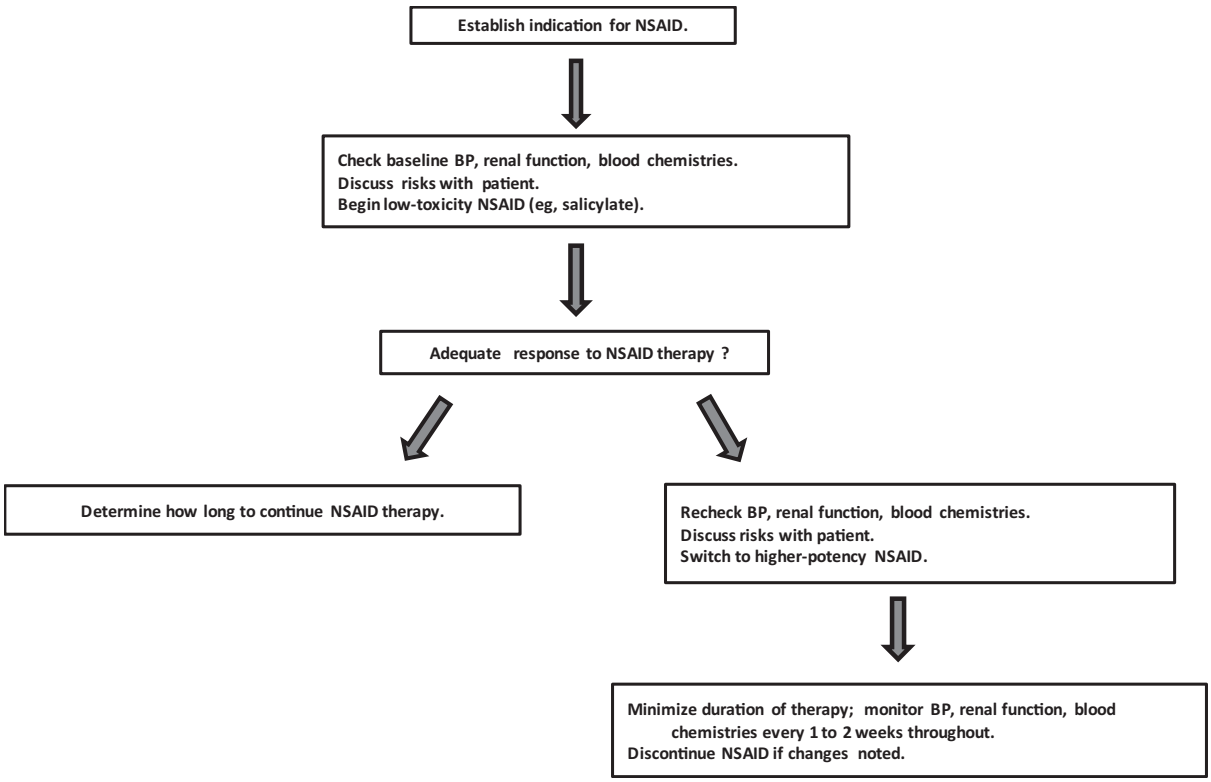


FIGURE 65.3 **Suggested algorithm for safe treatment with NSAIDs in patients with CKD.** Patients with known risk factors should be monitored for renal complications throughout course of therapy. Low-toxicity NSAIDs, specifically nonacetylated salicylates, are less apt to cause renal side effects, but often have less therapeutic efficacy. When higher potency nonsteroidals are used in patients at risk, vigilance must be intensified. Alternatives to NSAIDs for the management of pain and inflammation are discussed in text.

acetaminophen does have slight nephrotoxic potential, this does not pose a significant risk until a very high cumulative dose exposure is reached. Opioids represent another option.

OPIOIDS AND CKD

Narcotic analgesics can be used as NSAID alternatives in patients with moderate to severe pain provided the clinician and patient are mindful of their risks. Clinical safety of these agents from the renal standpoint will be considered in the following section.

OPIOID-INDUCED NEPHROPATHIES

Although the direct nephrotoxicity of opioids is questionable, they have the ability to engender acute effects on prerenal, intrarenal, and postrenal physiology. Understanding these effects is essential to predicting the acute and long-term effects of opioids on kidney function.

Acute Renal Effects of Opioids

Prerenal renal azotemia due to opioids occurs as a result of opioid-induced hypotension, which arises through several mu opioid receptor (MOR)-mediated mechanisms. These include suppression of CNS sympathetic outflow, histamine-induced vasodilation, and blunting of reflex vasoconstriction in response to fluctuations in arterial blood gases.[105] Recent *in vivo* studies suggest this effect may also be mediated by nitric oxide[106,107], or by indirect activation of the apelin receptor.[108] Because of their hypotensive effect, opioids should be used with caution in CKD patients to avoid worsening of intradialytic hypotension and further decrease in renal perfusion in the setting of already compromised renal blood flow. Fentanyl, which has multiple pharmacokinetic properties favorable for use in renal impairment, appears to exert the least hemodynamic impact among opioids.

Acute intrarenal effects of opioids. Kidney injury due to rhabdomyolysis is commonly seen with opioid overdoses that result in prolonged immobilization. Animal studies suggest that opioid exposure itself also has the potential to exert physiological damage on the kidney at the cellular level. Morphine has been shown to compromise podocyte integrity, inducing microalbuminuria[109] and to induce mesangial cell proliferation and superoxide formation resulting in glomerular injury *in vitro*.[110–112] Perhaps related to these observations, Yatsynovich et al. described a case of a 61-year-old man with stage IIIa CKD attributed to chronic NSAID use for back pain. After two years of abstention from NSAIDs, during which time the patient had been using oxymorphone for analgesia, he developed proteinuria and acute-on-chronic renal failure. Renal biopsy revealed lamellated, phospholipid-like deposits in podocytes similar to those seen in Fabry's disease as well as in renal injury from other medications. The patient's kidneys recovered to baseline following abstinence from oxymorphone.[113] Therapeutic doses of tramadol and tapentadol have also been shown to produce histological changes in rat renal tissue mediated by oxidative stress[114] although we are unaware of any reports of human renal injury due to these agents.

Postrenal effects of opioids. Opioid-induced urinary retention results from MOR-mediated inhibition of the volume-evoked micturition reflex[115] and from decreased detrusor contractility *via* the inhibition of acetylcholine release by parasympathetic sacral neurons.[116,117] The anticholinergic activity of opioids does not correlate directly with their narcotic potency. Despite being among the weaker opioids, tramadol tends to exert the most potent anticholinergic effect among drugs in this class.[118]

Heroin Nephropathy and Other Renal Syndromes Associated with Opioid Abuse

"Heroin nephropathy" was widely reported in the 1970s and 1980s, although such reports have become rare in recent years. Whether this syndrome was attributable to the pharmacological properties of the active drug *per se*, to bulking agents and contaminants within the drug product, or to comorbidities and social factors associated with intravenous drug use (IVDU), has been debated. The preponderance of evidence favors the latter two explanations. Most cases were reported in users of "brown heroin," a variety originating predominantly in southwest Asia. Its brownish color reflects the specific chemical process by which it is formulated.[119] Phenacetin, a commonly used heroin additive, was banned by the FDA in 1983 because of its nephrotoxicity. The withdrawal of phenacetin may have contributed to the waning of the heroin nephropathy phenomenon.[120] A patient has been reported who developed acute renal injury due to crystallization of heroin in the renal tubules. Although this mechanism of renal injury is well known in relation to other pharmacologic agents, including NSAIDs, we know of only one such report of tubular injury due to heroin dissolubility.[121] Indeed, renal biopsies of patients with "heroin nephropathy" most commonly revealed the lesions of focal segmental glomerulosclerosis and membranoproliferative glomerulonephritis. These are also the lesions seen in the glomerulopathies associated with HIV and HCV infection,

also highly prevalent among IV drug users. It is speculated that advances in the diagnosis and treatment of these diseases have resulted in the reduced frequency with which heroin nephropathy is documented.[122–124] Infections associated with IVDU may have additional, indirect renal implications as they often result in exposure to nephrotoxic antiinfective agents. For example, tenofovir, a widely used antiretroviral agent for the treatment of both HIV and HBV infection, is known to cause ATN and Fanconi syndrome.[125–127] IVDU-associated bacterial infections such as infective endocarditis may also result in prolonged exposure to highly nephrotoxic antibiotics such as vancomycin and/or aminoglycosides, which may cause AIN and ATN, respectively.[128]

USE OF OPIOIDS IN PATIENTS WITH CKD

Recent evidence suggests that therapeutic use of opioids is widespread among patients with CKD and may even increase in patients with more advanced stages of CKD.[129] It behooves the nephrologist to have at least passing familiarity with the clinical pharmacology of these agents.

Agent-specific Considerations

As a family, the opioids vary widely in terms of their individual pharmacokinetics and routes of metabolism. This variability markedly influences the safety and proper prescription of each agent for use in patients with CKD. The following paragraphs, and Table 65.5, summarize the key considerations.

Morphine[130]: Morphine's kinetic and dynamic profiles make it unfavorable for use in patients with kidney disease. Symptoms of neurotoxicity such as cognitive impairment, tremors, and myoclonus can result from the glucuronidated morphine metabolite M3G, which tends to accumulate in patients with impaired renal function.[131] Morphine is also especially histaminergic[132] and therefore more likely to produce untoward hemodynamic effects than other drugs in this class.

Hydromorphone[133]: Hydromorphone's active metabolite HM3G has been shown to have neurotoxic effects similar to those produced by toxic morphine metabolites.[134,135] However, it is considered safer and possibly more effective than morphine.[136,137]

Codeine[138]: Codeine's metabolism and excretion are quite variable and subject to the influence of factors besides renal function, particularly CYP2D6 activity.[139,140] Codeine is converted into multiple metabolites, including morphine, *via* the CYP2D6 pathway. Given its unpredictable kinetics, and the likelihood of accumulation of downstream toxic metabolites, codeine is not recommended in kidney disease.

Hydrocodone[141,142]: As hydrocodone is eliminated primarily *via* the kidneys, patients with renal disease are at increased risk of sedation and respiratory depression. Dosage adjustment and careful titration are warranted.

Oxycodone[143]: Oxycodone is extensively renally eliminated and minimally dialyzable.[144] Renal dosing adjustments and careful titration are warranted with its use.

Meperidine[145]: The antinociceptive properties of meperidine have been shown to be minimal relative to the toxicity of its primary metabolite, normeperidine. Its place in pain management is, therefore, limited.[146] Because meperidine and normeperidine are extensively renally eliminated, its use is discouraged in renal failure. However, both meperidine and normeperidine are effectively removed by dialysis.[147]

Tramadol[148]: Tramadol exerts a weak narcotic effect and was only recently added to the DEA list of controlled substances. Approximately 30% of tramadol is eliminated by the kidney, resulting in its prolonged duration of effect with renal impairment. Because of its structural similarity to meperidine, tramadol shares many of its off-target anticholinergic and serotonergic effects and a propensity to cause seizures. Reduced dosing frequency in patients with renal failure and avoidance of use all together in patients with seizure history are therefore recommended.

Fentanyl[149,150]: Because less than 10% of active drug is excreted in the urine, fentanyl is unlikely to accumulate in patients with mild to moderate renal disease or when given in appropriately adjusted doses to patients with

TABLE 65.5 Suggested Dosing of Opioids as a Function of GFR[153–155]

GFR (mL/min)	Methadone	Oxycodone	Hydromorphone	Hydrocodone	Oxymorphone	Fentanyl	Tramadol	Morphine
>60	5 mg PO 2.5 mg IV	5–10 mg PO	1–2 mg PO 0.25–0.5 mg IV	5–10 mg PO	5 mg PO	25–50 mcg IV	50 mg PO	10 mg PO 2.5–5 mg IV
30–60	100*	50*	50*	75*	75*	100*	100*	50*
<30	75*	25*	25*	50*	50*	75*	Dose q12 hours	25*

Note: Further dose reduction should be considered for patients with eGFR <10 mL/min/1.73 m^2. Use of codeine, morphine, or meperidine is not recommended in CKD. Dosing recommendations are for immediate release dosage forms only.

** Percent of starting dose for GFR >60 mL/min.*

severe renal disease. The most commonly used nonparenteral formulation is the transdermal patch. Unfortunately, transdermal delivery delays the onset and duration of action by up to 12 hours from the time the patch is applied or removed, making it somewhat more difficult to monitor and titrate. As such, the patch is not recommended in patients who are opioid naïve, and further caution must be exercised when initiating its use in patients with kidney disease.

Methadone[151]: Methadone is notoriously difficult to titrate for several reasons including its tendency to accumulate in tissues, its long elimination half-life relative to duration of analgesia, and its somewhat idiosyncratic dose–response relationship. However, like fentanyl, less than 10% of active methadone is excreted in the urine, resulting in pharmacokinetics that are only minimally altered in the setting of renal impairment. Unlike other opioids, methadone can cause cardiac arrhythmias when combined with other QT-interval-prolonging agents. Patients with renal failure may be more susceptible to such drug–drug interactions.[152]

Dialytic Considerations

Because the narcotic effects of opioids, with few exceptions, are readily reversible with naloxone, the safety implications of nondialyzability are generally minimal. As dialyzability is inversely proportional to molecular weight, volume of distribution, protein binding, and water solubility, it is not surprising that pharmacokinetic studies have found methadone and fentanyl concentrations least affected by hemodialysis,[156–159] whereas drugs like morphine may be so readily dialyzed that a rebound effect may be observed as the elimination from the plasma during dialysis may exceed the rate of drug transfer to and from the CNS.[160] The chemical properties of each opioid agent that may affect its dialyzability are listed in Table 65.6.

Conclusions

The combined prevalence of NSAID use and CKD throughout the modern world represents a substantial hazard for untoward interactions. Fortunately, most adverse renal effects of NSAIDs are reversible, and patients at highest risk are readily identifiable. The presence of risk factors does not categorically preclude the use of NSAIDs when indications arise, as long as careful physician oversight of NSAID therapy is provided. An algorithm illustrating an approach we recommend is shown in Figure 65.3. When NSAID therapy is indicated for a patient with renal risk factors, it may be worth starting with one of the better tolerated agents such as a nonacetylated salicylate. While less often associated with renal side effects, these agents lack the antiinflammatory potency of most other NSAIDs. They are unlikely to be of benefit in a highly active inflammatory state such as acute gouty arthritis or a flare of systemic lupus. If they are tried, and fail to engender the desired therapeutic response, a trial of a more potent NSAID such as naproxen, indomethacin, or ibuprofen may be considered, provided the patient is closely monitored.

NSAIDs are extremely effective in the treatment of a wide variety of inflammatory conditions and have an established role in the palliation of pain. What alternatives are available for patients who cannot tolerate them? The answer to this question clearly depends on the indication for treatment. Corticosteroids are an option for treating inflammatory disorders. The risks

TABLE 65.6 Drug-specific Factors Affecting the Dialyzability of Opioids[161]

Agent	Molecular Weight	Volume of Distribution (L)	Protein Binding	Water Solubility
Methadone	309.4	1–8	85–90%	–
Oxycodone	315.4	2.6	38–45%	+
Hydromorphone	285.3	4	8–19%	+
Hydrocodone	299.8	Not reported	36%	–
Oxymorphone	301.3	2–4	10–12%	++
Fentanyl	336.5	4–6	79–87%	–
Tramadol	263.3	2.6–2.9	20%	–
Morphine	285.3	1–6	20–35%	++
Codeine	299.4	3–6	7–25%	–
Meperidine	247.3	3–4	65–75%	+

associated with systemic steroid therapy must be weighed against the use of other approaches if this option is under consideration. If the inflammatory condition is localized (such as a monoarthritis or bursitis), it may respond to direct injection, which lessens systemic exposure. CKD patients with gout or pseudogout can be safely treated with colchicine, provided the clinician titrates the dose carefully so as to minimize gastrointestinal symptoms. If colchicine therapy is to last longer than a week, the white blood cell count should be monitored.

Acetaminophen is a good alternative to NSAIDs for management of mild to moderate pain. Although, as noted, acetaminophen does have mild nephrotoxic potential, this does not represent a significant risk until a very high cumulative dose exposure is reached. Narcotic analgesics can be used as NSAID alternatives in patients with moderate to severe pain, provided the clinician and patient are mindful of the well-known risks associated with these agents.

Serious problems are associated with the widespread use of opioids, including misuse, abuse, overprescription, and diversion. Nevertheless, these drugs remain a valuable therapeutic tool in the treatment of pain refractory to nonnarcotic analgesics. Pharmacokinetics of many opioids are altered in CKD, and they vary in their dialyzability. For these reasons, dosing modifications are often necessary.

References

1. Zhou Y, Boudreau DM, Freedman AN. Trends in the use of aspirin and nonsteroidal anti- inflammatory drugs in the general U.S. population. *Pharmacoepidemiol Drug Saf* 2014;**23**:43–50.
2. Consumer reports staff. *The nonsteroidal anti-inflammatory drugs: treating osteoarthritis and pain. Comparing drug effectiveness, safety, and price*. Consumer Reports Online. 2011. p. 1–22.
3. Otskuka N, Yataba I, Matsushita I, Matsumoto H, Hoshino Y, Terada Y. A minimal impact of long-term S-flurbiprofen plaster application on kidney function in osteoarthritis patients. *Clin Exp Nephrol* 2017;**21**:1060–7.
4. Kikuchi H, Aoyagi M, Nagahama K, Yajima Y, Yamamura C, Arai Y, Hirasawa S, Aki S, Inaba N, Tanaka H, Tamura T. Nephrotic-range proteiniuria and interstitial nephritis associated with the use of topical loxoprofen patch. *Intern Med* 2014;**53**: 1131–5.
5. Green T, Gonzalez AA, Mitchell MD, Navar GL. The complex interplay between cyclooxygenase-2 and angiotensin II in regulating kidney function. *Curr Opin Nephrol Hypertens* 2012;**21**:7–14.
6. Kirschenbaum MA, White N, Stein JH, Ferris TF. Redistribution of renal cortical blood flow during inhibition of rostaglandin synthesis. *Am J Physiol* 1974;**227**:801–5.
7. Wiseman EH, Reinert H. Anti-inflammatory drugs and renal papillary necrosis. *Agents Actions* 1975;**5**:322–5.
8. Shah GM, Muhalwas KK, Winer RL. Renal papillary necrosis due to ibuprofen. *Arthritis Rheum* 1981;**24**:1208–10.
9. Lourie SH, Denman SJ, Schroeder ET. Association of renal papillary necrosis and ankylosing spondylitis. *Arthritis Rheum* 1977; **20**:917–21.
10. Morales A, Steyn J. Papillary necrosis following phenylbutazone ingestion. *Arch Surg* 1971;**103**:420–1.
11. Husserl FE, Lange RK, Kantrow Jr CM. Renal papillary necrosis and pyelonephritis accompanying fenoprofen therapy. *J Am Med Assoc* 1979;**242**:1896–8.
12. Gokal R, Matthews DR. Renal papillary necrosis after aspirin and alclofenac. *Br Med J* 1977;**2**:1517–8.
13. Krishnaswamy S, Nanra RS. "Phenacetin nephropathy" without phenacetin. *Austr NZ Med J* 1976;**6**:88 [abstract].
14. Atta MG, Whelton A. Acute renal papillary necrosis induced by ibuprofen. *Am J Therapeut* 1997;**4**:55.
15. Segasothy M, Chin GL, Sia KK, Zulfiqar A, Samad SA. Chronic nephrotoxicity of anti-inflammatory drugs used in the treatment of arthritis. *Br J Rheumatol* 1995;**34**:162–5.
16. Sandler DP, Burr FR, Weinberg CR. Nonsteroidal anti-inflammatory drugs and the risk for chronic renal disease. *Ann Intern Med* 1991;**115**:165–72.
17. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1994;**331**: 1675–9.
18. Chang YK, Liu JS, Hsu YH, Tarng DC, Hsu CC. Increased risk of end-stage renal disease (ESRD) requiring chronic dialysis is associated with use of nonsteroidal anit-inflammatory drugs (NSAIDs): nationwide case-crossover study. *Medicine* 2015;**94**: e1362.
19. Curhan GC, Knight EL, Rosner B, Hankinson SE, Stampfer MJ. Lifetime nonnarcotic analgesic use and decline in renal function in women. *Arch Intern Med* 2004;**164**:1519–24.
20. Rexrode KM, Buring JE, Glynn RJ, Stampfer MJ, Youngman LD, Gaziano JM. Analgesic use and renal function in men. *J Am Med Assoc* 2001;**286**:315–21.
21. Kurth T, Glynn RJ, Walker AM, Rexrode KM, Buring JE, Stampfer MJ, Hennekens CH, Gaziano JM. Analgesic use and change in kidney function in apparently healthy men. *Am J Kidney Dis* 2003;**42**:234–44.
22. Ibáñez L, Morlans M, Vidal X, Martínez MJ, Laporte JR. Case-control study of regular analgesic and nonsteroidal anti-inflammatory use and end-stage renal disease. *Kidney Int* 2005; **67**:2393–8.
23. van der Woude FJ, Heinemann LA, Graf H, et al. Analgesics use and ESRD in younger age: a case-control study. *BMC Nephrol* 2007;**8**:15.
24. Klag MJ, Whelton PK, Pernerger TV. Analgesics and chronic renal disease. *Am J Therapeut* 2002;**9**:169–70.
25. Pommer W, Bronder E, Greiser E, Helmert U, Jesdinsky HJ, Klimpel A, Moldzahn M. Regular analgesic intake and the risk of end-stage renal failure. *Am J Nephrol* 1989;**9**:403–12.
26. Kristensen SL, Fosbøl EL, Kamper AL, Køber L, Hommel K, Lamberts M, Abildstrøm SZ, Blicher TM, Torp-Pedersen C, Gislason GH. Use of nonsteroidal anti-inflammatory drugs prior to chronic renal replacement therapy initiation: a nationwide study. *Pharmacoepidemiol Drug Saf* 2012;**21**:428–34.
27. Pan Y, Zhang L, Wang F, Li X, Wang H. Status of nonsteroidal anti-inflammatory drugs use and its association with chronic kidney disease: a cross-sectional survey in China. *Nephrology* 2014;**19**: 655–60.
28. Plantinga L, Grubbs V, Sarkar U, Hsu C-Y, Hedgeman E, Robinson B, Saran R, Geiss L, Nilka RB, Eberhardt M, Powe N, CDC CKD Surveillance Team. Nonsteroidal anti-inflammatory

drug use among persons with chronic kidney disease in the United States. *Ann Fam Med* 2011;**9**:423–30.
29. Segasothy M, Samad SA, Zulfigar A, Bennett WM. Chronic renal disease and papillary necrosis associated with the long-term use of nonsteroidal anti-inflammatory drugs as the sole or predominant analgesic. *Am J Kidney Dis* 1994;**24**:17–24.
30. Henrich WL, Clark RL, Kelly JP, et al. Non-contrast-enhanced computed tomography and analgesic-related kidney disease: report of the National Analgesic Nephropathy Study. *J Am Soc Nephrol* 2006;**17**:1472–80.
31. Duggin GC. Combination analgesic-induced kidney disease: the Australian experience. *Am J Kidney Dis* 1996;**28**(Suppl. 1):S39–47.
32. Eknoyan G. Current status of chronic analgesic and nonsteroidal anti-inflammatory drug nephropathy. *Curr Opin Nephrol Hypertens* 1994;**3**:182–8.
33. Bennett WM, Porter GA. Analgesic nephropathy and the use of nonsteroidal anti-inflammatory drugs in renal patients: new insight. *J Nephrol* 1998;**11**:70–5.
34. Clive DM, Stoff JS. Renal syndromes associated with nonsteroidal antiinflammatory drugs. *N Engl J Med* 1984;**310**:563–72.
35. Schlondorff D. Renal complications of nonsteroidal anti-inflammatory drugs. *Kidney Int* 1993;**44**:643.
36. Brater DC. Clinical aspects of renal prostaglandins and NSAID therapy. *Semin Arthritis Rheum* 1988;**17**:17–22.
37. Brater DC. Anti-inflammatory agents and renal function. *Semin Arthritis Rheum* 2002;**32**:33–42.
38. Whelton A. Renal and related cardiovascular effects of conventional and COX-2-specific NSAIDs and NSAID analgesics. *AM J Therap* 2000;**7**:63–74.
39. Gambaro G, Perazella MA. Adverse renal effects of antiinflammatory agents: evaluation of selective and nonselective cyclooxygenase inhibitors. *J Intern Med* 2003;**253**:643–52.
40. Henrich WL. Nephrotoxicity of nonsteroidal anti-inflammatory agents. *Am J Kidney Dis* 1983;**2**:478–84.
41. Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. *BMJ* 2013;**346**:e8525.
42. Nygard P, Jansman FG, Kruik-Kolloffel WJ, Barnaart AF, Brouwers JR. Effects of short-term addition of NSAID to diuretics and/or RAAS-inhibitors on blood pressure and renal function. *Int J Clin Pharm* 2012;**34**:468–74.
43. Thomas MC. Diuretics, ACE inhibitors, and NSAIDs—the triple whammy. *Med J Aust* 2000;**172**:184–5.
44. Manoni AA, Kholmurodova F, Mayner L, Hakendorf P, Woodman RJ. The concomitant use of diuretics, non-steroidal anti-inflammatory drugs, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (triple whammy), Extreme heat, and in-hosptial acute kidney injury in older medical patients. *Adv Ther* 2017;**34**:2534–41.
45. Camin RM, Cols M, Chevarria JL, Osuna RG, Carreras M, Lisbona JM, Coderch J. Acute kidney injury secondary to a combination of renin-angiotensin system inhibitors, diuretics and NSAIDS: "the triple whammy". *Nefrologia* 2015;**35**:197–206.
46. Dreischulte T, Morales DR, Bell S, Guthrie B. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. *Kidney Int* 2015;**88**:396–403.
47. Kimberly RP, Gill Jr JR, Bowden RE, Keiser HR, Plotz PH. Elevated urinary prostaglandins and the effects of aspirin on renal function in lupus erythematosus. *Ann Intern Med* 1978;**89**:336–41.
48. Kimberly RP, Bowden RE, Keiser HR, Plotz PH. Reduction of renal function by newer nonsteroidal anti-inflammatory drugs. *Am J Med* 1978;**64**:804–7.
49. Deen WM, Maddox DA, Robertson CR, Brenner BM. Dynamics of glomerular ultrafiltration in the rat. VII. Response to reduced renal mass. *Am J Physiol* 1974;**227**:556–62.
50. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol* 1981;**241**:F85–93.
51. Sanchez PL, Salgado LM, Ferreri NR, Escalante B. Effect of cyclooxygenase-2 inhibition on renal function after renal ablation. *Hypertension* 1999;**34**:848–53.
52. Allon M, Lawson L, Eckman JR, Delaney V, Bourke E. Effects of nonsteroidal antiinflammatory drugs on renal function in sickle cell anemia. *Kidney Int* 1988;**34**:500–6.
53. Cherney DZI, Miller JA, Scholey JW, Bradley TJ, Storach C, Curtis JR, Dekker MG, Nasrallah R, Hebert RL, Sochett EB. *Diabetes* 2008;**57**:688–95.
54. Montini G, Sacchetto E, Murer L, Dall'amico R, Masiero M, Passerini-Glazel G, Zacchello G. Renal glomerular response to the inhibition of prostaglandin E2 synthesis and protein loading after the relief of unilateral ureteropelvic junction obstruction. *J Urol* 2000;**163**:556–60.
55. Nesher G, Zimran A, Hershko C. Reduced incidence of hyperkalemia and azotemia in patients receiving sulindac compared with indomethacin. *Nephron* 1988;**48**:291–5.
56. Ciabattoni G, Pugliese F, Cinotti GA, Patrono C. Renal effects of anti-inflammatory drags. *Eur J Rheumatol Inflamm* 1980;**3**:210–21.
57. Ungorasert P, Cheungpasitporn W, Crowson CS, Matteson EL. Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: a systematic review and meta-analysis of observational studies. *Eur J Intern Med* 2015;**26**:285–91.
58. Perez-Gutthann S, Garcia Rodriguez LA, Raiford DS, Duque Oliart A, Ris Romeu J. Nonsteroidal anti-inflammatory drugs and the risk of hospitalization for acute renal failure. *Arch Intern Med* 1996;**156**:2433–9.
59. Patrono C, Pierucci A. Renal effects of nonsteroidal anti-inflammatory drugs in chronic glomerular disease. *Am J Med* 1986;**81**(Suppl. 2B):71–83.
60. Pierucci A, SImonetti BM, Pecci G, Mavrikakis G, Feriozzi S, Patrignani P, Ciabattoni G, Patrono C. Improvement of renal function with selective thromboxane antagonism in lupus nephritis. *N Engl J Med* 1989;**320**:421–5.
61. Harris RC. An update on cyclooxygenase-2 expression and metabolites in the kidney. *Curr Opin Nephrol Hypertens* 2008;**17**:64–9.
62. Noroian G, Clive DM. Cox-2 antagonists and the kidney: a case for caution. *Drug Saf* 2002;**25**:165–72.
63. Perazella MA. Drug-induced renal failure: update on new medications and unique mechanisms of nephrotoxicity. *Am J Med Sci* 2003;**325**:349–62.
64. Patrono C, Patrignani P, Garcia Rodriguez LA. Cyclooxygenase-selective inhibition of prostanoid formation: transducing biochemical selectivity into clinical read-outs. *J Clin Investig* 2001;**108**:7–13.
65. Spalding WM, Reeves MJ, Whelton A. Thromboembolic cardiovascular risk among arthritis patients using cyclooxygenase-2 selective inhibitor or nonselective cyclooxygenase inhibitor nonsteroidal antiinflammatory drugs. *Am J Therapeut* 2007;**14**: 3–12.
66. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs. An update for clinicians: a scientific statement from the American Heart Association. *Circulation* 2007;**115**:1622–33.
67. Kearney PM, Balgent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomized trials. *BMJ* 2006;**332**:1302–8.

68. Roth-Cline MD. Clinical trials in the wake of Vioxx: requiring statistically extreme evidence of benefit to ensure the safety of new drugs. *Circulation* 2006;**113**:2253–9.
69. Sturmer T, Erb A, Keller F, Gunther KP, Brenner H. Determinants of impaired renal function with use of nonsteroidal anti-inflammatory drugs: the importance of half-life and other medications. *Am J Med* 2001;**111**:521–7.
70. Murray MD, Black PK, Kuzmik DD, Haag KM, Manatunca AK, Mullin MA, Hall SD, Brater DC. Acute and chronic effects of nonsteroidal antiinflammatory drugs on glomerular filtration rate in elderly patients. *Am J Med Sci* 1995;**310**:188–97.
71. Henry D, Page J, Whyte I, Nanra R, Hall C. Consumption of non-steroidal anti-inflammatory drugs and the development of functional renal impairment in elderly subjects. Results of a case-control study. *Br J Clin Pharmacol* 1997;**44**:85–90.
72. Whelton A, Schulman G, Wallemark C, Drower EJ, Isakson PC, Verburg KM, Geis GS. Effects of celecoxib and naproxen on renal function in the elderly. *Arch Intern Med* 2000;**160**:1465–70.
73. Gurwitz J, Clive DM, Rossetti R, Stoff JS. Effects of nonsteroidal antiinflammatory drugs on renal function in the elderly. *J Nephrol* 1991;**3**:163–7.
74. Gurwitz JH, Avorn J, Ross-Degnan D, Lipsitz LA. Nonsteroidal anti-inflammatory-associated azotemia in the very old. *J Am Med Assoc* 1990;**264**:471–5.
75. Heap GA, So K, Weedon M, Edney N, et al. Clinical features and HLA association of 5-aminosylaicylate (5-ASA)-induced nephrotoxicity in inflammatory bowel disease. *J Crohn's Colitis* 2016;**10**: 149–58.
76. Magalhaes-Costa P, Matos L, Chagas C. Chronic tubulointerstitial nephritis induced by 5-aminosalicylate in an ulcerative colitis patient: a rare but serious event. *BMJ Case Rep* 2015. bcr2014207928.
77. Gooch K, Culleton BF, Manns BJ, Zhang J, Alfonso H, Tonelli M, Frank C, Klarenbach S, Hemmelgarn BR. NSAID use and progression of chronic kidney disease. *Am J Med* 2007;**120**:280e1–7.
78. Kuo HW, Tsai SS, Tiao MM, Liu YC, Lee IM, Yang CY. Analgesic use and the risk for progression of chronic kidney disease. *Pharmacoepidemiol Drug Saf* 2010;**19**:745–751.
79. Nderitu P, Doos L, Jones PW, Davies SJ, Kadam UT. Nonsteroidal anti-inflammatory drugs and chronic kidney disease progression: a systematic review. *Fam Pract* 2013;**30**:247–55.
80. Lafrance JP, Miller DR. Dispensed selective and nonselective nonsteroidal anti-inflammatory drugs and the risk of moderate to severe hyperkalemia: a nested case-control study. *Am J Kidney Dis* 2012;**60**:82–9.
81. Zimran A, Kramer M, Plaskin M, Hershko C. Incidence of hyperkalemia induced by indomethacin in a hospital population. *Br Med J* 1985;**291**:107–8.
82. Mactier RA, Khanna R. Hyperkalemia induced by indomethacin and naproxen and reversed by fludrocortisone. *South Med J* 1988;**81**:799–801.
83. Sanjad SA, Keenan BS, Hill LL. Renal hypoprostaglandinism, hypertension, and type VIV renal tubular acidosis reversed by furosemide. *Ann Intern Med* 1983;**99**:624–7.
84. Clive D, Gurwitz J, Rossetti R. Potassium homeostasis with indomethacin therapy in normal subjects. *Am J Kidney Dis* 1992: 16–21.
85. Perazella MA, Mahnensmith RL. Hyperkalemia in the elderly: drugs exacerbate impaired potassium homeostasis. *J Gen Intern Med* 1997;**12**:646–56.
86. Dzau VJ, Packer M, Lilly LS, Swartz SL, Hollenberg NK, Williams GH. Prostaglandins in severe congestive heart failure. Relation to activation of the renin–angiotensin system and hyponatremia. *N Engl J Med* 1984;**310**:347–52.
87. Frishman WH. Effects of nonsteroidal anti-inflammatory drug therapy on blood pressure and peripheral edema. *Am J Cardiol* 2002;**89**(Suppl. 1):18D–25D.
88. Catella-Lawson F, McAdam B, Morrison BW, Kapoor S, Kujubu D, Antes L, Lasseter KC, Quan H, Gertz BJ, FitzGerald GA. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. *J Pharmacol Exp Ther* 1999; **289**:735–41.
89. Thakur V, Cook ME, Wallin JD. Antihypertensive effect of the combination of fosinopril and HCTZ is resistant to interference by nonsteroidal anti-inflammatory drugs. *Am J Hypertens* 1999; **12**:925–8.
90. Hitoglou-Makedou A, Lawson M, Turner P, Ferber HP. Comparison of chlortenoxicam and indomethacin on frusemide-induced diuresis. *Postgrad Med* 1989;**65**:821–3.
91. Nies AS. Renal effects of nonsteroidal anti-inflammatory drugs. *Agents Actions* 1988;**24**(Suppl. 1):95–106.
92. Herchuelz A, Derenne F, Deger F, Juvent M, Van Ganse E, Staroukine M, Verniory A, Boeynaems JM, Douchamps J. Interaction between nonsteroidal anti-inflammatory drugs and loop diuretics: modulation by sodium balance. *J Pharmacol Exp Ther* 1989;**248**:1175–81.
93. Dixey JJ, Noormohamed FH, Lant AF, Brewerton DA. The effects of naproxen and sulindac on renal function and their interaction with hydrochlorothiazide and piretanide in man. *Br J Clin Pharmacol* 1987;**23**:55–63.
94. Koopmans PP, Thien T, Thomas CM, Van den Berg RJ, Gribnau FW. The effects of sulindac and indomethacin on the anti-hypertensive and diuretic action of hydrochlorothiazide in patients with mild to moderate essential hypertension. *Br J Clin Pharmacol* 1986;**21**:417–23.
95. Salvetti A, Magagna A, Abdel-Haq B, Lenzi M, Giovanetti R. Nifedipine interactions in hypertensive patients. *Cardiovasc Drugs Ther* 1990;**4**(Suppl. 5):963–8.
96. Stokes GS, Brooks PM, Johnston HJ, Monaghan JC, Okoro EO, Kelly D. The effects of sulindac and diclofenac in essential hyupertension controlled by treatment with a beta blocker and/or diuretic. *Clin Exp Hypertens* 1991;**13**:1169–78.
97. Wong DG, Spence JD, Lamki L, Freeman D, McDonald JW. Effect of non-steroidal anti-inflammatory drugs on control of hypertension by beta-blockers and diuretics. *Lancet* 1986;**1**:997–1001.
98. White WB, Kent J, Taylor A, Verburg KM, Lefkowith JB, Whelton A. Effects of celecoxib on ambulatory blood pressure in hypertensive patients on ACE inhibitors. *Hypertension* 2002; **39**:929–34.
99. Whelton A, Fort JG, Puma JA, Normandin D, Bellow AE, Verburg KM, Success VI Study Group. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *Am J Therapeut* 2001;**8**:85–95.
100. Sowers JR, White WB, Pitt B, Whelton A, Simon LS, Winer N, Kivitz A, van Ingen H, Brabant T, Fort JG, The Crescent Investigators. The effects of cyclooxygenase-2 inhibitors and nonsteroidal anti-inflammatory therapy on 24-hour blood pressure in patients with hypertension, osteoarthritis, and Type 2 diabetes mellitus. *Arch Intern Med* 2005;**165**:161–8.
101. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med* 1994;**121**:289–300.

102. Wilson SL, Poulter NR. The effect of non-steroidal anti-inflammatory drugs and other commonly used non-narcotic analgesics on blood pressure level in adults. *J Hypertens* 2006;**24**: 1457–69.
103. Dedier J, Stampfer MJ, Hankinson SE, Willett WC, Speizer FE, Curhan GC. Nonnarcotic analgesic use and the risk of hypertension in US women. *Hypertension* 2002;**40**:604–8.
104. Fallone CA, Mayrand S. Gastroesophageal reflux and hyperacidity in chronic renal failure. *Perit Dial Int* 2001;**21**:S295–9.
105. Yaksh TL, Wallace MS, Tony L, et al. Opioids, analgesia, and pain management. In: *Goodman & Gilman's: the pharmacological basis of therapeutics*. 12th ed. New York, NY: McGraw-Hill; 2006.
106. Kuczeriszka M, Lipkowski AW, Sadowski J, et al. An endomorphine analog ([d-Ala(2)]-Endomorphin 2, TAPP) lowers blood pressure and enhances tissue nitric oxide in anesthetized rats. *Pharmacol Rep* 2016;**68**(3):616–9.
107. Pourshanazari A, Allahtavakoli M, Hassanshahi G. Effects of low-dose morphine on nitric oxide concentration and angiogenesis in two-kidney one clip hypertensive rats. *Iran J Basic Med Sci* 2011; **14**(6):560–7.
108. Rostamzadeh F, Najafipour H, Yeganeh-hajahmadi M, et al. Opioid receptors mediate inotropic and depressor effects of apelin in rats with 2K1C-induced chronic renovascular hypertension. *Clin Exp Pharmacol Physiol* 2018;**45**(2):187–97.
109. Lan X, Rai P, Chandel N, et al. Morphine induces albuminuria by compromising podocyte integrity. *PLoS One* 2013;**8**(3):e55748.
110. Singhal PC, Pamarthi M, Shah R, et al. Morphine stimulates superoxide formation by glomerular mesangial cells. *Inflammation* 1994;**18**:293–9.
111. Sharp BM, Keane WF, Suh HJ, et al. Opioid peptides rapidly stimulate superoxide production by human polymorphonuclear leukocytes and macrophages. *Endocrinology* 1985;**117**:793–5.
112. Weber ML, Farooqui M, Nguyen J, et al. Morphine induces mesangial cell proliferation and glomerulopathy via kappa-opioid receptors. *Am J Renal Physiol* 2008;**294**:F1388–1397.
113. Yatsynovich Y, Souza D, Maroz N. Oxymorphone hydrochloride extended-release (OPANA®) associated with acute kidney injury in a chronic pain patient: a case report. *Anesth-Analg Case Reports* 2017;**9**:324–7.
114. Barbosa J, Faria J, Leal S, et al. Acute administration of tramadol and tapentadol at effective analgesic and maximum tolerated doses causes hepato- and nephrotoxic effects in Wistar rats. *Toxicology* 2017;**389**:118–29.
115. Matsumoto S, Levendusky MC, Longhurst PA, et al. Activation of mu opioid receptors in the ventrolateral periaqueductal gray inhibits reflex micturition in anesthetized rats. *Neurosci Lett* 2004; **363**(2):116–9.
116. Baldini G, Bagry H, Aprikian A, et al. Postoperative urinary retention: anesthetic and perioperative considerations. *Anesthesiology* 2009;**110**(5):1139–57.
117. Malinovsky JM, Le Normand L, Lepage JY, et al. The urodynamic effects of intravenous opioids and ketoprofen in humans. *Anesth Analg* 1998;**87**:456–61.
118. Kupp M. Drugs with anticholinergic activity. *Prescriber's Lett* 2011; **18**(12):271223.
119. Ciccarone D. Heroin in black, brown, and white: structural factors and medical consequences in the US heroin market. *Int J Drug Policy* 2009;**20**:277–82.
120. Broséus J, Gentile N, Esseiva P. The cutting of cocaine and heroin: a critical review. *Forensic Sci Int* 2016;**262**:73–83.
121. Bautista JEK, Merhi B, Gregory O, Hu S, Henriksen K, Gohh R. Heroin crystal nephropathy. *Clin Kidney J* 2015;**8**:339–42.
122. Friedman EA, Tao TK. Disappearance of uremia due to heroin-associated nephropathy. *Am J Kidney Dis* 1995;**25**:689–93.
123. Jaffe JA, Kimmel PL. Chronic nephropathies of cocaine and heroin abuse: a critical review. *Clin J Am Soc Nephrol* 2006;**1**(4): 655–67.
124. do Sameiro Faria M, Sampaio S, Faria V, Carvalho E. Nephropathy associated with heroin abuse in Caucasian patients. *Nephrol Dial Transplant* 2003;**18**(11):2308–13.
125. Herlitz LC, Mohan S, Stokes MB, et al. Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities. *Kidney Int* 2010;**78**(11):1171–7.
126. Hamzah L, Jose S, Booth JW, et al. Treatment-limiting renal tubulopathy in patients treated with tenofovir disoproxil fumarate. *J Infect* 2017;**74**(5):492–500.
127. Rifkin B, Perazella M. Tenofovir-associated nephrotoxicity: fanconi syndrome and renal failure. *Am J Med* 2004;**117**:282–3.
128. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications. *Circulation* 2015;**132**:1435–86.
129. Novick TK, Surapaneni A, Shin J-I, et al. Prevalence of opioid, gabapentinoid, and NSAID use in patients with CKD. *CJASN* 2018;**13**:1886–8.
130. *Morphine sulfate tablet [prescribing information]*. Eatontown, NJ: West-Ward Pharmaceuticals; April 2017.
131. Milne RW, Nation RL, Somogyi AA, et al. The influence of renal function on the renal clearance of morphine and its glucuronide metabolites in intensive-care patients. *Br J Clin Pharmacol* 1992; **34**(1):53–9.
132. Baldo BA, Pham NH. Histamine-releasing and allergenic properties of opioid analgesic drugs: resolving the two. *Anaesth Intensive Care* 2012;**40**(2):216–35.
133. *Dilaudid, Dilaudid-HP (hydromorphone) [prescribing information]*. Stamford, CT: Purdue Pharma; December 2016.
134. Paramanandam G, Prommer E, Schwenke DC. Adverse effects in hospice patients with chronic kidney disease receiving hydromorphone. *J Palliat Med* 2011;**14**(9):1029–33.
135. Lee KA, Ganta N, Horton JR, Chai E. Evidence for neurotoxicity due to morphine or hydromorphone use in renal impairment: a systematic review. *J Palliat Med* 2016;**19**(11):1179–87.
136. Lee M, Leng M, Tiernan E. Retrospective study of the use of hydromorphone in palliative care patients with normal and abnormal urea and creatinine. *Palliat Med* 2001;**15**(1):26–34.
137. Felden L, Walter C, Harder S, et al. Comparative clinical effects of hydromorphone and morphine: a meta-analysis. *Br J Anaesth* 2011;**107**(3):319–28.
138. *Codeine sulfate tablets [prescribing information]*. Eatontown, NJ: West-Ward Pharmaceuticals Corp; August 2017.
139. Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part II. *Clin Pharmacokinet* 2009;**48**(12):761–804.
140. Madadi P, Amstutz U, Rieder M, et al. CPNDS Clinical Recommendations Group. Clinical practice guideline: CYP2D6 genotyping for safe and efficacious codeine therapy. *J Popul Ther Clin Pharmacol* 2013;**20**(3):e369–96.
141. *Vicodin, Vicodin ES, Vicodin HP (hydrocodone bitartrate/acetaminophen) [prescribing information]*. North Chicago, IL: AbbVie; February 2017.
142. *Zohydro ER (hydrocodone) [prescribing information]*. Morristown, NJ: Pernix Therapeutics; December 2016.

143. *Oxycodone hydrochloride tablet [prescribing information]*. Laurelton, NY: Epic Pharma; July 2017.
144. Tran BW, Kohan LR, Vorenkamp KE. Postoperative oxycodone toxicity in a patient with chronic pain and end-stage renal disease. *Anesth Analg Case Rep* 2015;**4**(4):44–6.
145. *Meperidine hydrochloride [prescribing information]*. Eatontown, NJ: West-Ward Pharmaceuticals; September 2017.
146. Institute for Safe Medication Practice (ISMP). *High alert medication feature: reducing patient harm from opiates*. ISMP Medication Safety Alert; February 22, 2007. Available at: http://www.ismp.org/Newsletters/acutecare/articles/20070222.asp.
147. Hsu CH, Lin TC, Lu CC, et al. Clearance of meperidine and its metabolite normeperidine in hemodialysis patients with chronic noncancer pain. *J Pain Symptom Mgmt* 2014;**47**(4):801–5.
148. *Ultram (tramadol) [prescribing information]*. Titusville, NJ: Janssen Pharmaceuticals Inc; August 2017.
149. *Duragesic (fentanyl transdermal system) [prescribing information]*. Titusville, NJ: Janssen; March 2017.
150. *Abstral (fentanyl) [prescribing information]*. Solana Beach, CA: Sentynl Therapeutics Inc; May 2017.
151. *Dolophine (methadone) [prescribing information]*. Eatontown, NJ: West-Ward Pharmaceuticals; February 2018.
152. Di Iorio B, Bellasi A. QT interval in CKD and haemodialysis patients. *Clin Kidney J* 2013;**6**(2):137–43.
153. Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Mgmt* 2004;**28**(5):497–504.
154. Gelot S, Nakhla E. Opioid dosing in renal and hepatic impairment. *US Pharm* 2014;**39**(8):34–8.
155. *Lexicomp database*. Riverwoods, IL: Wolters Kluwer Health, Inc.; 2016. Available at: http://online.lexi.com.
156. Bastani B, Jamal JA. Removal of morphine but not fentanyl during haemodialysis. *Nephrol Dial Transplant* 1997;**12**:2804.
157. Furlan V, Hafi A, Dessalles MC, et al. Methadone is poorly removed by haemodialysis. *Nephrol Dial Transplant* 1999;**14**:254–5.
158. Joh J, Sila MK, Bastani B. Nondialyzability of fentanyl with high-efficiency and high-flux membranes. *Anesth Analg* 1998; **86**(2):447.
159. Perlman R, Giladi H, Brecht K, et al. Intradialytic clearance of opioids: methadone versus hydromorphone. *Pain* 2013;**154**(12): 2794–800.
160. Angst MS, Bührer M, Lötsch J. Insidious intoxication after morphine treatment in renal failure: delayed onset of morphine-6-glucuronide action. *Anesthesiology* 2000;**92**(5):1473–6.
161. National Center for Biotechnology Information. PubChem Compound Database. https://pubchem.ncbi.nlm.nih.gov/. [accessed August 29, 2018]
162. Davis DP, Videen JS, Marino A, Vilke GM, Dunford JV, Van Camp SP, Maharam LG. Exercise-associated hyponatremia in marathon runners: a two-year experience. *J Emerg Med* 2001;**21**: 47–57.
163. Hew TD, Chorley JN, Cianca JC, Divine JG. The incidence, risk factors, and clinical manifestations of hyponatremia in marathon runners. *Clin J Sport Med* 2003;**13**:41–7.
164. Baker J, Cotter JD, Gerrard DF, Bell ML, Walker RJ. Effects of indomethacin and celecoxib on renal function in athletes. *Med Sci Sports Exerc* 2005;**37**:712–7.

QUESTIONS AND ANSWERS

Question 1

A 64-year-old man is hospitalized for worsening shortness of breath. Ten days ago, he saw his physician for pain due to osteoarthritis of the knees and was given a prescription for naproxen (750 mg twice a day). He has a history of dilated cardiomyopathy felt to be of ischemic etiology, type 2 diabetes mellitus, and hypertension. He has remained on his other medications, which include lisinopril (20 mg a day), furosemide (20 mg twice a day), and glyburide (10 mg a day). On examination, BP = 150/95 mm Hg, heart rate = 98 bpm, respirations = 20/min. His O_2 saturation is 88% on room air. He appears short of breath. Crackles are heard over both lung fields, and 2+ pitting edema is present in the ankles and feet. Blood chemistries are as follows:

Sodium 133 mEq/L, potassium 6.0 mEq/L, chloride 109 mEq/L, bicarbonate 22 mEq/L, BUN 24 mg/dL, S[Cr] 1.1 mg/dL (baseline = 0.9 mg/dL), and glucose = 140 mg/dL.

A urinalysis is unremarkable.

ECG reveals no changes from his baseline. Chest X-ray reveals incipient pulmonary edema and blunting of the costophrenic recesses bilaterally.

Discontinuing his naproxen is unlikely to improve which of the following?

A. His ventricular function
B. His peripheral edema
C. His blood pressure
D. His hyperkalemia
E. His pulmonary edema

Answer: A

This 64-year-old man presents with signs and symptoms of decompensated heart failure. This is a well-known phenomenon associated with NSAID use in patients with precarious hemodynamics and chronic prerenal azotemia ("cardiorenal syndrome"). Because of their antinatriuretic effects, NSAIDs may cause peripheral and pulmonary edema. They can also worsen the degree of azotemia by causing autoregulatory failure in the intrarenal circulation. In addition to his worsened renal function, suppression of the renin–angiotensin–aldosterone axis leads to hyperkalemia. All these effects are mediated by abrogation of the compensatory physiologic effects of prostaglandins. NSAIDs have no direct or indirect effect on ventricular performance.

Question 2

A 35-year-old woman with stage 3 CKD due to reflux nephropathy decides to try ibuprofen in an over-the-counter formulation to relieve her dysmenorrhea. She has no other medical problems. Her only prescription medications include fosinopril (40 mg a day) and a prenatal-type multivitamin. She gets rapid improvement in her dysmenorrhea, but on the third day of taking it, she develops epigastric pain and nausea. She sees her physician who notes some localized epigastric tenderness on exam. She orders blood tests, recommends discontinuing the ibuprofen, and tells her to return tomorrow for follow-up.

Which of the following statements is TRUE?

A. Over-the-counter NSAID preparations are too mild to affect her renal function
B. The patient's symptoms probably reflect uremic gastritis
C. Stopping ibuprofen will likely resolve her epigastric pain and tenderness
D. Substituting a COX-2-specific NSAID is less likely to affect her kidney function
E. Substituting a COX-2-specific NSAID is likely to worsen her abdominal complaints

Answer: C

Gastric upset is one of the most common side effects of NSAIDs and, in contrast to most of the renal complications, may occur in otherwise normal individuals. Gastric symptoms may occur even with low-dose formulations such as those sold over-the-counter. Although this woman has underlying CKD, three days is much too rapid a time course for her to have developed uremic gastritis. There is no reason why she could not have cholelithiasis, but the time course points to the NSAID as the source of her abdominal discomfort. COX-2-specific NSAIDs are better tolerated by the GI tract, but just as risky from the renal standpoint.

Question 3

A 42-year-old man has been referred to you for evaluation of stage 4 CKD of unknown etiology. He recently emigrated from east Africa where he did not receive regular healthcare and can provide little information about his personal health history. He does not consume tobacco or alcohol and uses only one medication for aches, pains, and headaches. He shows you a bottle of this drug, but the label is written in his native language, and you cannot read it. The patient appears somewhat malnourished in appearance, but otherwise his examination, including his blood pressure, is unremarkable.

Blood chemistries are as follows: sodium 140 mEq/L, potassium 5.4 mEq/L, chloride 100 mEq/L, bicarbonate 24 mEq/L, BUN 30 mg/dL, S[Cr] 1.8 mg/dL, glucose 110 mg/dL, calcium 8.0 mg/dL, and albumin 3.4 g/dL. Urinalysis reveals 1+ proteinuria and no other notable findings.

A sonogram of his kidneys reveals them to be 8 and 9 cm in length with increased echogenicity, irregular contours, and findings consistent with papillary necrosis.

Which of the following possible etiologies for his renal disease is the LEAST likely?

A. Tuberculosis
B. Schistosomal nephropathy
C. NSAID-induced nephropathy
D. Non-NSAID analgesic nephropathy
E. Sickle cell nephropathy

Answer: B

All of the answer options represent diseases a patient with this geographic background could have, and all but one of them can cause papillary necrosis: schistosomal nephropathy, which is a glomerular disease. Renal tuberculosis would be an important "rule-out" in a patient of third-world origin presenting in this fashion. Sickle cell nephropathy must be considered in an African patient. Both of these diseases could account for his cachectic appearance. Lastly, until we have discerned the identity of the medication he takes for chronic aches and headaches, we must consider the possibility that it contains phenacetin or a nonsteroidal drug, either of which (especially the former) might cause papillary necrosis.

Question 4

A 77-year-old woman has a history of hypertension which has been very well controlled on atenolol (25 mg a day) and hydrochlorothiazide (25 mg a day). 5 days ago, she developed a painful monoarthritis of her right food diagnosed as gout. She was given a prescription for indomethacin (75 mg twice a day). Her foot pain improved dramatically, but over the past day-and-a-half she has been feeling "spacey" and a little nauseated. Other than a BP of 160/85 mm Hg, some residual right foot warmth and tenderness, and some subtle signs of confusion, her physical examination is unremarkable. Routine blood chemistries and a CBC are sent. Her serum sodium concentration is found to be 120 mEq/dL.

Which of the following statements is FALSE?

A. Indomethacin can potentiate the actions of antidiuretic hormone in the distal nephron
B. Indomethacin tends to increase urinary sodium excretion
C. Indomethacin can exacerbate hypertension even in previously well-controlled patients
D. Indomethacin is effective for treating gouty arthritis
E. Her indomethacin should be stopped and her hydrochlorothiazide put on hold

Answer: B

Indomethacin is effective in treating gouty arthritis and is a satisfactory alternative to steroids and colchicine. It is also a potent NSAID and has been implicated in more reports of renal side effects than any other drug in that family. Because prostaglandins counteract the effects of ADH on the collecting tubule, NSAIDs potentiate the activity of that hormone and can cause hyponatremia. For this reason, medications that can impair urinary dilution, like thiazides, should be avoided by patients taking NSAIDs. Prostaglandins inhibit tubular sodium reabsorption; they are natural natriuretic hormones. For this reason, NSAIDs can cause sodium retention and this can exacerbate hypertension.

Question 5

An 88-year-old woman complains of back pain and is found to have a compression fracture of her thoracic spine. She had tried taking acetaminophen without relief. Because she does not tolerate opiates well, her physician wishes to prescribe ketorolac for analgesia. The patient's medical history is remarkable for osteoporosis, congestive heart failure, and stage 2 CKD (baseline S[Cr] = 1.1 mg/dL). Her medications include enalapril (10 mg twice a day), furosemide (20 mg twice a day), alendronate (35 mg once every a week), and aspirin (81 mg a day).

How many risk factors does she have for untoward renal effects due to the ketorolac and what are they?

A. One
B. Two
C. Four
D. Five
E. Seven

Answer: C

She has four risk factors for untoward renal effects from the ketorolac: her (1) advanced age, (2) underlying renal insufficiency, (3) history of congestive heart failure, and (4) medications (ACE inhibitor and diuretic).

Question 6

A 29-year-old competitive distance runner collapses at the end of half-marathon and is transported to the emergency room of a local hospital. On arrival, she suffers a generalized seizure, following which she remains unresponsive for several hours. Her medical history is entirely unremarkable; her only medication is diclofenac 75 mg twice a day.

On physical examination, BP = 150/100 mm Hg, HR = 110/bpm, regular, and respirations = 14/min. She is afebrile and has a room air oxygen saturation of

99%. She is moving all extremities but is unresponsive. She is diaphoretic but does not appear noticeably volume depleted.

A cranial CT scan shows no evidence of trauma or hemorrhage, but there is a suggestion of cerebral edema.

A complete blood count, blood chemistry panel, and arterial blood gases are sent. The only abnormality is a serum sodium concentration of 119 mEq/L.

Which of the following statements about her presentation is TRUE?

A. She has acute hyponatremic encephalopathy
B. Diclofenac causes salt wasting by the kidney
C. Based on her high blood pressure, it is unlikely she is truly volume depleted
D. Diclofenac does not interact with ADH
E. Diclofenac probably triggered inappropriate ADH release

Answer: A

This patient has acute hyponatremic encephalopathy, an emergent and sometimes fatal condition that can occur in distance runners who drink water faster than they can metabolize it. As a result, osmotic dysequilibrium develops between the CNS and the bloodstream, leading to cerebral edema. Although diclofenac does not cause inappropriate ADH release, it, like other NSAIDs, potentiates the action of ADH on the renal collecting duct and can thus exacerbate hyponatremia of any etiology. Diclofenac, like all NSAIDs, is antinatriuretic. Many of the reports of acute hyponatremic encephalopathy in runners involved those who were taking NSAIDs.[162–164]

Question 7

A 31-year-old man with a longstanding history of intravenous heroin abuse is referred for evaluation of hematuria and proteinuria. Physical examination is remarkable for BP 140/95 mm Hg, diffuse lymphadenopathy, and scattered maculopapular, purplish lesions over his lower legs. BUN is 30 mg/dL, S[Cr] 1.8 mg/dL. Urinalysis reveals 2 to 3+ proteinuria and 1+ occult blood. Sediment contains 5–10 dysmorphic red blood cells per hpf and occasional finely granular casts.

In addition to renal biopsy, which of the following tests is/are indicated?

A. HIV serology
B. Cryoglobulins
C. Viral hepatitis panel
D. Urine toxicology
E. Antinuclear antibody

Answer: A, B, and C

This patient's history of intravenous heroin abuse places him at risk for HIV and chronic viral hepatitis infection. Both of these infections are associated with glomerulopathic syndromes. Hepatitis C is associated with membranoproliferative glomerulonephritis and cryoglobulinemic vasculitis, which could account for the lesions on lower extremities as well as the renal abnormalities. HIV-associated nephropathy (HIVAN) could also present in this fashion. The syndrome known as heroin nephropathy presents with FSGS-like histopathology and a similar presentation to this patient's and is of unclear pathogenesis, possibly representing one of the above viral-associated glomerulopathies or a reaction to impurities in the heroin. Various glomerulonephridites have also been associated with HIV infection. Even if his urine were to test positive for opioids, this would not refine the differential diagnosis at all, nor would it add anything to what we already know about his history. The patient's presentation makes lupus nephritis unlikely.[123,124]

CHAPTER

66

Dyslipidemia and Chronic Kidney Disease

Scott Reule[a], *Areef Ishani*[a], *David Goldsmith*[b]

[a]Minneapolis VA Health Care System, University of Minnesota, Minneapolis, MN, United States;
[b]Guy's and St Thomas' Hospital, London, United Kingdom

Abstract

Dyslipidemia in patients with chronic kidney disease (CKD) is common, characterized by high triglyceride levels and low HDL concentrations, while total and LDL cholesterol (LDL-C) are normal or low. Most CKD patients are at very high risk of cardiovascular events. CKD patients with low as well as high levels of total and LDL-C are at the highest risk of developing adverse outcomes. Thus, elevated cholesterol seems unsuitable as the sole criterion for prescription of statins in CKD patients. The decision to treat patients should be based on pretreatment risk of cardiovascular events and not solely pretreatment LDL-C.

The new Kidney Disease: Improving Global Outcomes clinical practice guidelines on lipid management recommend fixed statin or statin/ezetimibe treatment in adults aged ≥50 years with eGFR <60 mL/min/1.73 m^2 but not treated with chronic dialysis or kidney transplantation. In dialysis patients, the magnitude of any relative reduction in risk appears to be substantially smaller than in earlier stages of CKD. Initiation of statin treatment is not recommended for most prevalent hemodialysis patients. Treatment escalation with higher doses of statins is not recommended because higher doses of statins have not been proven to be safe in the setting of CKD. Because LDL-C levels do not necessarily suggest the need to increase statin doses, follow-up measurement of lipid levels is not recommended.

THE TYPICAL LIPID PROFILE IN CKD PATIENTS

Disturbance in serum lipid constituents is a common and well-recognized feature of chronic kidney diseases (CKDs). However, as so many body systems adapt, change, or fail in the context of CKD, it is imperative to understand whether these lipid disturbances are etiopathogenically relevant to patient outcomes, which are, as is widely known, dire regarding cardiovascular disease. With trials reported over the last two decades, some new insights have been made regarding this important matter. Hyperlipidemia or dyslipidemia in patients with CKD is typically characterized by high triglyceride (TG) levels and low high-density lipoprotein (HDL) concentrations, while total and low-density lipoprotein concentrations (LDL-C) are normal or low.[1,2] Patients with proteinuria and patients treated with peritoneal dialysis (PD) have higher levels of LDL-C than nonproteinuric CKD or hemodialysis (HD) patients. The distribution of lipid profile can vary with respect to stage of CKD, the presence of the nephrotic syndrome, and type of renal replacement therapy (RRT) employed. The typical distribution of lipid among patients with various stages of CKD and end-stage renal disease (ESRD) is shown in Table 66.1.[3] Although the lipid abnormalities delineated by routine laboratory measurements may not seem to be numerically impressive, more sophisticated research analyses reveal profound underlying disturbances in lipid metabolism. One example is a shift in the composition and size distribution of all lipoproteins. The best example is the shift in the composition and size distribution of LDL to increased content of small dense LDL, which is then susceptible to undergoing oxidation during prolonged circulation.

PATHOPHYSIOLOGY OF DYSLIPIDEMIA IN CKD AND END-STAGE RENAL DISEASE

The concentration of TG-rich lipoproteins (very low–density lipoprotein (VLDL), intermediate-density lipoprotein (IDL)) is increased in CKD and ESRD patients, mainly as a result of decreased catabolism, particularly in the postprandial phase. Lipolysis of the highly atherogenic VLDL and chylomicron remnants is impaired, partly due to decreased lipoprotein lipase (LPL) on the vascular endothelium and partly due to increased levels of the major LPL inhibitory

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00066-8

TABLE 66.1 The Typical Lipid Profile of Patients With CKD

	CKD 1–5	Nephrotic Syndrome	Hemodialysis	Peritoneal Dialysis
Total Cholesterol	↗	↑↑	↔↓	↑
LDL-C	↔↓	↑↑	↔↓	↑
HDL-C	↓	↓	↓	↓
Non-HDL-C	↗	↑↑	↑	↑
TG	↗	↑↑	↑	↑
Lp(a)	↗	↑↑	↑	↑↑

Non-HDL cholesterol includes cholesterol in LDL, VLDL, IDL, and chylomicron and its remnant. Explanation of arrows: normal (↔), increased (↑), significantly increased (↑↑), and decreased (↓) plasma levels compared with nonuremic individuals; increasing (↗) and decreasing (↘) plasma levels with decreasing GFR.

apolipoprotein, apo CIII. Increased levels of small dense LDL result from increased TG concentration, which, by the action of cholesterol ester transfer protein and hepatic lipase, are involved in the formation of small dense LDL.

Functional deficiencies in lecithin:cholesterol acyltransferase (LCAT) and LPL activity affect HDL maturation and disorders. Processes favoring HDL maturation are associated with a greater abundance of large mature HDL, affecting serum levels. The formation of HDL particles is mediated by LCAT, resulting in the esterification of cholesterol—as well as by LPL. In addition, elevated levels of lipoprotein(a) (Lp(a)) have been found in CKD patients.[4–8] Lp(a) is an LDL-like particle which has an additional protein, apolipoprotein(a). Lp(a) constitutes an important independent risk factor for the development of atherosclerosis.

IMPACT OF PROTEINURIA ON DYSLIPIDEMIA

Patients with nephrotic syndrome have the most prominent abnormalities in lipid metabolism. About half of the patients have total cholesterol concentrations above 300 mg/dL, and 80% of the patients had LDL-C levels above 130 mg/dL.[7,9] Many patients also have elevated levels of TGs. Additionally, HDL-C levels are distributed abnormally (increased HDL_3 fraction and decreased HDL_2 fraction). Dyslipidemia in the nephrotic syndrome results from increased hepatic synthesis and decreased catabolism of lipoproteins. Increased TG-rich lipoprotein concentration, VLDL, and IDL primarily result from decreased clearance, partly due to reduced LPL activity. LPL is necessary for normal lipolysis. In addition, both LDL and Lp(a) synthesis are increased, due to decreased activity of LCAT, and the number of spherical HDL particles is decreased. These particles are important carriers for apo CII, a cofactor determining LPL activity and VLDL levels.[10,11]

IMPACT OF DIALYSIS ON DYSLIPIDEMIA

Dyslipidemia becomes more pronounced as decrements in glomerular filtration rate (GFR) advance to CKD Stage 5 requiring dialysis. An increase in plasma TGs, VLDL, and IDL, along with a reduction in HDL-C, is typical. HD and PD appear to have different effects on uremic dyslipidemia.[12,13] Patients treated with PD have higher cholesterol, TG, LDL, and Lp(a) levels than patients treated with HD, where total cholesterol and LDL-C can be normal or low. Possible reasons may be a considerable loss of protein (7–14 g/day) into the peritoneal dialysate, and the absorption of glucose (150–200 g/day) from the dialysis fluid. This leads to an increase in the pool size of TGs and apoB100 in the VLDL fraction of PD patients.

WHY SHOULD PATIENTS WITH CKD STAGES 3–5 BE TREATED WITH A STATIN?

Recently, KDIGO (Kidney Disease: Improving Global Outcomes) released the Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. Stratified analyses of CKD patients included in randomized controlled trials and the SHARP study suggest CKD patients should be treated with statins. The SHARP trial included 9270 participants with CKD who received simvastatin 20 mg plus ezetimibe 10 mg daily or placebo and followed them for a mean of 4.9 years. 67% of participants (n = 6247) had CKD not treated with dialysis at randomization, and 23% (n = 2094) had diabetes. In the overall study, statin plus ezetimibe therapy led to a significant 17% reduction (HR 0.83; 95% CI 0.74–0.94) in the relative hazard of the primary outcome of major atherosclerotic events (coronary death, MI, nonhemorrhagic stroke, or any revascularization) compared with placebo, driven by significant reductions in nonhemorrhagic stroke and coronary revascularization. SHARP

indicated that risk for the primary outcome of major atherosclerotic events other than death was reduced by simvastatin/ezetimibe among a wide range of patients with CKD; however, there was no demonstrable effect on mortality in this trial.

In the nondialysis CKD subgroup (mean estimated GFR (eGFR) of 26.6 mL/min/1.73 m^2), treatment with simvastatin plus ezetimibe led to a 22% reduction in major atherosclerotic events (HR 0.78; 95% CI 0.67−0.91). These results were similar in all CKD subgroups defined by eGFR category (eGFR 30−60 mL/min/1.73 m^2 HR 0.75, 95% CI 0.57−1.00, eGFR 15−30 mL/min/1.73 m^2 HR 0.78 95% CI 0.62−0.98; eGFR <15 mL/min/1.73 m^2 HR 0.82, 95% CI 0.59−1.13; p for difference between groups 0.73). Treatment did not reduce the risk in any of the prespecified renal outcomes of CKD progression or incident RRT, however. The risk of serious adverse events was similar in participants assigned to treatment or control. These data are supported by *post hoc* analyses of randomized trials of statin vs. placebo that focus on the subset of participants with CKD at baseline. In general, these analyses suggest that statins reduce the relative risk of cardiovascular events to a similar extent among patients with and without CKD, but that the absolute benefit of treatment is larger in patients with CKD due to their higher baseline risk (>10 events per 1000 patient years among patients >50 years of age and eGFR <60 mL/min/1.73 m^2, for example). Most of the participants with CKD in these analyses had eGFR 45−59 mL/min/1.73 m^2 and very few had eGFR less than 30 mL/min/1.73 m^2. However, treatment with a statin plus ezetimibe reduced the risk of major atherosclerotic events in the subgroup of participants (n = 2565) in SHARP with eGFR of 15−30 mL/min/1.73 m^2 (HR 0.78; 95% CI 0.62−0.98). Based on the results of the SHARP trial, treatment with a statin or statin/ezetimibe therapy is indicated across a broad range of CKD stages.

WHY NOT PERFORM FREQUENT FOLLOW-UP MEASUREMENTS OF SERUM LIPIDS?

Previous guidelines have emphasized treatment escalation to achieve specific LDL-C targets by increasing the dose of statin and/or combination therapy. Given the lack of data to support this approach, the substantial variability in LDL-C measurements and the potential for comedication-related toxicity, this approach is not recommended for people with CKD by KDIGO. Because higher risk of future coronary events, rather than elevated LDL-C, is the primary indication for initiating lipid-lowering treatment in CKD patients, follow-up monitoring of LDL-C is not required for many patients given within person variability of LDL-C over time, reducing the utility of follow-up measurements.[14,15] It is also unnecessary to measure LDL-C in many situations where the results likely would not change management, for example, patients already receiving a statin. However, in patients with nondiabetic, stable CKD 3b, reassessment of lipid status in follow-up may result in significant cardiac risk stratification increases, such that prescription of a statin should be considered.

As the link between LDL-C and adverse clinical outcomes is less robust in people with CKD than among those without CKD, the value of measuring LDL-C to assess prognosis is unclear. This care algorithm has never been subjected to clinical trial testing, though clearly it should be part of ongoing research efforts.

There is no direct evidence that following lipid levels during treatment will improve clinical outcomes or encourage adherence to statin therapy. However, some patients may prefer to know their lipid levels during follow-up or may increase their adherence to statin treatment in response to feedback about these levels. This KDIGO guideline is not graded, meaning it is used to provide guidance based on common sense or when the topic does not allow adequate application of evidence.

INCIDENT DIALYSIS PATIENTS

Current guidelines recommend withholding initiation of statin therapy among patients with dialysis-dependent CKD (KDIGO level 2A). However, 2141 (34%) of SHARP patients without kidney failure at baseline initiated dialysis during the trial and were included as "nondialysis" patients. Overall benefit was observed in this subgroup. As incident dialysis patients may be systematically different from those who are already prevalent dialysis patients (such as those included in the major trials of lipid-lowering treatment in dialysis patients), it is reasonable to continue statins in patients already receiving them at the time of dialysis initiation. It is important for the clinician to recognize that this may lead to less clinical benefit than in patients without CKD, possibly exposing these patients to the risks of drug−drug interactions, increased pill burden, and the inherent low risk of liver and muscle damage caused by statin exposure. Discontinuing statin or statin/ezetimibe treatment may be reasonable through value-based shared decision-making, placing a higher value on the risk of drug−drug interactions, polypharmacy, and drug toxicity compared with the relatively small potential relative risk reduction in vascular events.

STATIN TREATMENT IN PREVALENT DIALYSIS PATIENTS

The 4D Study (Die Deutsche Diabetes Dialyze Studie)

The 4D, a multicenter, double-blind, randomized trial assigned 1255 HD patients with type 2 diabetes to receive placebo or 20 mg of atorvastatin daily. After 4 weeks of treatment, atorvastatin reduced the median LDL-C level by 42%, while those in the placebo group had a 1.3% reduction in LDL-C. At least 1 mmol/L (39 mg/dL) difference in LDL-C level was maintained throughout the treatment period. During a median follow-up of 4 years, 469 patients (37%) reached the primary endpoint (a composite of cardiac death, nonfatal MI, and fatal and nonfatal stroke). 226 had been assigned to atorvastatin and 243 assigned to placebo (RR 0.92; 95% CI 0.77−1.10; $p = 0.37$). Atorvastatin had no effect on the individual components of the primary endpoint with the exception of fatal stroke, in which atorvastatin was associated with an increased relative risk (RR 2.03; 95% CI 1.05−3.93; $p = 0.04$). The secondary endpoint of combined cardiac events (RR 0.82; 95% CI 0.68−0.99; $p = 0.03$) was significantly reduced, but not all combined cerebrovascular events (RR 1.12; 95% CI 0.81−1.55; $p = 0.49$) or total mortality (RR 0.93; 95% CI 0.79−1.08; $p = 0.33$).

Aurora Study

In this international double-blind randomized trial, 2776 HD patients were assigned to receive rosuvastatin 10 mg daily or placebo, and followed for a median of 3.8 years. Despite the mean reduction in LDL-C of 43% (42 mg/dL) in the intervention group, the combined primary endpoint of death from cardiovascular causes, nonfatal MI, or nonfatal stroke was not reduced (HR 0.96; 95% CI 0.84−1.11; $p = 0.59$). In addition, rosuvastatin did not significantly reduce the risk of individual components of the primary endpoint, nor of all-cause mortality (all $p > 0.05$).

SHARP (STUDY OF HEART AND RENAL PROTECTION)

This international double-blind randomized trial assigned 9270 participants older than 40 years with CKD to receive simvastatin 20 mg plus ezetimibe 10 mg daily or placebo, and followed them for a mean of 4.9 years. 33% of the patients ($n = 3023$) were treated with maintenance dialysis at randomization. Mean reduction in LDL-C among the treatment group was 0.83 mmol/L (32 mg/dL), compared with placebo. While there was an overall reduction in the combined primary outcome, combination treatment did not significantly reduce the risk of the primary outcome in the subgroup of over 3000 patients treated with dialysis at baseline (HR 0.90; 95% CI 0.75−1.08). SHARP, however, was not powered to assess difference in major atherosclerotic events in dialysis vs. CKD subgroups. The study was powered for an overall effect and not to examine subgroups. The p for interaction (an underpowered test) was not significant comparing those on dialysis vs. nondialysis CKD ($p = 0.21$).

A systematic review pooling data from all available randomized trials done in CKD populations reported significant heterogeneity between dialysis and nondialysis patients for the benefit of statins on major cardiovascular events (HR for dialysis 0.96; 95% CI 0.88−1.03; HR for nondialysis 0.76; 95% CI 0.72−0.79; p for heterogeneity <0.001).[16] When findings from SHARP, 4D, and AURORA are considered together, the clinical benefit of statins or statin/ezetimibe therapy in prevalent dialysis patients is uncertain. Another meta-analysis confirmed these results, although the data were analyzed in a different manner.[17,18]

Even if statins truly do prevent cardiovascular events in prevalent dialysis patients, it is clear that the magnitude of any relative reduction in risk is substantially smaller than in earlier stages of CKD. However, if this speculative benefit among dialysis patients is confirmed in future studies, the absolute benefit might be comparable to that in people with less severe CKD, due to the higher event rate among dialysis patients. It is possible that the smaller relative risk reduction noted in SHARP may be explained by lower baseline LDL-C levels as well as less use of LDL lowering therapy in the subgroup of dialysis patients. The findings of SHARP suggest that every 1 mmol/L reduction in LDL-C led to a risk reduction of 19% in major atherosclerotic events overall; however, risk reduction among those treated with dialysis was lower at 16% per 1 mmol/L reduction. These findings are likely due to the finding of approximately one-third less reduction in LDL concentration among dialysis patients in comparison with the nondialysis CKD group (0.60 mmol/L (23 mg/dL) reduction in dialysis subjects vs. 0.96 mmol/L (37 mg/dL) reduction in nondialysis subjects).

In total, these trials failed to show a conclusive benefit of statin treatment (alone or in combination) among prevalent dialysis patients.[19−21] Therefore, initiation of statin treatment is not recommended for most prevalent HD patients (KDIGO level 2A). KDIGO stated that patients and their medical teams might decide to deploy statin-based treatment if they are still interested in a relatively uncertain and small reduction in cardiovascular events. Because the presence of a high LDL-C might increase the likelihood of benefit from statin therapy in a

dialysis patient, patients who meet this criterion may be more accepting of receiving statin treatment, recognizing that any potential benefit remains entirely speculative in 2019, while the small risks are certain. Other factors that might influence a patient's decision to ask for statin treatment could include a recent cardiovascular event (myocardial infarction or stroke) or longer anticipated life expectancy (both of which would favor treatment), and more severe comorbidity or higher current medication burden (both of which would favor lack of treatment). It would certainly be troubling to find a patient with a strong atherosclerotic risk and history being denied access to statin-based therapy by rote application of weak guidelines.

RESULTS FROM TRIALS IN THE GENERAL POPULATION

Trials and comorbidity had an impact on a strong recommendation in younger patients and those with earlier CKD stages. Most patients with CKD and eGFR $\geq$60 mL/min/1.73 m^2 have albuminuria and slightly reduced or normal eGFR. Most such patients would have been included but not recognized in trials of statins done in the general population. The benefit of statin monotherapy in reduction of incident cardiovascular disease (defined as incident MI, stroke, or need for coronary revascularization) appears similar in people with and without albuminuria (HR for albuminuric patients 0.59; 95 % CI 0.35−0.98 for albuminuric patients; HR for nonalbuminuric patients 0.64; 95% CI 0.46−0.89; p for interaction = 0.7).[22,23] Given the high cardiovascular risk among people with CKD and eGFR categories G1−G2, the large body of evidence supporting the efficacy of statins in the general population, and the lack of justification for a new trial done specifically in people with CKD and eGFR categories G1 or G2, high priority should be given to treatment in these patients.

PROMISING NEW THERAPIES IN THE TREATMENT OF DYSLIPIDEMIA AND CKD

Proprotein convertase subtilisin/kexin 9 (PSCK9) is an enzyme encoded on chromosome 1 that is part of the subtilisin-like proprotein convertase family. PSCK9 plays a role in cholesterol and fatty acid metabolism. It is expressed on various tissues including the liver, intestine, and kidney. PCSK9 may be involved in kidney development.[24] It is secreted as an inactive protein that undergoes proteolytic cleavage, leading to activation and subsequent binding to LDL receptors expressed on various tissues. Blockage of PCSK9 leads to increased expression of LDL receptors, resulting in significant reductions in LDL concentration. Development and subsequent approval of two monoclonal antibodies (alirocumab and evolocumab) targeting PSCK9 have been shown to significantly reduce LDL-C concentrations.[25] A *post hoc* review of eight studies pooled compared LDL-C lowering efficacy among subgroups with an eGFR 30−59 mL/min/1.73 m^2 vs. those with eGFR $\geq$60 mL/min/1.73 m^2. Treatment consisted of alirlocumab vs. placebo or ezetimibe plus statin. Baseline LDL-C concentrations were comparable and reductions in concentration ranged from 40% to 68% after 24 weeks of treatment regardless of eGFR.[26] Recent American College of Cardiology recommendations have suggested that PSCK9 be among the nonstatin options to consider as add-on therapy among those with high cardiovascular risk, not achieving a target LDL-C or <50% reduction in LDL concentration.[27] Once again, however, any utilization of this novel therapy in CKD patients has been hindered by the systematic exclusion of such patients in regulatory registration trials, a trend that has held back therapeutic progress in CKD by decades.

CONCLUSION

Dyslipidemia in patients with CKD is common, characterized by high TG levels and low HDL concentrations, while total and LDL cholesterol (LDL-C) levels are normal or low. Most CKD patients are at very high risk of cardiovascular events. CKD patients with low as well as high levels of total cholesterol and LDL-C are at the highest risk of adverse outcomes, due to a variety of reasons, including the long lag between risk factor development and outcome. This may cloud the interpretation of association with causality, as the patient's own phenotype and comorbidity may change as well.

Recent large clinical trials and guidelines have better informed treatment of patients with CKD and dyslipidemia. Elevated cholesterol concentrations *per se* as the sole criterion for prescription of statins in patients with CKD are unsuitable. The decision to treat such patients should be based on pretreatment risk of cardiovascular events and not on LDL-C, even though the vast bulk of that potential cardiovascular disease may be refractory to the use of statin-based therapies. One of the most concerning and frequent causes of death in maintenance dialysis patients is "sudden cardiac death" which is unaffected by ambient serum cholesterol (and subfraction) concentrations. Shared information-delivery and decision-making between physicians and CKD patients regarding potential treatment of lipid disorders

("individualization") in light of recent findings and guidelines is imperative, and vastly preferable to the application of weak guidelines to a complex patient population by rote.

References

1. Prinsen BH, de Sain-van der Velden MG, de Koning EJ, Koomans HA, Berger R, Rabelink TJ. Hypertriglyceridemia in patients with chronic renal failure: possible mechanisms. *Kidney Int Suppl* 2003:S121–4.
2. Ritz E, Wanner C. Lipid abnormalities and cardiovascular risk in renal disease. *J Am Soc Nephrol* 2008;**19**:1065–70.
3. Kwan BC, Kronenberg F, Beddhu S, Cheung AK. Lipoprotein metabolism and lipid management in chronic kidney disease. *J Am Soc Nephrol* 2007;**18**:1246–61.
4. Frischmann ME, Kronenberg F, Trenkwalder E, et al. In vivo turnover study demonstrates diminished clearance of lipoprotein(a) in hemodialysis patients. *Kidney Int* 2007;**71**:1036–43.
5. Kronenberg F, Konig P, Neyer U, et al. Multicenter study of lipoprotein(a) and apolipoprotein(a) phenotypes in patients with end-stage renal disease treated by hemodialysis or continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol* 1995;**6**:110–20.
6. Levine DM, Gordon BR. Lipoprotein(a) levels in patients receiving renal replacement therapy: methodologic issues and clinical implications. *Am J Kidney Dis* 1995;**26**:162–9.
7. Kronenberg F, Lingenhel A, Lhotta K, et al. Lipoprotein(a)- and low-density lipoprotein-derived cholesterol in nephrotic syndrome: impact on lipid-lowering therapy? *Kidney Int* 2004;**66**: 348–54.
8. Longenecker JC, Klag MJ, Marcovina SM, et al. High lipoprotein(a) levels and small apolipoprotein(a) size prospectively predict cardiovascular events in dialysis patients. *J Am Soc Nephrol* 2005;**16**: 1794–802.
9. Radhakrishnan J, Appel AS, Valeri A, Appel GB. The nephrotic syndrome, lipids, and risk factors for cardiovascular disease. *Am J Kidney Dis* 1993;**22**:135–42.
10. De Sain-Van Der Velden MG, Reijngoud DJ, Kaysen GA, et al. Evidence for increased synthesis of lipoprotein(a) in the nephrotic syndrome. *J Am Soc Nephrol* 1998;**9**:1474–81.
11. de Sain-van der Velden MG, Kaysen GA, Barrett HA, et al. Increased VLDL in nephrotic patients results from a decreased catabolism while increased LDL results from increased synthesis. *Kidney Int* 1998;**53**:994–1001.
12. Attman PO, Samuelsson OG, Moberly J, et al. Apolipoprotein B-containing lipoproteins in renal failure: the relation to mode of dialysis. *Kidney Int* 1999;**55**:1536–42.
13. Deighan CJ, Caslake MJ, McConnell M, Boulton-Jones JM, Packard CJ. Atherogenic lipoprotein phenotype in end-stage renal failure: origin and extent of small dense low-density lipoprotein formation. *Am J Kidney Dis* 2000;**35**:852–62.
14. Krane V, Winkler K, Drechsler C, et al. Association of LDL cholesterol and inflammation with cardiovascular events and mortality in hemodialysis patients with type 2 diabetes mellitus. *Am J Kidney Dis* 2009;**54**:902–11.
15. Iseki K, Yamazato M, Tozawa M, Takishita S. Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients. *Kidney Int* 2002;**61**:1887–93.
16. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2012;**157**:263–75.
17. Upadhyay A, Earley A, Lamont JL, Haynes S, Wanner C, Balk EM. Lipid-lowering therapy in persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2012;**157**: 251–62.
18. Hou W, Lv J, Perkovic V, et al. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. *Eur Heart J* 2013;**34**:1807–17.
19. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**:2181–92.
20. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;**353**:238–48.
21. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;**360**:1395–407.
22. Colhoun HM, Betteridge DJ, Durrington PN, et al. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). *Am J Kidney Dis* 2009;**54**: 810–9.
23. Tonelli M, Jose P, Curhan G, et al. Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial. *BMJ* 2006; **332**:1426.
24. Seidah NG, Benjannet S, Wickham L, et al. The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation. *Proc Natl Acad Sci USA* 2003;**100**:928–33.
25. Cainzos-Achirica M, Martin SS, Cornell JE, Mulrow CD, Guallar E. PCSK9 inhibitors: a new era in lipid-lowering treatment? *Ann Intern Med* 2015;**163**:64–5.
26. Toth PP, Dwyer JP, Cannon CP, et al. Efficacy and safety of lipid lowering by alirocumab in chronic kidney disease. *Kidney Int* 2018;**93**:1397–408.
27. Landmesser U, Chapman MJ, Stock JK, et al. 2017 update of ESC/EAS task force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. *Eur Heart J* 2018;**39**:1131–43.

QUESTIONS AND ANSWERS

Question 1

A 64-year-old man with ESRD treated with maintenance HD, controlled hypertension, hyperlipidemia, gastroesophageal reflux, and gout undergoes routine lipid screening. Current medications are carvedilol 25 mg twice daily, amlodipine 10 mg daily, simvastatin 20 mg daily, ranitidine 150 mg daily, and calcium acetate 667 mg three times daily with meals. He follows a sodium restricted diet and tries to limit his daily fluid intake as instructed. He has not had problems with hypotension on HD. His laboratory values return with LDL-C 105 mg/dL, total cholesterol 260 mg/dL, TGs 220 mg/dL, and HDL 30 mg/dL. You review the results with the patient.

What is the next step in treatment?

A. Switch to rosuvastatin 10 mg daily, his LDL is not at goal
B. Add fenofibrate and recheck TGs
C. Use of statin therapy confers substantial mortality risk benefit compared with those not on statins
D. Increase simvastatin to 80 mg daily
E. No change in medication therapy

Answer: E

Routine surveillance of lipid profile in prevalent dialysis patients has not been recommended by KDIGO (*not graded*), although it may be considered if it may influence adherence to therapy in a patient centered approach (A incorrect). Targeting TG levels and routine TG surveillance is not recommended (B incorrect). The patient is currently receiving treatment with statin therapy. Neither existing treatment nor dose escalation of statin therapy has been shown to be effective in reduction of mortality in patients receiving HD (C and D incorrect). No evidence links routine surveillance of lipid profile with improved outcomes.

Question 2

A nonsmoking 58-year-old administrative assistant is referred to the outpatient clinic with S[Cr] 1.8 mg/dL for treatment of potential hyperlipidemia. The history, classification, and prognosis evaluation confirmed CKD CGA category G3bA3 (cause, eGFR, albuminuria). Renal biopsy 10 years ago showed IgA nephropathy. The CKD-EPI equation revealed Stage 3b with eGFR 43 mL/min/1.73 m^2. 24-hour urinary protein excretion was 2.45 g and albuminuria was 1.8 g.

Which ONE of the following is recommended as part of the management of this patient?

A. Evaluation with a lipid profile (TC, LDL-C, HDL-C, TGs)
B. Measuring a lipid profile is not recommended because treatment is ineffective
C. Measurement of Lp(a) should guide treatment decisions
D. Measurement of LCAT should guide treatment decisions
E. Treatments should target an LDL-C goal as this patient is at substantial cardiovascular risk

Answer: A

Evaluation of a lipid profile is recommended by KDIGO and is the correct answer. Initial evaluation of the lipid profile is intended to diagnose severe hypertriglyceridemia and/or hypercholesterolemia while ruling out any underlying secondary causes. No direct evidence indicates that measuring lipid status will lead to better clinical outcomes. However, measuring lipid status is noninvasive, inexpensive, and might improve the health of people with secondary dyslipidemia. A relatively strong recommendation is notable, given the low quality of the reporting evidence (*Grading 1C*). The true effect may be substantially different from the estimate of the effect. The SHARP trial demonstrated a benefit of treating Stage 3−5 CKD patients with a statin and ezetimibe (B is incorrect). Although Lp(a) is increased in CKD and is an independent risk factor for atherosclerosis, it is not routinely measured or used as a guide to treatment decisions (C is incorrect). LCAT activity is decreased in CKD but is not routinely measured and does not guide treatment decisions (D incorrect). Treat to target LDL-C levels is not recommended (E incorrect).

Question 3

The results of the lipid profile for this patient were as follows: total cholesterol 236 mg/dL, HDL-C 39 mg/dL, TG 165 mg/dL, LDL-C 142 mg/dL calculated using the Friedewald formula (Friedewald formula is applicable when TGs are <400 mg/dL).

Which ONE of the following is NOT TRUE regarding the management of this patient?

A. Start simvastatin 20 mg po qd and ezetimibe 10 mg po qd
B. Therapeutic lifestyle changes are advised
C. No lipid treatment is indicated
D. Treat other cardiovascular risk factors such as hypertension
E. Start fish oil therapy given his elevated TG level

Answer: C

Serum LDL-C concentrations were 142 mg/dL with otherwise "unremarkable" serum lipid concentrations (TGs and HDL cholesterol). Overall, the lipid profile was typical for CKD patients, similar to type 2 diabetes

mellitus, with slightly elevated TG concentrations (>150 mg/dL) and low HDL cholesterol (<45 mg/dL). Answer A, starting statin and ezetimibe treatment, is reasonable based on the results of the SHARP trial. During the visit, other actions were taken, such as advising lifestyle changes such as weight loss and a low fat diet (Answer B), and treating other cardiovascular risk factors such as hypertension (Answer D). The patient confirmed being able to take the number of pills prescribed. Answer C would be incorrect as the patient will receive a multitargeted approach to lipid care as outlined in the other answers. Fish oil therapy has been studied in the context of IgA nephropathy; however, targeting TG levels in isolation has not demonstrated benefit in CKD patients (E incorrect).

Question 4

Six months later, the patient returns to the outpatient renal clinic. He complains that his primary physician has forgotten to measure his cholesterol. He wants to know his cholesterol level. The patient denies any side effects. A lipid profile is repeated with the following results: total cholesterol 155 mg/dL, HDL-C 35 mg/dL, TG 189 mg/dL, and LDL-C 82 mg/dL.

Which ONE of the following is the best treatment decision for this patient?

A. Increase the simvastatin to lower total cholesterol to <130 mg/dL
B. Continue same dosages of the statin and ezetimibe
C. No change in treatment but repeat lipid levels in 3 months
D. Add gemfibrozil to lower TG levels
E. Switch to rosuvastatin therapy

Answer: B

Answer B is correct, as simvastatin and ezetimibe treatment were effective. The effect most likely is a combination of true drug effects and reduction of residual albuminuria. Current guidelines do not recommend treatment to target; therefore, it is not necessary to repeat lipid levels (C incorrect). KDIGO guidelines provide potential reasons to remeasure serum lipids in people with CKD, including assessment of adherence to statin treatment, change in dialytic modality or concern about the presence of a new secondary cause of dyslipidemia, or to assess 10-year cardiovascular risk in patients aged <50 years and not currently receiving a statin. Gemfibrozil can reduce TG levels but would not be indicated at the borderline high levels seen in this patient (D incorrect). There is no evidence to support changing to alternative agents such as rosuvastin or change of current therapy with a treat to target goal (A and D incorrect).

Question 5

You review the results of his lipid profile and make recommendations to the patient. You counsel the patient regarding cardiovascular risk and benefits of your approach to care, with an individualized approach given comorbidities and pill burden.

Which of the following is true about this patient?

A. Cardiovascular risk among those with CKD is lower than in the general population
B. Benefit of statin therapy among those with albuminuric CKD and preserved eGFR is similar to those without CKD
C. There appears to be benefit of rosuvastatin over other agents for treatment of hyperlipidemia
D. There is no increased risk of cardiovascular event
E. Among patients with late-stage CKD, particularly among those treated with dialysis, a reduction in cardiovascular risk is commensurate with absolute reduction in LDL-C value

Answer: B

Current literature suggests that statins reduce the relative risk of cardiovascular events to a similar extent among patients with and without CKD, but that the absolute benefit of treatment is larger in patients with CKD due to their higher baseline risk (>10 events per 1000 patient years among patients >50 years of age and eGFR <60 mL/min/1.73 m^2). Choices A and D are incorrect. The benefit of statin monotherapy in reduction of incident cardiovascular disease (defined as incident myocardial infarction, stroke, or need for coronary revascularization) appears similar in people with and without albuminuria (HR for albuminuric patients 0.59 for albuminuric patients; HR for nonalbuminuric patients 0.64; p for interaction = 0.7). B is correct. There is a paucity of evidence to suggest benefit of one statin over other agents (C incorrect). The findings of SHARP suggested that a decrease of 1 mmol/L in LDL-C was associated with a 19% RR reduction in major cardiovascular events; however, these observations where lower among those receiving maintenance dialysis (16% reduction). Although these findings may have been explained by baseline differences in LDL-C values, conclusive evidence is yet to be demonstrated (E incorrect).

Question 6

One year later, the eGFR has fallen to 35 mL/min/1.73 m^2. The annual loss of eGFR is approximately 4 mL/min/1.73 m^2. The patient asks about continuation of treatment because the pill burden is high.

Which ONE of the following is TRUE regarding best management of this patient?

A. Stop lipid therapy when patient starts dialysis
B. Stop lipid therapy if patient receives a kidney transplant
C. Decrease lipid therapy because the LDL-C is too low
D. Continue lifelong lipid-lowering treatment even after initiation of dialysis
E. Continue therapy and consider intensification given worsening eGFR

Answer: D

Lipid-lowering treatment should be continued even when RRT will become necessary (KDIGO, *grading 2C*). Answer A is therefore incorrect, although individualized treatment decisions are needed. Each patient needs help arriving at a management decision consistent with her or his values and preferences. The risk of future coronary events in kidney transplant recipients is markedly elevated. Data from the placebo arm of the ALERT trial (Assessment of Lescol in Renal Transplantation trial) suggest that the rate of cardiovascular death or nonfatal MI is approximately 21.5 per 1000 patient years. Current KDIGO guidelines recommend adult kidney transplant recipients be treated with a statin (*grading 2B*) making Answer B incorrect. There is no target for LDL-C levels and no evidence that low values have adverse effects (C incorrect). There is no evidence to suggest that intensification of therapy is needed with decreasing eGFR (E incorrect).

CHAPTER

67

Nephrolithiasis, Nephrocalcinosis, and Hypercalciuria

Anirban Bose, David A. Bushinsky

Division of Nephrology, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY, United States

Abstract

The incidence of kidney stones is rising worldwide. Kidney stones cause significant morbidity and are associated with chronic kidney disease (CKD). Because the incidence of recurrent stones decreases with progressive CKD, it may be underrecognized as the cause of end-stage renal disease. Kidney stones form when urine becomes supersaturated with respect to the specific components of the stone's constituents. A metabolic evaluation for the underlying causes of kidney stones is recommended after the initial episode. Urinary supersaturation studies and analysis of any passed stones help guide treatment. General measures to prevent recurrence of calcium-based stones include dietary modifications to increase fluid intake, reduce intake of salt and animal protein, and encourage consumption of age- and gender-appropriate amounts of calcium. Measures to reduce urinary supersaturation are highly effective in lowering recurrent stone formation. Thiazide diuretics are a cornerstone of therapy in hypercalciuric patients, whereas potassium citrate is also highly effective in reducing recurrent stone formation.

INTRODUCTION

Kidney stones have a propensity to afflict people in industrialized nations but also cause significant morbidity worldwide.[1] Their annual incidence is more than 1 per 1000 persons[2] resulting in nearly two million physician-office visits in the year 2000, with estimated annual costs totaling $2 to 5.5 billion.[1,3] The incidence of nephrolithiasis in the US has increased from approximately 3% in the late 1970s to about 5% in the 1990s, paralleling the rising rates of obesity, type-2 diabetes, and insulin resistance.[4] Kidney stones affect men more frequently than women. The incidence peaks among patients in their 30s and 40s before declining in frequency in the sixth to seventh decade of life.[5–7] In addition to age and sex, race and geographic location influence the prevalence of stones. Caucasians are more likely to develop stones compared to African Americans, Hispanics, and Asian Americans, and the disease affects more people in hotter climates.[8] In the Middle East, more than 70% of kidney stones are composed of uric acid, whereas a similar percentage of patients in the US have calcium-based stones.[8] In 2008 melamine-adulterated milk in China led to a large number of Chinese babies developing kidney stones and, in some cases, renal failure due to obstructive nephropathy.[9]

Kidney stones result in substantial morbidity. The severe pain of renal colic can lead to frequent hospitalizations, shock wave lithotripsy, or invasive surgical procedures. Though rarely a cause of end-stage renal disease (ESRD), nephrolithiasis has been associated with chronic kidney disease (CKD) in various populations.[10,11] Patients with kidney stones have an increase in aortic calcification, and kidney stones are associated with adverse cardiovascular events,[12,13] especially in men and an increase in stroke, especially in women.[14] There is a significant decrease in bone mineral density leading to fracture in patients with nephrolithiasis.[15,16]

TYPES OF STONES

In the US, calcium-based stones account for more than 75% of all stones passed. As shown in Figure 67.1, uric acid and struvite stones account for approximately 10–20% of cases, whereas cystine stones are seen in 1–2% of all stone formers. The recurrence rate of calcium oxalate nephrolithiasis is about 50% at 5–10 years. Recurrence rates are higher for cystine, uric acid, and struvite stones.[12,13]

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00067-X

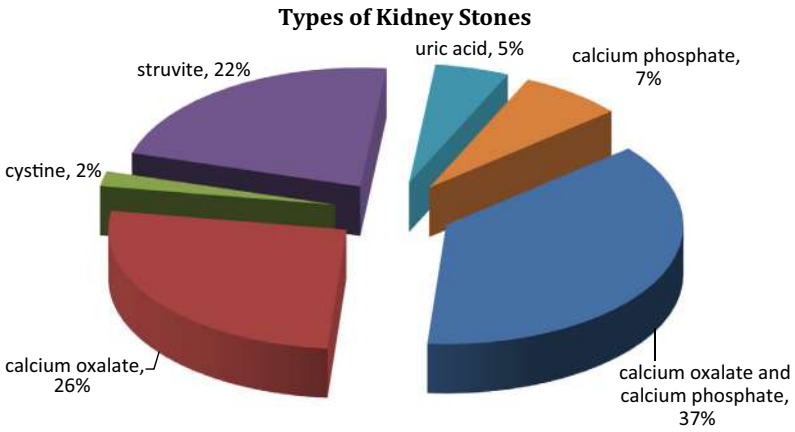


FIGURE 67.1 Stone types.

Pathogenesis of Kidney Stone Formation

The final common pathway of stone formation is the supersaturation of urine with the ionic constituents of the specific stone. Saturation refers to the driving force for formation of the solid phase and takes into account the ambient conditions, concentrations, and free-ion activities of stone components that influence their solubility. Thus, saturation is not just a simple function of ionic molar concentrations. Using calcium oxalate as an example, even if the concentration of these free ions is increased in urine, other substances such as citrate, potassium, and magnesium act as inhibitors and prevent crystallization. The interaction with these other solutes decreases the free ion activity and allows the lithogenic constituents to increase in concentration to levels that would otherwise cause crystal formation in water. Thus lithogenicity could result from increased excretion of poorly soluble substances or decreased excretion of inhibitors of stone formation. Other factors such as urine pH influence supersaturation by affecting the solubility of these ions.

When urine becomes supersaturated, free ions have a greater propensity to combine to form the more stable, solid phase.[17] This process is called nucleation. Nucleation can happen from similar ions (homogeneous nucleation) or around dissimilar crystals or sloughed epithelial cells (heterogeneous nucleation). If several small crystals bond together and grow in size (aggregation), this crystal complex can cause obstruction in the urinary tract.

Calcium oxalate crystals often initially adhere to calcium phosphate deposits, so called Randall's plaques, which are located on the renal papillae (Figure 67.2). This adherence and subsequent growth occurs only in urine that is supersaturated with respect to calcium oxalate. With continued urinary supersaturation the stone increases in size and, if it breaks off from the Randall's plaque, it may be large enough to obstruct the ureter causing clinically significant stone disease.[18]

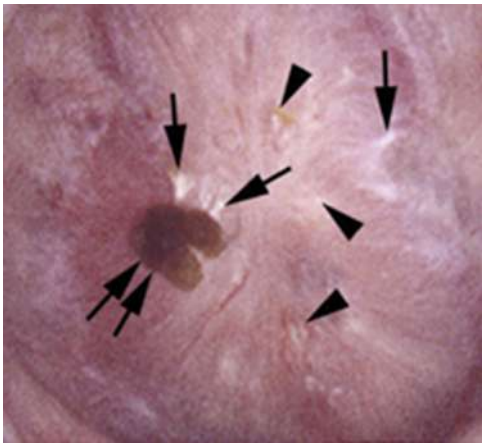


FIGURE 67.2 An attached stone (*double arrow*) is seen resting on a region of white plaque (*single arrows*) and intermixed with small areas of white (*single arrow*) and yellow plaques (*arrowheads*). *From Evan AP, Lingeman JE, Worcester EM, Bledsoe SB, Sommer AJ, Williams Jr JC, Krambeck AE, Philips CL, Coe FL. Renal histopathology and crystal deposits in patients with small bowel resection and calcium oxalate stone disease.* Kidney Int *2010;78:310–7.*

Risk Factors for Stone Formation

Various clinical conditions and dietary habits increase the risk of nephrolithiasis. Diets high in sodium and animal protein increase urinary calcium excretion and increase the risk of stone formation.[19–21] High-oxalate or high-purine diets also lead to increased risk of stone formation by increasing urinary supersaturation with respect to calcium oxalate and uric acid respectively.[19,20,22–24] Low fluid intake is a crucial risk factor for stone formation because a low urine volume increases urinary supersaturation of all stone types.[25–29] These factors are discussed in more detail under dietary interventions for the treatment of kidney stones. Prior history of nephrolithiasis,[30] family history of nephrolithiasis,[31] recent gastric bypass procedures, bariatric

surgery, or short bowel syndrome are all associated with increased risk of stone formation.[32,33] Recurrent urinary tract infections with urease-producing organism such as Proteus or Klebsiella predispose to the formation of struvite stones. Medications such as indinavir, acyclovir, sulfadiazine, ceftriaxone, and triamterene can crystallize and form stones in urine.[34–36] The risk of nephrolithiasis is higher in patients with hypertension, diabetes, obesity, metabolic syndrome, and gout.[4,37,38] Fructose, a ubiquitous sweetener in processed American foods, is associated with significant risk of developing nephrolithiasis. Although the mechanism is unknown, fructose is the only known carbohydrate that increases uric acid production.[39]

GENETIC CAUSES OF STONE FORMATION

X-Linked Hypercalciuric Nephrolithiasis (Dent's Disease and Others)

This X-linked disorder of proximal renal tubular dysfunction manifests as hypercalciuria, low–molecular weight proteinuria, nephrocalcinosis, hypophosphatemic rickets, and renal failure.[40–44] Dent's disease has been linked to mutations affecting the genes encoding the Cl^-/H^+ exchanger ClCN5 in the majority of patients, and/or inositol polyphosphate 5-phosphatase (OCRL1). Both genes are on the X chromosome.[40–42] How defects in these genes lead to the array of these proximal tubular disorders is not yet understood. Parathyroid hormone (PTH) tends to be quite low and $1,25(OH)_2D_3$ high in the majority of patients.

Bartter Syndrome

Bartter syndrome is caused by at least five genetic mutations, predominantly autosomal recessive, which lead to sodium chloride wasting at the thick ascending limb (TAL) of the loop of Henle.[20,45,46] These genes, all expressed in the TAL, cause a defect in sodium transport that leads to a reduction in the transtubular potential difference, resulting in a decrease in paracellular calcium reabsorption in the TAL leading to hypercalciuria, nephrocalcinosis, and nephrolithiasis.

Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is an autosomal recessive disorder genetic disorder resulting from the defective production of either of the tight junction proteins, claudin 16, and claudin 19. FHHNC results in hypomagnesemia, hypercalciuria, nephrolithiasis, and distal renal tubular acidosis. Polyuria and severe nephrocalcinosis also ensue, and progressive kidney failure is common by late childhood.[45,47–49]

Distal Renal Tubular Acidosis

Distal RTA (dRTA) is caused by dysfunctional α-intercalated cells, resulting in defective acid excretion and the inability to maximally acidify the urine.[45,46,50–54] The ensuing metabolic acidosis, hypocitraturia, hypokalemia, and hypercalciuria cause nephrocalcinosis, and primarily calcium phosphate stones. dRTA can be inherited or be secondary to Sjögren's syndrome or induced transiently with carbonic anhydrase inhibitors such as acetazolamide.[55,56]

Hereditary Hypophosphatemic Rickets with Hypercalciuria

Hereditary hypophosphatemic rickets with hypercalciuria is an autosomal form of hypophosphatemic rickets, caused by mutations in solute carrier family 34, member 3 (SLC34A3), the gene that encodes the sodium Na^+-dependent phosphate cotransporter 2c (NPT2c). Hereditary hypophosphatemic rickets with hypercalciuria manifests clinically as hypophosphatemia secondary to renal phosphate wasting.[57–60] Hypophosphatemia directly increases $1,25(OH)_2D_3$, which leads to increased intestinal calcium absorption and hypercalciuria. The bone pain, muscle weakness, limb deformities, and rickets resolve with administration of oral phosphate.

Primary Hyperoxaluria and Cystinuria

Primary hyperoxaluria (PHO) and cystinuria are each discussed in their respective sections in Specific Therapy below.

Others Causes

Numerous other monogenic disorders cause hypercalciuria, either by augmenting bone resorption (osteogenesis imperfecta type 1, multiple endocrine neoplasia type 1 with hyperparathyroidism, McCune-Albright syndrome, infantile hypophosphatemia) or by increasing intestinal absorption of calcium (hypophosphatemia, Down syndrome, congenital lactate deficiency) and can also lead to nephrolithiasis or nephrocalcinosis.[17,61–64] Pseudoxanthoma elasticum is caused by mutations of the *ABCC6* gene that results in low urinary pyrophosphate levels and development of Randall's plaques in both mice and humans beings.[65]

CLINICAL PRESENTATION

The clinical presentation depends on the size, type, and location of the stone. Commonly, stones present with pain or hematuria but can vary from asymptomatic small stones discovered on incidental imaging to large calculi that cause obstruction and renal failure. Large obstructing staghorn calculi may be asymptomatic. Therefore nephrolithiasis should be in the differential diagnosis of unexplained CKD.[66]

Pain

The passage of stones often results in ureteric colic that is abrupt in onset, excruciating, and frequently accompanied by hematuria, nausea, and vomiting. The pain generally migrates from the flank toward the abdomen and into the groin as the stone moves toward the uretero-vesicle junction. Nephrolithiasis can also produce a dull, poorly localizing pain or be an incidentally discovered radiologic finding unrelated to the actual cause of flank pain.

Hematuria

Hematuria occurs in 90–95% of patients with acute unilateral flank pain caused by stones. It may be microscopic or macroscopic.[67,68] Large calculi generally cause macroscopic hematuria and, expectedly, are often associated with bouts of colic. In patients with hematuria, it is always important to consider diagnoses other than kidney stones, including tumors and infection throughout the kidney and genitourinary tract, glomerular and interstitial diseases, and hypercalciuria in children.[69]

Rarer Presentations

Less common presentations of nephrolithiasis include urinary tract infections and acute kidney injury (AKI) if the stone is obstructing a single functioning kidney, or if both kidneys are obstructed simultaneously. Staghorn calculi often do not produce symptoms unless the stone results in obstruction, leading to renal failure that may occur in more than a quarter of these patients.[70]

THE BASIC EVALUATION

History

Stone History

A chronology of stone events should be generated. Age at first stone, size and number of stones formed, frequency of passage, and stone type are all useful, to judge not only the severity of the stone disease but also to provide clues regarding the origin of the patient's nephrolithiasis. Presentation characteristics of each stone type are discussed subsequently under their individual descriptions.

Medical History

Systemic disorders that can cause nephrolithiasis are sought in the medical history. Clues to diseases that cause hypercalcemia (such as sarcoidosis, hyperparathyroidism), hyperoxaluria (such as sprue, Crohn's disease), or hyperuricemia in patients with and without gout are often uncovered with direct questioning or after examination of the medical record.

Family History

A number of stone disorders are inherited, making the family history an important component of the basic evaluation. Stones arising in childhood or young adulthood can be related to autosomal recessive disorders such as cystinuria and primary oxaluria.

Medications

Calcium-containing supplements can result in hypercalciuria from the increased absorption of calcium, increasing its filtered load and, ultimately, the excretion of calcium.[71] Loop diuretics promote renal tubular excretion of calcium and are associated with nephrocalcinosis in neonates who have received the drug.[72,73] Acetazolamide induces a mild metabolic acidosis and alkaline urine, favorable conditions for the development of calcium phosphate stones. Uricosuric medications, such as salicylates and probenecid, have been implicated in uric acid lithiasis.[74] Triamterene, indinavir, sulfadiazine, and intravenous (IV) acyclovir can precipitate as crystals in the urine. The end product of Vitamin C metabolism generates oxalate, and, when taken in large doses, Vitamin C may predispose to stone formation.[75,76]

Diet

A thorough review of the patient's diet and fluid intake may illuminate relevant risk factors, such as ingestion of foods high in sodium, animal protein, oxalate, or purine. Low water intake to avoid frequent trips to the restroom, as often practiced by surgeons and traveling salesmen, also predisposes to nephrolithiasis. Many patients are erroneously counseled by physicians to avoid calcium-containing foods, a suggestion that is not only associated with increased risk of stone formation; low-calcium diets may also result in bone demineralization, a serious concern in women with kidney stones.[77–79]

DIFFERENTIAL DIAGNOSIS

Pyelonephritis

Fever is an uncommon finding in patients with simple stones without concurrent infection. Thus, fever should trigger an evaluation for pyelonephritis that can complicate stones. Struvite stones are often associated with infections by urease-producing organisms. Xanthogranulomatous pyelonephritis is a form of chronic pyelonephritis often associated with kidney stones that can produce significant destruction of the renal parenchyma. Xanthogranulomatous pyelonephritis may mimic a tumor radiologically.[80]

Ectopic Pregnancy, Rupture or Torsion of Ovarian Cysts, Dysmenorrhea

Flank pain associated with these conditions can closely mimic the pain caused by stones. Hematuria is frequently misdiagnosed to have been caused by stone disease if the urine is contaminated with vaginal blood.[81]

Acute Appendicitis, Diverticulitis, Intestinal Obstruction, Mesenteric Ischemia, and Biliary Colic

These conditions can mimic the pain seen with kidney stones and the accompanying nausea and vomiting. However hematuria is unusual in these cases, and abdominal signs on physical examination are more prominent than with renal colic.[82]

Loin Pain Hematuria Syndrome

Typically a disease of young or middle-aged women, this poorly understood condition can cause hematuria, both microscopic and macroscopic, and must be in the differential diagnosis of all conditions that cause flank pain and hematuria.[83] This diagnosis is made by excluding other conditions such as small stones, tumors, urinary infections, and glomerular disease.[84]

Clot-Colic, Debris-Colic

Bleeding into the renal pelvis from tumors or after kidney biopsy can produce clots that obstruct the ureter and cause pain.[85] Papillary necrosis secondary to diabetes, analgesic abuse, or infections can also present similarly.[86,87]

DIAGNOSIS

Suspicion for nephrolithiasis, or workup of other causes of abdominal pain with or without hematuria, typically involves radiological evaluation to help differentiate the disorders. The tests that can be performed in such a situation include a Kidney Ureter Bladder (KUB) radiograph, an ultrasound, a computed tomographic (CT) scan, an intravenous pyelogram (IVP), or a magnetic resonance image (MRI). We do not recommend routine radiographic procedures. They should only be performed when the outcome is likely to alter therapy.

Abdominal X-Ray/KUB

Although 90% of urinary calculi (calcium, struvite, and cystine) are radio-opaque, the sensitivity of a KUB is 45–59% and specificity is 71–77%.[88] In addition to uric acid stones being radiolucent, such a low diagnostic yield is likely because of problems with stones being obscured by stool, bowel gas, or overlying vertebrae.

Intravenous Pyelography

IVP is more sensitive (64–87%) and specific (92–94%) than a KUB for the detection of renal calculi.[89] IVP can also identify structural abnormalities of the urinary tract that predispose to stone formation. During acute colic an IVP may even help move the stone along the ureter by creating a strong osmotic diuretic effect. However, IVPs can miss nonobstructing radiolucent stones that do not generate a "filling defect," carry the risk of contrast exposure in patients with compromised renal function, carry the risk of radiation exposure, and sometimes need reimaging at 12–24 hours in patients with high-grade obstruction because of inadequate concentration of the contrast medium.[89] With the current availability of other radiographic tests, an IVP is rarely indicated in contemporary practice.

Renal Ultrasonography

Ultrasonography is easily performed and very sensitive at detecting the presence of stones and of obstruction.[90] Ultrasound is the imaging modality of choice when radiation exposure must be minimized, such as in young women, especially if they are pregnant. Emergency department patients with suspected nephrolithiasis who initially have ultrasonography have lower total radiation exposure than those initially evaluated with CT, without any difference in serious adverse events, missed important diagnoses, pain scores, or subsequent emergency department visits or hospitalizations.[91,92]

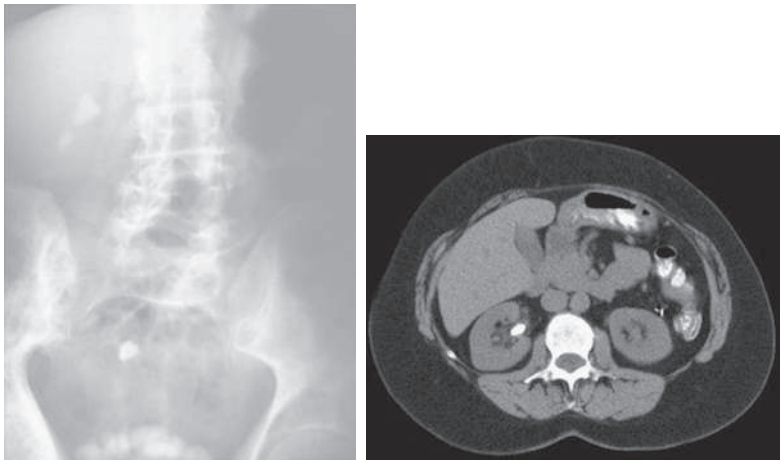


FIGURE 67.3 Renal stones on abdominal X-ray and CT scan. A radiolucent kidney stone can be seen on the KUB at the uretero–vescial junction. A large stone is seen in the renal pelvis of the right kidney. *From www.gehealthcare.com/usen/ct/products/urologyimagegallery.html.*

Noncontrast Helical CT

Noncontrast helical CT can detect most stones with a sensitivity of 95–98% and specificity of 98%.[90,93] Noncontrast helical CT has been shown to be superior to IVP as a diagnostic modality.[94] Based on the Hounsfield density of the identified stone, cystine and uric acid stones can be differentiated from calcium-bearing stones using this technique.[95] A helical CT is also useful to detect other causes of abdominal pain and thus is the imaging modality of choice for most cases.[96] However, a CT is more expensive than other tests and has the added disadvantage of increased exposure to radiation. Often a noncontrast helical CT is followed by a contrast study. This practice should be avoided unless absolutely necessary, as the radiation exposure is doubled and the patient is exposed to the risks of the contrast medium.

MRI

Although quite sensitive (82%) and specific (98%) for detecting kidney stones, this modality is rarely used as a diagnostic test except in situations where it is important to avoid radiation.[90]

Although most stones are detected using one or a combination of the above radiological techniques, HIV protease inhibitor–induced stones are not radiopaque and often do not manifest signs of obstruction, leading to the diagnosis being missed on IVP, ultrasound, and noncontrast CT scan.[34,35] In such patients, contrast-enhanced CT scanning may be required to establish the diagnosis[97] (Figure 67.3).

NEPHROLITHIASIS AND CHRONIC KIDNEY DISEASE

Nephrolithiasis is associated with a twofold increase in CKD that is independent of other risk factors such as diabetes and hypertension found in stone formers.[98–100] A French study estimated the incidence rate of ESRD because of nephrolithiasis to be about 3.1 cases per million population per year.[101] A Canadian study demonstrated that although only 0.8% of patients with ESRD had nephrolithiasis, any previous stone episode was associated with an increased risk of ESRD (hazard ratio 2.16).[10] This risk was greater in women than in men. Approximately 40% of stone formers who develop ESRD had a solitary functioning kidney.[102] The most common reasons for loss of a single kidney in stone formers were staghorn calculi, high stone burden, infection, and ureteral obstruction.[103]

The mechanism of development of renal damage with stone disease probably arises from ureteral obstruction causing parenchymal damage.[98] Animal models suggest that unilateral ureteral obstruction causes intense renal vasoconstriction and reduces renal blood flow and glomerular filtration rate (GFR).[104] Other injury-producing events induced by obstruction include increased interstitial volume, matrix deposition, monocyte infiltration, and fibroblast differentiation, leading to upregulation of TGF-β and TNF-α, and progression to tubule-interstitial inflammation and fibrosis.[105,106] Brushite (CaHP) stone formers have an increased risk of cortical fibrosis.[107]

The formation of Randall's plaques in brushite stone formers is associated with duct plugging, collecting

duct cell death, and inflammation.[18] In patients with staghorn calculi, a renal biopsy often demonstrates extensive inflammation and macrophage infiltration.[108] Other stone-forming diseases such as PHO, cystinuria, and Dent's disease have all been associated with crystal formation in the renal parenchyma that presumably triggers subsequent inflammation and CKD.[109]

With declining GFR, urinary calcium excretion decreases.[110] Evidence suggests that stone recurrence rates are lower in stone formers with reduced GFR.[111] Thus there may be significant underrecognition of the contribution of kidney stones to the development of CKD.

MANAGEMENT

Management of Acute Renal Colic

Management of acute renal colic is centered on pain control with adequate analgesia, assessment of the stone size/location to determine its likelihood of passing, and evaluation of coexistent conditions or complications that might necessitate urgent urologic intervention.

Analgesia is achieved by use of either nonsteroidal antiinflammatory drugs (NSAIDs) or opiates. A systematic review found both were equally effective in achieving analgesia.[112] A combination may be superior to either one alone.[113,114]

NSAID administration avoids the nausea and vomiting common to opiates but carries the risk of worsening AKI in an obstructed kidney. Also, NSAIDs must be stopped 3 days before planned lithotripsy to avoid excessive bleeding.[115]

The more distal the stone in the ureter, the more likely it is to pass spontaneously. In the kidney, stones in the lower pole are associated with poor clearance after lithotripsy and may need percutaneous lithotomy for removal if they are more than 10 mm in size.[116] Stones 2–4 mm in diameter have a 76% chance of passing spontaneously, 5–7 mm a 60% chance, 7–9 mm a 48% chance, and greater than 9 mm a 24% chance of passing spontanuously.[117–119] If the decision is made to allow a stone to pass spontaneously, patients must have repeat radiographic examinations to document the stone's passage. Patients should be followed weekly for any signs of sepsis or worsening renal function.

Medical expulsive therapy has been utilized to speed stone passage. A general consensus is that this form of therapy may be used for ureteral stones less than 10 mm in diameter in patients with normal renal function, controllable pain, no evidence of infection, or significant ureteral obstruction for up to 4 weeks. Although the results of individual studies have varied, a recent meta-analysis of 67 trials including over ten thousand patients demonstrated that an alpha-adrenergic blocker, such as tamsulosin (0.4 mg/day), was effective in improving stone clearance, reducing the time to stone passage by 3.4 days with a slight increase in major adverse events.[120] There were fewer hospitalizations in the treated patients with no change in the rate of surgical intervention. Two other smaller meta-analyses confirmed that therapy with tamsulosin also leads to a greater likelihood of stone passage.[121] Other agents such as the selective alpha-1A adrenoreceptor receptor antagonist silodosin (8 mg/day) appear to speed stone passage as well.[122]

For patients presenting with acute renal colic and signs of sepsis, anuria, acute renal failure, intractable vomiting, or intractable pain or with a stone larger than 10 mm, an urgent urologic consultation is essential to relieve the obstruction.[123,124]

Metabolic Evaluation of Kidney Stone Formers

Most patients need a metabolic evaluation to identify lithogenic risk. It is recommended that this be performed 4–6 weeks after an acute episode, when the patient is eating a usual diet.[125] After the initial episode of nephrolithiasis, observational studies estimate that the likelihood of recurrence, in the absence of specific treatment to prevent recurrence, is quite variable, ranging from about 5% per year for the first 5 years[29] to 50% at 5 years.[126,127]

Given the success of the general measures to prevent recurrent stone formation, such as ample fluid intake, sodium reduction, age- and gender-appropriate calcium intake, and reduction of dietary protein, some have recommended that a comprehensive evaluation be reserved for patients with multiple stones, a strong family history of stones, those passing gravel, those with metabolically active stones (stones that grow in size or number on follow up), in children, in demographic groups not prone to forming stones and in those in whom the stones are not made of calcium. However, studies have shown that first-time stone formers have the same underlying metabolic risk factors and severity of stone disease as recurrent stone formers.[127] We recommend at least a basic metabolic evaluation on all stone formers.

The basic metabolic evaluation includes measurement of S[Na], serum potassium concentration (S[K]), S[Cl], bicarbonate, serum creatinine concentration (S[Cr]), serum calcium concentration (S[Ca]), serum phosphate concentration (S[P]), and serum uric acid concentration, urine analysis, and urine culture. A PTH level should be measured if the S[Ca] is elevated or even at the upper limit of normal, and if the S[P] is decreased or even at the lower limit of normal. The presence of hypokalemia and metabolic acidosis may suggest a renal tubular acidosis. Urine analysis might reveal crystals of uric acid, cystine,

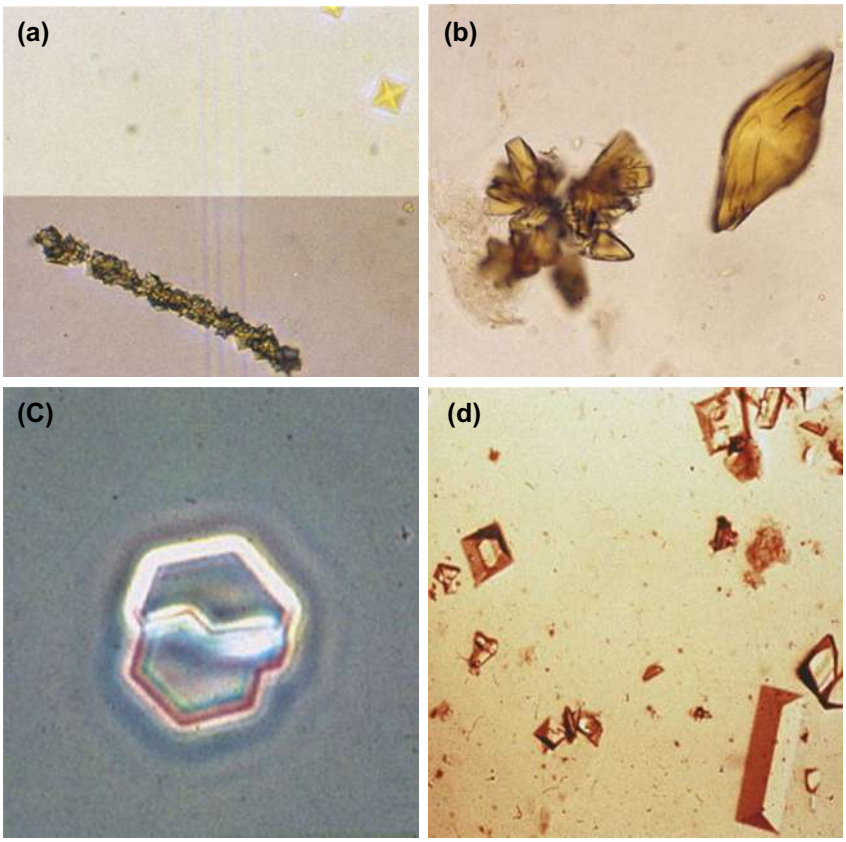


FIGURE 67.4 Crystals seen in urine of stone formers. (a) Calcium oxalate; (b) Urate; (c) Cystine; (d) Struvite. *From Monk RD, Bushinsky DA. Nephrolithiasis and nephrocalcinosis. In:* Comprehensive clinical nephrology. *London: Mosby; 2010.*

calcium oxalate, calcium phosphate, or magnesium ammonium phosphate (Figure 67.4) (Table 67.1).

The comprehensive evaluation includes all of the above, as well as a 24-hour urine collection for assessment of urinary volume and ion excretion, with the supersaturation calculated for the calcium oxalate, calcium phosphate, and uric acid solid phases. Supersaturation of urine correlates well with stone composition[128] and involves the measurement of urinary volume, pH, calcium, oxalate, citrate, uric acid, creatinine, sodium, potassium, magnesium, sulfate, phosphate, chloride, and urine urea nitrogen. Patients should collect their urine on a typical day while eating a typical diet and should be instructed appropriately to obtain an accurate urine collection (Table 67.2).

GENERAL MEASURES TO PREVENT STONE RECURRENCE

The goal of treatment is to lower urinary supersaturation, as an undersaturated urine reliably predicts freedom from recurrence.[2,5]

Fluid Intake

Fluid intake resulting in a urine volume of more than 2−2.5 L a day has been shown to reduce the incidence of stone formation[29,129] and is a mainstay of therapy for nephrolithiasis. Because the risk of stone formation is maximal at night when urine concentration is increased, patients should be encouraged to drink enough water to provoke nocturia and drink more fluid before returning to bed.[2]

Dietary Salt Intake

As illustrated in Figure 67.5, urine calcium excretion parallels urinary sodium excretion.[20] Therefore limiting dietary salt intake (<2 g/day) will reduce urinary supersaturation for calcium-containing stones.[130]

Dietary Protein Intake

Consumption of animal protein is a risk factor for calcium as well as uric acid stone formation.[131] The acid generated from this diet causes efflux of calcium from bone[132] and increases filtered load of calcium. An acidic

TABLE 67.1 Basic Evaluation of Nephrolithiasis

Stone history
Number of stones formed
Frequency of stones formed
Age at first onset
Size of stones passed or still present
Stone type if known
Side of kidney involved
Need for urologic intervention
Response to surgical procedure
Presence of urine infection
Medical history
Medications
Family history
Occupation, lifestyle
Fluid intake, diet
Physical examination
Laboratory data
Urine analysis
Urine culture
Stone analysis
Blood chemistry
Sodium, Potassium, Chloride, Bicarbonate, Creatinine, Calcium, Phosphorus, Uric acid, iPTH
Radiologic evaluation
KUB
Helical CT
IVU
Ultrasound

TABLE 67.2 The Comprehensive Evaluation and Urinary Supersaturation

OPTIMAL 24-HOUR URINE VALUES IN RECURRENT NEPHROLITHIASIS
Urine volume >2.5 L
Calcium <4 mg/kg or <300 mg in men and <250 mg in women
Oxalate <40 mg
Uric acid <800 mg in men and <750 mg in women
Citrate >320 mg
Sodium <3000 mg
Phosphorus <1100 mg
URINE SUPERSATURATION VALUES
Calcium oxalate supersaturation <5
Calcium phosphate supersaturation 0.5–2
Uric acid supersaturation 0–1

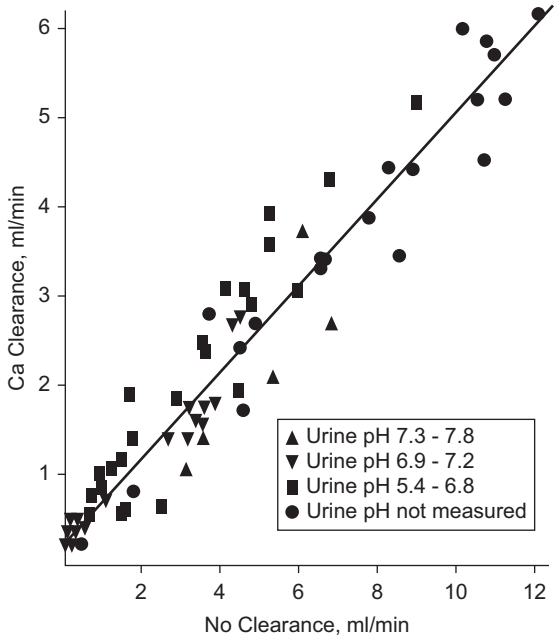


FIGURE 67.5 Relationship between urinary calcium and sodium excretion. This study shows how urinary calcium excretion parallels urinary sodium excretion. There is almost a linear relationship between the urinary excretion of calcium and sodium, making sodium restriction in diet imperative in the treatment of hypercalciuria. *From Walser.* Am J Physiol *1961;**200**:1099.*

tubular fluid decreases renal tubular calcium reabsorption leading to increased calcium excretion. Reduced urinary citrate excretion[133] and lowered calcium solubility because of the presence of sulfates from the acidic amino acids are other lithogenic effects of such a diet.[132] Reducing the animal protein content of diet to 0.8–1.0 g/kg/day can help reduce the risk of stone formation.[78]

Dietary Calcium

In the intestine dietary calcium binds dietary oxalate, which leads to decreased oxalate absorption and a reduction in oxaluria.[77,134] Thus, patients on a low-calcium diet have a significantly increased incidence of stone formation compared to patients on a normal calcium diet.[77,78] The beneficial effect of dietary calcium is abrogated in women taking calcium supplements, likely because the supplement is often taken between meals. The supplement generally rapidly dissolves, resulting in a bolus of calcium that is quickly absorbed, leading to increased urinary supersaturation.[134–136] Although a low-calcium, low-oxalate diet can also reduce urine supersaturation with respect to calcium oxalate,[19] given the risk of bone demineralization with this approach it should be avoided. It is currently

recommended that most patients consume an age-appropriate calcium diet.[79,135] The current recommendations regarding daily elemental calcium intake are 1000 mg for men aged 19–70 and 1200 mg from age 71. For women it is 1000 mg from ages 19 to 50 and 1200 mg after age 51.[137]

TREATMENT OF SPECIFIC STONE TYPES

Calcium Stones and Hypercalciuria

Most calcium-based kidney stones are composed of calcium oxalate but can also contain calcium phosphate or uric acid. In addition to the increased risk associated with low-fluid consumption, high- or low-calcium intake, high-sodium and high–animal protein intake, the specific metabolic risk factors for development of calcium stones include hypercalciuria, hyperoxaluria, hyperuricosuria, and renal tubular acidosis. Most causes of hypercalcemia (hyperparathyroidism, vitamin D intoxication, for example) can cause hypercalciuria because of the increased filtered load of calcium, which is incompletely reabsorbed. Hypercalciuria is defined as daily urinary calcium excretion exceeding 250 mg in women and 275–300 mg in men.[17] Although we set arbitrary levels for defining hypercalciuria, it is clear that stone formation is a continuous function of urine calcium excretion—the higher the urinary calcium, the greater the supersaturation of the urine and the greater the risk for stone formation.

Idiopathic Hypercalciuria

Idiopathic hypercalciuria (IH) is defined as excessive urinary calcium excretion in the setting of normocalcemia and the absence of secondary causes of hypercalciuria. IH is the most common cause of calcium-containing kidney stones.[20,61] The mechanism by which IH leads to hypercalciuria is not known. It had been postulated that IH comprises three distinct disorders: excessive intestinal calcium absorption, decreased renal tubular calcium reabsorption, and enhanced bone demineralization. In a genetic strain of hypercalciuric stone-forming rats, hypercalciuria appears to be due to an excessive number of enteric Vitamin D receptors, leading to a generalized disorder of calcium transport at all sites of calcium transport, including the kidneys, intestine, and bone.[138,139] In humans, intestinal calcium absorption is significantly higher in subjects with IH.[140] Urinary excretion of calcium is also increased, thus placing many of these patients in net negative calcium balance if they consume a low-calcium diet.[17]

It was previously considered important to determine whether a patient with IH tended to have excessive GI calcium absorption (absorptive hypercalciuria) or excessive renal calcium excretion (renal leak).[19,141] Patients with excessive renal calcium excretion were prescribed thiazide diuretics, and those thought to have a predominantly absorptive defect were prescribed a low-calcium diet. However, many patients with IH had urinary calcium excretion that exceeded their intake,[142] and a low-calcium diet can result in a dangerous reduction in bone mineral density, especially in women.[15,143–145] Additionally, a low-calcium diet increases the risk of recurrent stone formation, presumably due to enhanced oxalate absorption and excretion.[77–79] There is no benefit, and a number of well-documented risks, to advising a low-calcium diet to prevent recurrent stone formation in patients with IH. We do not advise trying to determine the cause of the IH and never recommend a low-calcium diet to any stone patient.

Thiazide diuretics such as hydrochlorothiazide, chlorthalidone, and indapamide can significantly decrease urinary calcium excretion and reduce the incidence of stone formation.[28,146,147] Thiazides also may improve bone mineralization and reduce the risk of fractures.[28,148,149] A S[K] should be checked within 7–10 days of starting a thiazide diuretic and hypokalemia supplemented with potassium citrate. Alternatively, a potassium sparing diuretic such as amiloride can be added to further reduce hypercalciuria.[150] The potassium sparing diuretic, triamterene, should be avoided as it can itself form a stone.

Hyperoxaluria

Hyperoxaluria results from excessive dietary intake (dietary oxaluria), gastrointestinal disorders or surgery that lead to excess oxalate absorption (enteric oxaluria), or rarely an enzyme deficiency that results in excessive production of oxalate (PHO). Dietary oxaluria from oxalate-rich foods (Table 67.3) generally does not raise urinary oxalate above 60–80 mg/day.[151] Although most dietary oxalate is of plant origin, a high-protein diet stimulates endogenous oxalate production. Dietary oxalate becomes even more important in patients on a low-calcium diet, where the unbound oxalate is absorbed instead of precipitating with calcium in the intestine. Complex formation of intestinal oxalate with calcium supports the recommendation that patients with oxalate stones consume a normal calcium diet in addition to restricting high-oxalate foods. Enteric oxaluria is a feature of patients with gastrointestinal disorders such as celiac disease, Crohn's colitis, chronic pancreatitis, short bowel syndrome, and following some types of bariatric surgery, where the shortened bowel length allows for excessive oxalate absorption. The urinary oxalate excretion in enteric hyperoxaluria is often greater

TABLE 67.3 Foods High in Oxalate

Vegetables
Green beans
Beets
Green onions
Leeks
Leafy greens (spinach, Swiss chard, rhubarb, kale, collard greens, escarole, dandelion greens)
Okra
Peppers
Rutabagas
Fruits
Elderberry
Figs
Strawberries
Blueberries
Raspberries
Grains and starches
Buckwheat
Wheat bran
Rye or Wheat Crispbread
Beverages
Beer: dark, robust
Cocoa
Black tea
Coffee: instant
Legumes and Nuts
Almonds
Peanuts
Pistachios
Pecans
Hazelnuts
Miscellaneous
Chocolate
Orange peel
Lemon peel

than 60 mg/day (often more than 100 mg/day), which imparts a higher risk of nephrolithiasis.[152] Enteric oxaluria is persistent and needs aggressive and lifelong therapy for the hyperoxaluria, acidosis, hypokalemia, and hypocitraturia to not only prevent nephrolithiasis but also CKD.[153,154]

PHO, results in excessive oxalate production that deposits in different tissues and causes cardiomyopathy, bone marrow suppression, and renal failure at an early age.[155] PHO arises from various genetic mutations of oxalate production by the liver. PHO type 1 (80% of the cases) is due to a defect in the gene encoding the hepatic enzyme alanine glyoxylate aminotransferase involved in the conversion of glyoxylate to glycine. PHO type 2 (10% of cases) is due to a defect in the gene that encodes for the hepatic enzyme glyoxylate reductase/hydroxypyruvate reductase, involved in the conversion of glyoxylate to glycolate. PHO type 3 represents a defect in the HOGA1 gene that encodes for the mitochondrial 4-hydroxy-2-oxoglutarate aldolase enzyme, accounting for the remaining cases of PHO. In all of these, urinary oxalate excretion is increased, often to more than 300 mg/day[156] and patients can present in childhood with nephrocalcinosis. Systemic deposition of oxalate in organs leads to renal failure, cardiac defects, joint immobility, gangrene, and bone marrow suppression.[155,156]

Treatment of dietary hyperoxaluria consists of restricting dietary oxalate intake and using calcium carbonate with meals to bind oxalate in the intestine. To prevent the sequestration of calcium by fatty acids, the diet should also be low in fat. Cholestyramine is effective in binding oxalate, but its unpleasant taste limits its use.[2] In patients with enteric oxaluria, treatment of the underlying malabsorption syndrome leads to reduced urinary oxalate secretion. The chronic diarrhea often associated with such colonic conditions leads to bicarbonate loss, hypokalemia, hypocitraturia, hypomagnesmia, and low urine volumes, increasing the risk of nephrolithiasis. In such situations, treatment should also include increased fluid intake, potassium citrate and magnesium supplementation. The treatment of PHO is best managed by specialists in this disorder. Treatment involves administration of high doses of pyridoxine and orthophosphate to reduce oxalate levels and inhibit urinary calcium oxalate precipitation.[155,157] Treatment with both pyridoxine and orthophosphate improved renal survival from 20% to 74% at 20 years in patients with PHO type I and II.[157] Liver transplantation to treat the enzyme deficiency is the definitive therapy for this condition,[158] but a combined kidney–liver transplant may be necessary if nephrocalcinosis has developed.[159]

Hypocitraturia

Citrate is an important inhibitor of calcium crystallization in the urine.[160] Conditions that acidify the proximal tubule cell (renal tubular acidosis, chronic diarrhea, hypokalemia) cause hypocitraturia. Other causes of hypocitraturia include high protein diets, exercise, infections, androgens, starvation, and acetazolamide therapy. Although a level below 320 mg/day/1 L of urine is defined as hypocitraturia, the risk of nephrolithiasis is a continuous function of urinary citrate concentration.[161]

Therapy involves dietary modification in the case of excessive protein intake and treatment with potassium citrate[162] or potassium–magnesium citrate.[163] Both citrate formulations have proven to be efficacious in prevention of calcium stone formation, even in patients who do not have hypocitraturia.[163] Patients with CKD should have S[K] monitored while on therapy.

Oxalobacter formigenes

Oxalobacter formingenes is an enteric bacterium that uses oxalate for energy. Studies have shown that patients colonized with the bacterium have lower urinary oxalate compared to those not colonized.[164,165] However data to show that probiotic supplementation to increase colonization with *Oxalobacte formingenes* would lead to reduction in urinary oxalate excretion are lacking.[166] An interesting study suggests that the increased incidence of stones in industrialized nations may be explained by the reduced enteric *Oxalobacte formingenes* colonization from substantial antibiotic use.[167]

Uric Acid Stones and Hyperuricosuria

Hyperuricosuria refers to the increased excretion of both uric acid as well as sodium urate. Like calcium, oxalate, and citrate excretion in urine, hyperuricosuria may be considered a continuous variable. In addition to excess uric acid/urate production, the key factors influencing solubility of these substances in urine are urine pH and urine volume. Most patients with uric acid kidney stones do not excrete excessive amounts of uric acid; rather they have a low urinary pH.[17] Of those with hyperuricosuria the most common cause is excessive intake of dietary purine from animal proteins.[168,169] Other causes of hyperuricosuria include gout, uricosuric medications such as atorvastatin, amlodipine, and losartan, and, less commonly, disorders of excess production such as myeloproliferative disorders, tumor lysis syndrome, hypoxanthine-guanine phosphoribosyl transferase deficiency or phosphoribosyl pyrophosphate excess.

Urine pH is the major determinant of uric acid nephropathy (Figure 67.6). The solubility of uric acid rises sixfold with an increase in urine pH from 5.3 to 6.5.[170] In a compilation of four studies, every patient with uric acid stones had a urine pH less than 6.[171–174] Even when the total amount of uric acid being excreted is not above normal, a low urinary pH leads to the formation of uric acid, which is poorly soluble as opposed to the urate anion that is more soluble.[170] A similar mechanism, where decreased ammoniagenesis leads to a lowered urine pH, is postulated to be the cause of uric acid stones in patients with type 2 diabetes, metabolic syndrome, and chronic diarrhea.[37,175]

Uric acid stones are not radio-opaque and an ultrasound, or CT with contrast may be needed to diagnose their presence. Treatment of uric acid stones involves alkalizing the urine, switching to a low animal protein diet, avoiding high-purine foods (Table 67.4), increasing urine volume, and lowering uric acid production.[17] Sufficient alkali should be prescribed to raise the urine pH to above 6.5.[176] Because there is no added benefit to raising the urine pH beyond 7.0, and there is a potential risk of forming calcium phosphate stones in alkaline urine, patients should be instructed to check their urine pH once a day and titrate their consumption of alkali to aim for a urine pH between 6.3 and 7.[177] Increasing urine pH with potassium citrate or potassium bicarbonate can dissolve uric acid stones.[178] In patients at risk for hyperkalemia, acetazolamide can be used instead of potassium citrate therapy to increase urinary bicarbonate excretion and urine pH and reduce the risk of uric acid stones.[179] If patients continue to form uric acid stones, or excrete uric acid in excess of 1000 mg/day, allopurinol is recommended to decrease uric acid stone formation.[180] Allopurinol has been shown to reduce the incidence of calcium stones in hyperuricosuric patients,[181] but must be used with caution in patients of Han Chinese descent who carry the HLA-B*5801 gene and have a high risk of cutaneous drug reactions.[182,183]

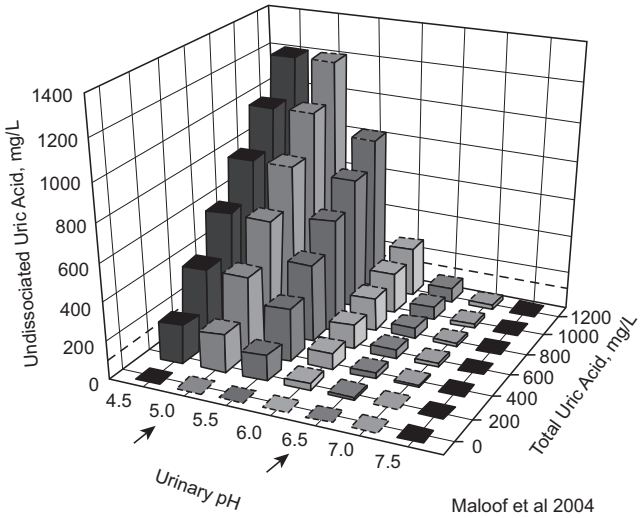


FIGURE 67.6 pH and solubility of uric acid. The solubility of Uric acid changes markedly with urine pH. At a urine pH of 5.5 slight increases in uric acid, even within the normal clinical range, lead to marked increase in undissolved uric acid. *From Maalouf N, Gaska MA, Abate N, Sakhaae K, Moe OW. New insights in the pathogenesis of uric acid nephrolithiasis.* Curr Opin Nephrol Hypertens *2004;**13**:181–9.*

TABLE 67.4 Foods High in Purine

Organ meats: Sweetbreads, Liver, Kidney, Brains, Heart
Shellfish
Meat: Beef, pork, lamb, poultry
Fish: Anchovies, sardines, herring, mackerel, cod, halibut, tuna, carp
Meat extracts: Bouillon, broth, consommé, stock
Gravies
Vegetables: asparagus, cauliflower, peas, spinach, mushrooms, lima beans, lentils

Calcium Phosphate Stones and Nephrocalcinosis

Some calcium stones are predominantly composed of calcium phosphate. Typically these patients are hypercalciuric and their urine volumes and urine pH are higher than observed in calcium oxalate stone formers.[184] The precise pathogenesis of such calcium phosphate stones is unclear, but the inciting event is thought to be a renal tubular acidosis that can be incomplete (no evidence of acidemia on serum chemistry but patients cannot properly acidify urine if challenged with an oral acid precursor such as ammonium chloride). In such cases, the urine pH stays above 6.1 and supersaturation of calcium phosphate is increased. Type 1 RTA is a dramatic example of this clinical scenario and can manifest as nephrocalcinosis where there is extensive deposition of calcium phosphate within the renal parenchyma. Drugs such as acetazolamide or topiramate also produce a similar urinary chemical milieu that is conducive to calcium phosphate stone formation.

Hyperphosphaturia is another risk factor that can lead to the development of calcium phosphate stones or nephrocalcinosis. Hyperphosphaturia contributes to stone formation in patients with hyperparathyroidism, vitamin D intoxication, tumor lysis syndrome, acute phosphate nephropathy after oral sodium phosphate bowel preparation, and inherited phosphate-wasting disorders. Treatment consists of general measures outlined above and therapy to lower urinary calcium excretion with thiazides. Alkali supplementation may be beneficial if there is acidemia. However, care must be taken to ensure that the urine pH does not increase to beyond 7, as that may worsen the supersaturation for calcium phosphate.

Struvite Stones

Also referred to as triple phosphate stones, struvite stones are seen in urine colonized with urea splitting organisms and are composed of magnesium ammonium phosphate (struvite) and hydrated calcium carbonate (apatite). Struvite stones are formed when urease-producing bacteria (Table 67.5) split urea and generate ammonia and an alkaline urine. Under these conditions phosphate combines with ammonium, magnesium, and calcium and leads to the formation of struvite. Untreated, they can grow rapidly and fill the renal-collecting system forming staghorn calculi. Women are more prone to forming such stones because of their increased risk of urinary tract infections.[185] Patients with urinary catheters, neurogenic bladders, spinal cord lesions, and anatomical abnormalities of the genitourinary tract are also predisposed to the development of struvite stones. Infection with urease-producing bacteria, alkaline urine, and large stones are very suggestive of struvite nephrolithiasis. Colony counts can be low, but speciation and sensitivities are necessary for diagnosis and treatment. If cultures are negative, a specific request should be made for *Ureaplasma urealyticum* that exhibits fastidious growth on regular culture medium.

TABLE 67.5 Infections Associated With Struvite Stone Formation (Urease-Producing Bacteria)

Proteus
Haemophilus
Yersinia
Staphylococcus epidermidis
Pseudomonas
Klebsiella
Serratia
Citrobacter
Ureaplasma

Left untreated, struvite stones can cause sepsis or lead to ESRD. Struvite stones therefore require aggressive medical and surgical therapy.[102] Early urological intervention is necessary for stone removal. Stones less than 2 cm may respond well to extracorporeal shock wave lithotripsy (ESWL). For larger stones, percutaneous lithotomy, with or without ESWL, is the preferred surgical intervention.[186] Stone fragments should be cultured and bacteria-specific antibiotics used until urine cultures remain sterile for 3 consecutive months. Surveillance cultures should be continued for a year.[187] Adjunctive medical therapies include urease inhibitors and chemolysis. Urease inhibitors such as acetohydroxamic acid are effective in inhibiting urease and can retard the growth of struvite stones and prevent new stone formation[188,189] but are limited by their side effects and use in patients with renal failure. Chemolysis—the irrigation of the kidney through a nephrostomy tube or ureter with a solution used to dissolve the stones—is currently rarely used because of the significant severe side effects[190,191] and might only be useful in patients with residual disease that cannot be cleared surgically.

Cystine Stones

About 1−2% of all kidney stones are composed of cystine. This genetic disorder of amino acid transport across the tubular membrane leads to reduced proximal tubular reabsorption of cystine from the filtrate and excess urine excretion of this sparingly soluble amino acid.[192,193] Normally, the daily volume of urine is adequate to keep the typical urinary cystine excretion of about 50 mg/day in solution. Patients with cystinuria

produce 250–1000 mg of cystine, which is exceedingly difficult to keep in solution, resulting in crystal and stone formation.[194] Cystine solubility rises markedly when urine pH is greater than 6.5. Because of their sulfur content, these stones are radio-opaque. Cystine stones should be suspected in patients with staghorn calculi. Visualization of the pathognomonic hexagonal crystals in urine (Figure 67.4) supports this diagnosis. Treatment is directed at increasing urine volume to 4 L/day, lowering urine sodium[195] and dietary protein intake,[196] and urinary alkalinization with potassium bicarbonate or acetazolamide.[179] d-Penicillamine[197,198] or tiopronin,[199,200] which form soluble heterodimers with cysteine and thereby reduce the cystine available for crystallization, may also be utilized. However, both these medications can produce similar side effects of loss of taste, fever, proteinuria, serum sickness reactions, and even nephrotic syndrome. Thus these drugs are added if stone formation continues despite conservative measures such as increasing fluids, dietary changes, and alkalinization.

CONCLUSIONS

Kidney stones are a cause of significant morbidity worldwide. After the initial episode a metabolic evaluation to search for the underlying causes is recommended in most patients, and especially in those with risk factors such as a family history of kidney stones, history of bowel surgery, or laboratory abnormalities that suggest other diagnoses. Most stones in patients in the US are calcium based. Kidney stones may lead to CKD, but because the incidence of recurrent stone formation decreases with progressive CKD, they may be underrecognized as a cause. Dietary modifications to increase fluid intake, reduce salt and animal protein intake, and encourage consumption of an age- and gender-appropriate amount of calcium, preferably from dairy, and not supplements may be recommended therapies. Restriction of oxalate rich foods is also utilized to reduce recurrence rates. Determination of urinary supersaturation and analysis of any passed stones guide treatment. Measures to reduce urinary supersaturation are highly effective in lowering recurrent stone formation. Reduced urinary pH is found in most patients with uric acid stones, and patients benefit from an increase in urinary pH. Targeted medical therapy can be initiated once a metabolic abnormality is found. Medications used to prevent stone recurrence are well tolerated and highly effective. Thiazide diuretics are a cornerstone of therapy in patients who form calcium-containing kidney stones. Potassium citrate is also highly effective in reducing recurrent stone formation.

References

1. Brener ZZ, Winchester JF, Salman H, Bergman M. Nephrolithiasis: evaluation and management. *South Med J* 2011;**104**(2):133–9.
2. Chen W, Monk RD, Bushinsky DA. Nephrolithiasis and nephrocalcinosis. In: Freehally, Floege, Tonelli, Johnson, editors. *Comprehensive clinical nephrology*. Edinburgh: Elsevier; 2019.
3. Saigal CS, Joyce G, Timilsina AR. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? *Kidney Int* 2005;**68**(4):1808–14.
4. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. *J Am Med Assoc* 2005;**293**(4):455–62.
5. Bushinsky DA. Nephrolithiasis. *J Am Soc Nephrol* 1998;**9**(5): 917–24.
6. Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. *N Engl J Med* 1992;**327**(16):1141–52.
7. Stamatelou KK, F ME, Jones CA. Time trends in reported prevalence of kidney stones in the United States. *Kidney Int* 2003;**63**: 1817–23.
8. Soucie JM, T MJ, Coates RJ. Demographic and geographic variability of kidney stones in the United States. *Kidney Int* 1994;**46**: 893–9.
9. Ding J. Childhood urinary stones induced by melamine-tainted formula: how much we know, how much we don't know. *Kidney Int* 2009;**75**(8):780–2.
10. Alexander RT, Hemmelgarn BR, Wiebe N, et al. Kidney stones and kidney function loss: a cohort study. *Br Med J* 2012;**345**.
11. Gillen DL, Worcester EM, Coe FL. Decreased renal function among adults with a history of nephrolithiasis: a study of NHANES III. *Kidney Int* 2005;**67**(2):685–90.
12. Coe FL. Recurrence of renal stones. *Lancet* 1980;**1**(8169):651.
13. Ferraro PM, Curhan GC, D'Addessi A, Gambaro G. Risk of recurrence of idiopathic calcium kidney stones: analysis of data from the literature. *J Nephrol* 2017;**30**(2):227–33.
14. Liu Y, Li S, Zeng Z, Wang J, Xie L, Li T, He Y, Qin X, Zhao J. Kidney stones and cardiovascular risk: a meta-analysis of cohort studies. *Am J Kidney Dis.* 2014;**64**(3):402–10. https://doi.org/10.1053/j.ajkd.2014.03.017. Epub 2014 May 5.
15. Sakhaee K, Maalouf NM, Kumar R, Pasch A, Moe OW. Nephrolithiasis-associated bone disease: pathogenesis and treatment options. *Kidney Int* 2011;**79**(4):393–403.
16. Stankus N, Hammes M, Gillen D, Worcester E. African American ESRD patients have a high pre-dialysis prevalence of kidney stones compared to NHANES III. *Urol Res* 2007;**35**(2):83–7.
17. Bushinsky DA, Coe FL, Moe OW. Nephrolithiasis. In: Brenner BM, editor. *The kidney*. 9th ed. Philadelphia: W.B. Saunders; 2012. p. 1455–507.
18. Evan A, Lingeman J, Coe FL, Worcester E. Randall's plaque: pathogenesis and role in calcium oxalate nephrolithiasis. *Kidney Int* 2006;**69**(8):1313–8.
19. Pak CY, Odvina CV, Pearle MS, et al. Effect of dietary modification on urinary stone risk factors. *Kidney Int* 2005;**68**(5):2264–73.
20. Moe OW, Preisig PA. Hypothesizing on the evolutionary origins of salt-induced hypercalciuria. *Curr Opin Nephrol Hypertens* 2005;**14**(4):368–72.
21. Breslau NA, Pak CY. Endocrine aspects of nephrolithiasis. *Special Top Endocrinol Metab* 1982;**3**:57–86.
22. Breslau NA. Pathogenesis and management of hypercalciuric nephrolithiasis. *Miner Electrol Metabol* 1994;**20**(6):328–39.
23. Rotily M, Leonetti F, Iovanna C, et al. Effects of low animal protein or high-fiber diets on urine composition in calcium nephrolithiasis. *Kidney Int* 2000;**57**(3):1115–23.
24. Liebman SE, Taylor JG, Bushinsky DA. Uric acid nephrolithiasis. *Curr Rheumatol Rep* 2007;**9**(3):251–7.
25. Pearle MS. Prevention of nephrolithiasis. *Curr Opin Nephrol Hypertens* 2001;**10**(2):203–9.

26. Mehandru S, Goldfarb DS. Nephrolithiasis complicating treatment of diabetes insipidus. *Urol Res* 2005;**33**(3):244–6.
27. Goldfarb S. The role of diet in the pathogenesis and therapy of nephrolithiasis. *Endocrinol Metab Clin N Am* 1990;**19**(4):805–20.
28. Fink HA, Wilt TJ, Eidman KE, et al. Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians Clinical Guideline. *Ann Intern Med* 2013;**158**(7):535–43.
29. Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Giannini A. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. *J Urol* 1996;**155**(3):839–43.
30. Hiatt RA, E B, Caan B, Quesenberry Jr CP, Duncan D, Citron JT. Randomized controlled trial of a low animal protein, high fiber diet in the prevention of recurrent calcium oxalate kidney stones. *Am J Epidemiol* 1996;**144**(1):25.
31. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. Family history and risk of kidney stones. *J Am Soc Nephrol* 1997;**8**(10):1568–73.
32. Asplin JR, Coe FL. Hyperoxaluria in kidney stone formers treated with modern bariatric surgery. *J Urol* 2007;**177**(2):565–9.
33. Duffey BG, P R, Makhlouf A, Kriedberg C, Stessman M, Hinck B, Ikramuddin S, Kellogg T, Slusarek B, Monga M. Roux-en-Y gastric bypass is associated with early increased risk factors for development of calcium oxalate nephrolithiasis. *J Am Coll Surg* 2008;**206**(3).
34. Kopp JB, Miller KD, Mican JA, et al. Crystalluria and urinary tract abnormalities associated with indinavir. *Ann Intern Med* 1997;**127**(2):119–25.
35. Clayman RV. Crystalluria and urinary tract abnormalities associated with indinavir. *J Urol* 1998;**160**(2):633.
36. Avci Z, Koktener A, Uras N, et al. Nephrolithiasis associated with ceftriaxone therapy: a prospective study in 51 children. *Arch Dis Child* 2004;**89**(11):1069–72.
37. Daudon M, Traxer O, Conort P, Lacour B, Jungers P. Type 2 diabetes increases the risk for uric acid stones. *J Am Soc Nephrol* 2006;**17**(7):2026–33.
38. Abate N, Chandalia M, Cabo-Chan AV, Moe OW, Sakhaee K. The metabolic syndrome and uric acid nephrolithiasis: novel features of renal manifestation of insulin resistance. *Kidney Int* 2004;**65**(2):386–92.
39. Taylor EN, Curhan GC. Fructose consumption and the risk of kidney stones. *Kidney Int* 2008;**73**(2):207–12.
40. Zhang Y, Fang X, Xu H, Shen Q. Genetic analysis of Dent's disease and functional research of CLCN5 mutations. *DNA Cell Biol* 2017;**36**(12):1151–8.
41. Blanchard A, Curis E, Guyon-Roger T, et al. Observations of a large Dent disease cohort. *Kidney Int* 2016;**90**(2):430–9.
42. Anglani F, D'Angelo A, Bertizzolo LM, et al. Nephrolithiasis, kidney failure and bone disorders in Dent disease patients with and without CLCN5 mutations. *SpringerPlus* 2015;**4**:492.
43. Scheinman SJ, Guay-Woodford LM, Thakker RV, Warnock DG. Genetic disorders of renal electrolyte transport. *N Engl J Med* 1999;**340**:1177–87.
44. Thakker RV. Pathogenesis of Dent's disease and related syndromes of X-linked nephrolithiasis. *Kidney Int* 2000;**57**:787–93.
45. Coe FL, Evan A, Worcester E. Kidney stone disease. *J Clin Investig* 2005;**115**(10):2598–608.
46. Sayer JA, Carr G, Simmons NL. Nephrocalcinosis: molecular insights into calcium precipitation within the kidney. *Clin Sci* 2004;**106**:549–61.
47. Godron A, Harambat J, Boccio V, et al. Familial hypomagnesemia with hypercalciuria and nephrocalcinosis: phenotype-genotype correlation and outcome in 32 patients with CLDN16 or CLDN19 mutations. *Clin J Am Soc Nephrol* 2012;**7**(5):801–9.
48. Stechman MJ, Loh NY, Thakker RV. Genetics of hypercalciuric nephrolithiasis: renal stone disease. *Acad Sci* 2007;**1116**:461–84.
49. Edvardsson VO, Goldfarb DS, Lieske JC, et al. Hereditary causes of kidney stones and chronic kidney disease. *Pediatr Nephrol* 2013;**28**(10):1923–42.
50. Gambaro G, Croppi E, Coe F, et al. Metabolic diagnosis and medical prevention of calcium nephrolithiasis and its systemic manifestations: a consensus statement. *J Nephrol* 2016;**29**(6):715–34.
51. Gomez J, Gil-Pena H, Santos F, et al. Primary distal renal tubular acidosis: novel findings in patients studied by next-generation sequencing. *Pediatr Res* 2018;**83**(1–1):190.
52. Santos F, Gil-Pena H, Alvarez-Alvarez S. Renal tubular acidosis. *Curr Opin Pediatr* 2017;**29**(2):206–10.
53. Moe OW, Bonny O. Genetic hypercalciuria. *J Am Soc Nephrol* 2005;**16**(3):729–45.
54. Nicoletta JA, Schwartz GJ. Distal renal tubular acidosis. *Curr Opin Pediatr* 2004;**16**:194–8.
55. Lim AK, Choi MJ. Distal renal tubular acidosis associated with Sjogren syndrome. *Intern Med J* 2013;**43**(12):1330–4.
56. Batlle D, Haque SK. Genetic causes and mechanisms of distal renal tubular acidosis. *Nephrol Dial Transplant* 2012;**27**(10):3691–704.
57. Dasgupta D, Wee MJ, Reyes M, et al. Mutations in SLC34A3/NPT2c are associated with kidney stones and nephrocalcinosis. *J Am Soc Nephrol* 2014;**25**(10):2366–75.
58. Bergwitz C, Roslin NM, Tieder M, et al. SLC34A3 mutations in patients with hereditary hypophosphatemic rickets with hypercalciuria predict a key role for the sodium-phosphate cotransporter NaP i -IIc in maintaining phosphate homeostasis. *Am J Hum Genet* 2006;**78**(2):179–92.
59. Levi M, Blaine J, Breusegem S, Takahashi H, Sorribas V, Barri N. Renal phosphate-wasting disorders. *Adv Chron Kidney Dis* 2006;**13**:155–65.
60. Fujiwara M, Namba N, Ozono K, Arisaka O, Yokoya S, Committee on Drugs JSfPE. Treatment of hypophosphatemic rickets with phosphate and active vitamin D in Japan: a questionnaire-based survey. *Clin Pediatr Endocrinol* 2013;**22**(1):9–14.
61. Arcidiacono T, Mingione A, Macrina L, Pivari F, Soldati L, Vezzoli G. Idiopathic calcium nephrolithiasis: a review of pathogenic mechanisms in the light of genetic studies. *Am J Nephrol* 2014;**40**(6):499–506.
62. Moe OW, Bushinsky DA. Genetic hypercalciuria: a major risk factor in kidney stones. In: Thakker RV, Whyte MP, Eisman JA, Igarashi T, editors. *Genetics of bone biology and skeletal disease*. London, UK: Elsevier; 2013. p. 585–604.
63. Lieske JC, Turner ST, Edeh SN, Smith JA, Kardia SLR. Heritability of urinary traits that contribute to nephrolithiasis. *Clin J Am Soc Nephrol* 2014;**9**(5):943–50.
64. Frick KK, Bushinsky DA. Molecular mechanisms of primary hypercalciuria. *J Am Soc Nephrol* 2003;**14**:1082–95.
65. Letavernier E, Kauffenstein G, Huguet L, Navasiolava N, Bouderlique E, Tang E, Delaitre L, Bazin D, de Frutos M, Gay C, Perez J, Verpont MC, Haymann JP, Pomozi V, Zoll J, Le Saux O, Daudon M, Leftheriotis G, Martin L. ABCC6 deficiency promotes development of Randall plaque. *J Am Soc Nephrol* 2018;**29**(9):2337–47. https://doi.org/10.1681/ASN.2017101148. Epub 2018 July 10.
66. Sigel A, Schrott KM, Breun H, Heger D. Staghorn calculus disease of the kidney - classification of 105 cases and review of literature. *Urol Ausg A* 1986;**25**(2):101–8.
67. Elton TJ, Roth CS, Berquist TH, Silverstein MD. A clinical prediction rule for the diagnosis of ureteral calculi in emergency departments. *J Gen Intern Med* 1993;**8**(2):57–62.
68. Kobayashi T, Nishizawa K, Mitsumori K, Ogura K. Impact of date of onset on the absence of hematuria in patients with acute renal colic. *J Urol* 2003;**170**(4 Pt 1):1093–6.
69. Stapleton FB, Roy 3rd S, Noe HN, Jerkins G. Hypercalciuria in children with hematuria. *N Engl J Med* 1984;**310**(21):1345–8.

70. Teichman JM, Long RD, Hulbert JC. Long-term renal fate and prognosis after staghorn calculus management. *J Urol* 1995; **153**(5):1403–7.
71. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006; **354**(7):669–83.
72. Gimpel C, Krause A, Franck P, Krueger M, von SC. Exposure to furosemide as the strongest risk factor for nephrocalcinosis in preterm infants. *Pediatr Int* 2010;**52**(1):51–6.
73. Schell-Feith EA, Kist-van Holthe JE, Conneman N, et al. Etiology of nephrocalcinosis in preterm neonates: association of nutritional intake and urinary parameters. *Kidney Int* 2000;**58**(5):2102–10.
74. Keith MP, Gilliland WR. Updates in the management of gout. *Am J Med* 2007;**120**(3):221–4.
75. Daudon M, Jungers P. Drug-induced renal calculi: epidemiology, prevention and management. *Drugs* 2004;**64**:245–75.
76. Taylor EN, Curhan GC. Determinants of 24-hour urinary oxalate excretion. *Clin J Am Soc Nephrol* 2008;**3**(5):1453–60.
77. Lemann Jr J, Pleuss JA, Worcester EA, Hornick L, Schrab D, Hoffman RG. Urinary oxalate excretion increases with body size and decreases with increasing dietary calcium intake among healthy adults. *Kidney Int* 1996;**49**(1):200–8 [Erratum: Kidney Int: 50:341,1996].
78. Borghi L, Schianchi T, Meschi T, et al. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. *N Engl J Med* 2002;**346**(2):77–84.
79. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med* 1993;**328**(12):833–8.
80. Chuang CK, Lai MK, Chang PL, et al. Xanthogranulomatous pyelonephritis: experience in 36 cases. *J Urol* 1992;**147**(2):333–6.
81. Ammerman S, Shafer MA, Snyder D. Ectopic pregnancy in adolescents: a clinical review for pediatricians. *J Pediatr* 1990;**117**(5): 677–86.
82. Yamamoto W, K H, Maekawa M, Fukui T. The relationship between abdominal pain regions and specific diseases: an epidemiologic approach to clinical practice. *J Epidemiol* 1997;**7**(1).
83. Weisberg LS, Bloom PB, Simmons RL, Viner ED. Loin pain hematuria syndrome. *Am J Nephrol* 1993;**13**(4):229–37.
84. Dube GK, Hamilton SE, Ratner LE, Nasr SH, Radhakrishnan J. Loin pain hematuria syndrome. *Kidney Int* 2006;**70**(12):2152–5.
85. Sarma DP, Deiparine EM, Weilbaecher TG. Partially calcified renal cell carcinoma mimicking renal calculus. *J La State Med Soc* 1990; **142**(1):24–6.
86. Stevens RJ, Werthammer S, Pearson JS. Renal papillary necrosis complicating diabetes mellitus; a review of the literature with case report. *W Va Med J* 1948;**44**(1):12–5.
87. Jung DC, Kim SH, Jung SI, Hwang SI. Renal papillary necrosis: review and comparison of findings at multi-detector row CT and intravenous urography. *Radiographics* 2006;**26**(6):1827–36.
88. Levine JA, Neitlich J, Verga M, Dalrymple N, Smith RC. Ureteral calculi in patients with flank pain: correlation of plain radiography with unenhanced helical CT. *Radiology* 1997;**204**(1):27–31.
89. Niall O, Russell J, MacGregor R, Duncan H, Mullins J. A comparison of noncontrast computerized tomography with excretory urography in the assessment of acute flank pain. *J Urol* 1999;**161**(2):534–7.
90. Brisbane W, Bailey MR, Sorensen MD. An overview of kidney stone imaging techniques. *Nat Rev Urol* 2016;**13**(11):654–62.
91. Smith-Bindman R, Aubin C, Bailitz J, et al. Ultrasonography versus computed tomography for suspected nephrolithiasis. *N Engl J Med* 2014;**371**(12):1100–10.
92. Metzler IS, Smith-Bindman R, Moghadassi M, Wang RC, Stoller ML, Chi T. Emergency department imaging modality effect on surgical management of nephrolithiasis: a multicenter, randomized clinical trial. *J Urol* 2017;**197**(3, Part 1):710–4.
93. Dalrymple NC, Verga M, Anderson KR, et al. The value of unenhanced helical computerized tomography in the management of acute flank pain. *J Urol* 1998;**159**(3):735–40.
94. Worster A, Preyra I, Weaver B, Haines T. The accuracy of noncontrast helical computed tomography versus intravenous pyelography in the diagnosis of suspected acute urolithiasis: a meta-analysis. *Ann Emerg Med* 2002;**40**(3):280–6.
95. Mostafavi MR, Ernst RD, Saltzman B. Accurate determination of chemical composition of urinary calculi by spiral computerized tomography. *J Urol* 1998;**159**(3):673–5.
96. Ha M, MacDonald RD. Impact of CT scan in patients with first episode of suspected nephrolithiasis. *J Emerg Med* 2004;**27**(3): 225–31.
97. Schwartz BF, Schenkman N, Armenakas NA, Stoller ML. Imaging characteristics of indinavir calculi. *J Urol* 1999;**161**(4):1085–7.
98. Keddis MT, Rule AD. Nephrolithiasis and loss of kidney function. *Curr Opin Nephrol Hypertens* 2013;**22**(4):390–6.
99. Vupputuri S, Soucie JM, McClellan W, Sandler DP. History of kidney stones as a possible risk factor for chronic kidney disease. *Ann Epidemiol* 2004;**14**(3):222–8.
100. El-Zoghby ZM, Lieske JC, Foley RN, et al. Urolithiasis and the risk of ESRD. *Clin J Am Soc Nephrol* 2012;**7**(9):1409–15.
101. Jungers P, Joly D, Barbey F, Choukroun G, Daudon M. Nephrolithiasis-induced ESRD: frequency, causes and prevention. *Néphrol Thérapeutique* 2005;**1**(5):301–10.
102. Jungers P, Joly D, Barbey F, Choukroun G, Daudon M. ESRD caused by nephrolithiasis: prevalence, mechanisms, and prevention. *Am J Kidney Dis* 2004;**44**(5):799–805.
103. Worcester E, Parks JH, Josephson MA, Thisted RA, Coe FL. Causes and consequences of kidney loss in patients with nephrolithiasis. *Kidney Int* 2003;**64**(6):2204–13.
104. Gaudio KM, S N, Hayslett JP, Kashgarian M. Renal perfusion and intratubular pressures during ureteral occlusion in rat. *Am J Physiol* 1980;**238**:(F)205–209.
105. Klahr S. Urinary tract obstruction. *Semin Nephrol* 2001;**21**:133–45.
106. Bander SJ, Buerkert JE, Martin D, Klahr S. Long-Term effects of 24-hr unilateral ureteral obstruction on renal-function in the rat. *Kidney Int* 1985;**28**(4):614–20.
107. Evan AP, Lingeman JE, Coe FL, et al. Crystal-associated nephropathy in patients with brushite nephrolithiasis. *Kidney Int* 2005; **67**(2):576–91.
108. Boonla C, Krieglstein K, Bovornpadungkitti S, et al. Fibrosis and evidence for epithelial-mesenchymal transition in the kidneys of patients with staghorn calculi. *BJU Int* 2011;**108**(8):1336–45.
109. Evan AP, Coe FL, Lingeman JE, et al. Renal crystal deposits and histopathology in patients with cystine stones. *Kidney Int* 2006; **69**(12):2227–35.
110. Craver L, Marco MP, Martinez I, et al. Mineral metabolism parameters throughout chronic kidney disease stages 1-5 – achievement of K/DOQI target ranges. *Nephrol Dial Transplant* 2007;**22**(4): 1171–6.
111. Marangella M, Bruno M, Cosseddu D, et al. Prevalence of chronic renal-insufficiency in the course of idiopathic recurrent calcium stone disease – risk-factors and patterns of progression. *Nephron* 1990;**54**(4):302–6.
112. Holdgate A, Pollock T. Systematic review of the relative efficacy of non-steroidal anti-inflammatory drugs and opioids in the treatment of acute renal colic. *BMJ* 2004;**328**(7453):1401.
113. Safdar B, Degutis LC, Landry K, Vedere SR, Moscovitz HC, D'Onofrio G. Intravenous morphine plus ketorolac is superior to either drug alone for treatment of acute renal colic. *Ann Emerg Med* 2006;**48**(2):173–81.
114. Teichman JM. Clinical practice. Acute renal colic from ureteral calculus. *N Engl J Med* 2004;**350**(7):684–93.
115. Knorr PA, Woodside JR. Large perirenal hematoma after extracorporeal shock-wave lithotripsy. *Urology* 1990;**35**(2):151–3.

116. Lingeman JE, Siegel YI, Steele B, Nyhuis AW, Woods JR. Management of lower pole nephrolithiasis: a critical analysis. *J Urol* 1994; **151**(3):663–7.
117. Miller OF, Kane CJ. Time to stone passage for observed ureteral calculi: a guide for patient education. *J Urol* 1999;**162**(3):688–90.
118. Coll DM, Varanelli MJ, Smith RC. Relationship of spontaneous passage of ureteral calculi to stone size and location as revealed by unenhanced helical CT. *Am J Roentgenol* 2002;**178**(1):101–3.
119. Ueno A, Kawamura T, Ogawa A, Takayasu H. Relation of spontaneous passage of ureteral calculi to size. *Urology* 1977; **10**(6):544–6.
120. Campschroer T, Zhu X, Vernooij RW, Lock MT. Alpha-blockers as medical expulsive therapy for ureteral stones. *Cochrane Database Syst Rev* 2018;**4**:CD008509.
121. Wang RC, Smith-Bindman R, Whitaker E, et al. Effect of tamsulosin on stone passage for ureteral stones: a systematic review and meta-analysis. *Ann Emerg Med* 2017;**69**(3):353–61. e3.
122. Liu XJ, Wen JG, Wan YD, Hu BW, Wang QW, Wang Y. Role of silodosin as medical expulsive therapy in ureteral calculi: a meta-analysis of randomized controlled trials. *Urolithiasis* 2018;**46**(2): 211–8.
123. Parmar MS. Kidney stones. *BMJ* 2004;**328**(7453):1420–4.
124. Portis AJ, Sundaram CP. Diagnosis and initial management of kidney stones. *Am Fam Physician* 2001;**63**(7):1329–38.
125. Hess B, Hasler-Strub U, Ackermann D, Jaeger P. Metabolic evaluation of patients with recurrent idiopathic calcium nephrolithiasis. *Nephrol Dial Transplant* 1997;**12**(7):1362–8.
126. Uribarri J, Oh MS, Carroll HJ. The first kidney stone. *Ann Intern Med* 1989;**111**(12):1006–9.
127. Sutherland JW, Parks JH, Coe FL. Recurrence after a single renal stone in a community practice. *Miner Electrol Metabol* 1985;**11**(4): 267–9.
128. Parks JH, Coward M, Coe FL. Correspondence between stone composition and urine supersaturation in nephrolithiasis. *Kidney Int* 1997;**51**(3):894–900.
129. Pak CY, Sakhaee K, Crowther C, Brinkley L. Evidence justifying a high fluid intake in treatment of nephrolithiasis. *Ann Intern Med* 1980;**93**(1):36–9.
130. Sakhaee K, Harvey JA, Padalino PK, Whitson P, Pak CY. The potential role of salt abuse on the risk for kidney stone formation. *J Urol* 1993;**150**(2 Pt 1):310–2.
131. Reddy ST, Wang CY, Sakhaee K, Brinkley L, Pak CY. Effect of low-carbohydrate high-protein diets on acid-base balance, stone-forming propensity, and calcium metabolism. *Am J Kidney Dis* 2002;**40**(2):265–74.
132. Lemann Jr J, Bushinsky DA, Hamm LL. Bone buffering of acid and base in humans. *Am J Physiol Renal Physiol* 2003;**285**(5):F811–32.
133. Hamm LL. Renal handling of citrate. *Kidney Int* 1990;**38**(4): 728–35.
134. Stauffer JQ. Hyperoxaluria and intestinal disease. The role of steatorrhea and dietary calcium in regulating intestinal oxalate absorption. *Am J Dig Dis* 1977;**22**(10):921–8.
135. Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ. Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. *Ann Intern Med* 1997;**126**(7):497.
136. Krieger NS, Bushinsky DA. The relation between bone and stone formation. *Calcif Tissue Int* 2013;**93**(4):374–81.
137. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. *Dietary reference intakes for calcium and vitamin D*; 2011. Washington (DC).
138. Frick KK, Krieger NS, Bushinsky DA. Modeling hypercalciuria in the genetic hypercalciuric stone-forming rat. *Curr Opin Nephrol Hypertens* 2015;**24**(4):336–44.
139. Bushinsky DA, LaPlante K, Asplin JR. Effect of cinacalcet on urine calcium excretion and supersaturation in genetic hypercalciuric stone-forming rats. *Kidney Int* 2006;**69**:1586–92.
140. Lemann Jr J. Pathogenesis of idiopathic hypercalciuria and nephrolithiasis. In: Coe FL, Favus MJ, editors. *Disorders of bone and mineral metabolism*. New York: Raven Press, Ltd.; 1992. p. 685–706.
141. Pak CYC, Ohata M, Lawrence EC, Snyder W. The hypercalciurias: causes, parathyroid functions, and diagnostic criteria. *J Clin Invest* 1974;**54**:387–400.
142. Coe FL, Favus MJ, Crockett T, et al. Effects of low-calcium diet on urine calcium excretion, parathyroid function and serum $1,25(OH)_2D_3$ levels in patients with idiopathic hypercalciuria and in normal subjects. *Am J Med* 1982;**72**:25–32.
143. Freundlich M, Alonzo E, Bellorin-Font E, Weisinger JR. Reduced bone mass in children with idiopathic hypercalciuria and in their asymptomatic mothers. *Nephrol Dial Transplant* 2002;**17**(8): 1396–401.
144. Monk RD, Bushinsky DA. Pathogenesis of idiopathic hypercalciuria. In: Coe F, Favus M, Pak C, Parks J, Preminger G, editors. *Kidney stones: medical and surgical management*. Philadelphia: Lippincott-Raven; 1996. p. 759–72.
145. Asplin JR, Bauer KA, Kinder J, et al. Bone mineral density and urine calcium excretion among subjects with and without nephrolithiasis. *Kidney Int* 2003;**63**:662–9.
146. Borghi L, Meschi T, Guerra A, Novarini A. Randomized prospective-study of a nonthiazide diuretic, indapamide, in preventing calcium stone recurrences. *J Cardiovasc Pharmacol* 1993; **22**:S78–86.
147. Laerum E, Larsen S. Thiazide prophylaxis of urolithiasis - a double-blind-study in general-practice. *Urol Res* 1984;**12**(1):42.
148. Herings RM, Stricker BH, de Boer A, Bakker A, Sturmans F, Stergachis A. Current use of thiazide diuretics and prevention of femur fractures. *J Clin Epidemiol* 1996;**49**(1):115–9.
149. Aung K, Htay T. Thiazide diuretics and the risk of hip fracture. *Cochrane Database Syst Rev* 2011;**10**:CD005185.
150. Alon U, Costanzo LS, Chan JC. Additive hypocalciuric effects of amiloride and hydrochlorothiazide in patients treated with calcitriol. *Miner Electrol Metabol* 1984;**10**(6):379–86.
151. Liebman M, Costa G. Effects of calcium and magnesium on urinary oxalate excretion after oxalate loads. *J Urol* 2000;**163**(5): 1565–9.
152. Obialo CI, Clayman RV, Matts JP, et al. Pathogenesis of nephrolithiasis post-partial ileal bypass surgery: case-control study. The POSCH Group. *Kidney Int* 1991;**39**(6):1249–54.
153. Nelson WK, Houghton SG, Milliner DS, Lieske JC, Sarr MG. Enteric hyperoxaluria, nephrolithiasis, and oxalate nephropathy: potentially serious and unappreciated complications of Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2005;**1**(5):481–5.
154. Hassan I, Juncos LA, Milliner DS, Sarmiento JM, Sarr MG. Chronic renal failure secondary to oxalate nephropathy: a preventable complication after jejunoileal bypass. *Mayo Clin Proc* 2001;**76**(7):758–60.
155. Cochat P, Rumsby G. Primary hyperoxaluria. *N Engl J Med* 2013; **369**(7):649–58.
156. Falk N, Castillo B, Gupta A, McKelvy B, Bhattacharjee M, Papasozomenos S. Primary hyperoxaluria type 1 with systemic calcium oxalate deposition: case report and literature review. *Ann Clin Lab Sci* 2013;**43**(3):328–31.
157. Milliner DS, Eickholt JT, Bergstralh EJ, Wilson DM, Smith LH. Results of long-term treatment with orthophosphate and pyridoxine in patients with primary hyperoxaluria. *N Engl J Med* 1994; **331**(23):1553–8.
158. Bastani B, Mistry BM, Nahass GT, Joh J, Dundoo G, Solomon H. Oxalate kinetics and reversal of the complications after orthotopic liver transplantation in a patient with primary hyperoxalosis type 1 awaiting renal transplantation. *Am J Nephrol* 1999;**19**(1):64–9.
159. Cochat P, Basmaison O. Current approaches to the management of primary hyperoxaluria. *Arch Dis Child* 2000;**82**(6):470–3.

160. Phillips R, Hanchanale VS, Myatt A, Somani B, Nabi G, Biyani CS. Citrate salts for preventing and treating calcium containing kidney stones in adults. *Cochrane Database Syst Rev* 2015;**10**: CD010057.
161. Curhan GC, Taylor EN. 24-H uric acid excretion and the risk of kidney stones. *J Urol* 2009;**181**(4):1721.
162. Barcelo P, Wuhl O, Servitge E, Rousaud A, Pak CYC. Randomized double-blind-study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J Urol* 1993;**150**(6):1761–4.
163. Ettinger B, Pak CYC, Citron JT, Thomas C, AdamsHuet B, Vangessel A. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J Urol* 1997;**158**(6):2069–73.
164. Kwak C, Park HK, Jeong BC, Kim HK, Kim EC, Kim HH. Correlation between urinary oxalate levels and the reduced colonization of the enteric bacterium oxalobacter formigenes in patients with calcium oxalate urolithiasis. *J Urol* 2003;**169**(4):328.
165. Kwak C, Kim HK, Kim EC, Choi MS, Kim HH. Urinary oxalate levels and the enteric bacterium Oxalobacter formigenes in patients with calcium oxalate urolithiasis. *Eur Urol* 2003;**44**(4):475–81.
166. Lieske JC, T W, De Simone C, O'Connor HM, Li X, Bergstralh EJ, Goldfarb DS. Diet, but not oral probiotics, effectively reduces urinary oxalate excretion and calcium oxalate supersaturation. *Kidney Int* 2010;**78**(11):1178–85.
167. Kharlamb V, Schelker J, Francois F, Jiang JQ, Holmes RP, Goldfarb DS. Oral antibiotic treatment of *Helicobacter pylori* leads to persistently reduced intestinal colonization rates with oxalobacter formigenes. *J Endourol* 2011;**25**(11):1781–5.
168. Coe FL. Hyperuricosuric calcium oxalate nephrolithiasis. *Adv Exp Med Biol* 1980;**128**:439–50.
169. Coe FL, Parks JH. Hyperuricosuria and calcium nephrolithiasis. *Urol Clin* 1981;**8**(2):227–44.
170. Coe FL. Uric acid and calcium oxalate nephrolithiasis. *Kidney Int* 1983;**24**(3):392–403.
171. Pak CY, Sakhaee K, Peterson RD, Poindexter JR, Frawley WH. Biochemical profile of idiopathic uric acid nephrolithiasis. *Kidney Int* 2001;**60**(2):757–61.
172. Sakhaee K, Adams-Huet B, Moe OW, Pak CY. Pathophysiologic basis for normouricosuric uric acid nephrolithiasis. *Kidney Int* 2002;**62**(3):971–9.
173. Negri AL, Spivacow R, Del Valle E, et al. Clinical and biochemical profile of patients with "pure" uric acid nephrolithiasis compared with "pure" calcium oxalate stone formers. *Urol Res* 2007;**35**(5): 247–51.
174. Pak CYC, Poindexter JR, Peterson RD, Koska J, Sakhaee K. Biochemical distinction between hyperuricosuric calcium urolithiasis and gouty diathesis. *Urology* 2002;**60**(5):789–94.
175. Cameron MA, Maalouf NM, Adams-Huet B, Moe OW, Sakhaee K. Urine composition in type 2 diabetes: predisposition to uric acid nephrolithiasis. *J Am Soc Nephrol* 2006;**17**(5):1422–8.
176. Pak CYC, Sakhaee K, Fuller C. Successful management of uric-acid nephrolithiasis with potassium citrate. *Kidney Int* 1986; **30**(3):422–8.
177. Rodman JS. Prophylaxis of uric-acid stones with alternate day doses of alkaline potassium-salts. *J Urol* 1991;**145**(1):97–9.
178. Trinchieri A, Esposito N, Castelnuovo C. Dissolution of radiolucent renal stones by oral alkalinization with potassium citrate/potassium bicarbonate. *Arch Ital Urol Androl* 2009;**81**(3):188–91.
179. Sterrett SP, Penniston KL, Wolf Jr JS, Nakada SY. Acetazolamide is an effective adjunct for urinary alkalization in patients with uric acid and cystine stone formation recalcitrant to potassium citrate. *Urology* 2008;**72**(2):278–81.
180. Kenny JE, Goldfarb DS. Update on the pathophysiology and management of uric acid renal stones. *Curr Rheumatol Rep* 2010;**12**(2): 125–9.
181. Ettinger B, Tang A, Citron JT, Livermore B, Williams T. Randomized trial of allopurinol in the prevention of calcium oxalate calculi. *N Engl J Med* 1986;**315**(22):1386–9.
182. Tassaneeyakul W, Jantararoungtong T, Chen P, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. *Pharmacogenetics Genom* 2009;**19**(9):704–9.
183. Somkrua R, Eickman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC Med Genet* 2011;**12**:118.
184. Parks JH, Worcester EM, Coe FL, Evan AP, Lingeman JE. Clinical implications of abundant calcium phosphate in routinely analyzed kidney stones. *Kidney Int* 2004;**66**(2):777–85.
185. Kristensen C, Parks JH, Lindheimer M, Coe FL. Reduced glomerular filtration rate and hypercalciuria in primary struvite nephrolithiasis. *Kidney Int* 1987;**32**(5):749–53.
186. Preminger GM, Assimos DG, Lingeman JE, et al. Chapter 1: AUA guideline on management of staghorn calculi: diagnosis and treatment recommendations. *J Urol* 2005;**173**(6):1991–2000.
187. Wong HY, R CR, Griffith DP. Medical management and prevention of struvite stones. In: Coe FL, F MJ, Pak CYC, editors. *Kidney stones: medical and surgical management*. Philadelphia Lippincott-Raven; 1996. p. 941–50.
188. Griffith DP, Gleeson MJ, Lee H, Longuet R, Deman E, Earle N. Randomized, double-blind trial of Lithostat (acetohydroxamic acid) in the palliative treatment of infection-induced urinary calculi. *Eur Urol* 1991;**20**(3):243–7.
189. Williams JJ, Rodman JS, Peterson CM. A randomized double-blind study of acetohydroxamic acid in struvite nephrolithiasis. *N Engl J Med* 1984;**311**(12):760–4.
190. Bernardo NO, Smith AD. Chemolysis of urinary calculi. *Urol Clin* 2000;**27**(2):355–65.
191. Dormia E, Dormia G, Malagola G, Minervini S. Experience with instrumental chemolysis for urolithiasis. *J Urol* 2003;**170**(4 Pt 1): 1105–10.
192. Mattoo A, Goldfarb DS. Cystinuria. *Semin Nephrol* 2008;**28**(2): 181–91.
193. Stapleton FB. Childhood stones. *Endocrinol Metab Clin N Am* 2002; **31**(4):1001–15. ix.
194. Goodyer P. The molecular basis of cystinuria. *Nephron Exp Nephrol* 2004;**98**(2):e45–9.
195. Jaeger P, Portmann L, Saunders A, Rosenberg LE, Thier SO. Anticystinuric effects of glutamine and of dietary-sodium restriction. *N Engl J Med* 1986;**315**(18):1120–3.
196. Goldfarb DS, Coe FL, Asplin JR. Urinary cystine excretion and capacity in patients with cystinuria. *Kidney Int* 2006;**69**(6): 1041–7.
197. Singer A, Das S. Cystinuria: a review of the pathophysiology and management. *J Urol* 1989;**142**(3):669–73.
198. Worcester EM, Coe FL. Clinical practice. Calcium kidney stones. *N Engl J Med* 2010;**363**(10):954–63.
199. Pak CY, Fuller C, Sakhaee K, Zerwekh JE, Adams BV. Management of cystine nephrolithiasis with alpha-mercaptopropionylglycine. *J Urol* 1986;**136**(5):1003–8.
200. Lindell A, Denneberg T, Hellgren E, Jeppsson JO, Tiselius HG. Clinical course and cystine stone formation during tiopronin treatment. *Urol Res* 1995;**23**(2):111–7.

QUESTIONS AND ANSWERS

Question 1

Which of the following diets is associated with an increased risk of nephrolithiasis?

A. Low-sodium diet
B. Low-calcium diet
C. Low-oxalate diet
D. Low-protein diet
E. Low-purine diet

Answer: B

All other diets reduce the risk of stone formation except a low-calcium diet, which has been associated with increased risk of stone formation. Dietary calcium binds dietary oxalate in the intestine, which decreases oxalate absorption and excretion. Eating a low-calcium diet results in unbound oxalate in the intestine leading to increased absorption and hyperoxaluria.

Question 2

A 32-year-old female presents to the emergency department with a 3-hour history of right flank pain radiating to her groin. She has profound nausea, but denies dysuria, gross hematuria, diarrhea, or fever. She is not on any medications. On examination, she is restless from pain.

Her blood pressure is 146/79 mm Hg, heart rate is 98/min, and temperature is 37°C (98.6°F). She has some right costo-vertebral angle tenderness on exam but no abdominal guarding or rigidity. Bowel sounds are heard.

Labs reveal S[Na] 142 mEq/L, potassium 3.9 mEq/L, chloride 114 mEq/L, bicarbonate 26 mEq/L, blood urea 23 mg/dL, and S[Cr] of 0.9 mg/dL. Urinalysis shows a specific gravity of 1.025, 3+ blood, and no protein are noted on dipstick. Urine microscopy shows greater than 50 erythrocytes/hpf, 3–5 leukocytes/hpf, and occasional calcium oxalate crystals.

What is the optimal radiologic procedure at this time to assist in diagnosis?

A. Plain radiography of the abdomen
B. Intravenous pyelography
C. Abdominal Ultrasonography
D. Noncontrast spiral computed tomography

Answer: C

Abdominal ultrasound is a safe test for initial assessment of abdominal pain in young women of childbearing age. Although her presentation is suspicious for nephrolithiasis, gynecological conditions such as ectopic pregnancy, ovarian torsion, and abdominal conditions such as acute appendicitis are included in the differential. Ultrasound has a low sensitivity but a high specificity for nephrolithiasis. All other tests include some form of radiation that is best avoided until she has had a negative pregnancy test. The most sensitive and specific test, once pregnancy has been ruled out, is a noncontrast computed tomography.

Question 3

A 37-year-old man presents for evaluation of recurrent kidney stones. He has passed six stones during the past 2 years. He is currently asymptomatic. He was diagnosed with ulcerative colitis 12 years ago and underwent a partial bowel resection 6 years ago. Since then he has not had any flares and has not noticed blood or mucus in his stool. He is not on any medications at this time. There is no family history of renal stone disease.

On examination, the patient is comfortable and without distress. His blood pressure is 115/74 mm Hg, pulse is 72/min, and he is afebrile. The rest of his exam is unremarkable.

Laboratory results demonstrate: hemoglobin, 13.2 g/dL; hematocrit, 39%; leukocyte count, 7.4×10^9 cells/μL; blood urea nitrogen 18 mg/dL; S[Cr] 1.9 mg/dL; S[Na], 138 mEq/L; S[K], 3.7 mEq/L; serum chloride, 109 mEq/L; serum bicarbonate, 24 mEq/L; S[Ca], 9.8 mg/dL; serum phosphorus, 3.2 mg/dL; urinalysis: pH, 6.0, specific gravity, 1.020, trace hematuria, no proteinuria; arterial blood: pH, 7.42.

His 24-hour urine studies show urine volume 1.8 L, urine Ca 205 mg, urine Na 2300 mg, urine oxalate 98 mg, urine citrate 300, urine phosphorus 800 mg, and urine uric acid 600 mg. Plain abdominal radiography reveals a 6-mm stone in the left kidney and a 2-mm stone in the right renal pelvis.

What is the most likely cause of this patient's renal stone disease?

A. IH
B. Primary hyperparathyroidism
C. Distal renal tubular acidosis
D. Enteric hyperoxaluria

Answer: D

The patient has enteric hyperoxaluria. With a history of ulcerative colitis and partial bowel resection, his risk of hyperoxaluria is very high because of the shortened bowel loop. He is not hypercalciuric (urine Ca less than 250 mg) and hyperparathyroidism is not likely to be the cause because most patients with hyperparathyroidism are hypercalciuric. dRTA is again unlikely because of the absence of acidosis and hypokalemia.

Question 4

A 40-year-old woman presents to the ED complaining of acute abdominal pain. She "knows" it is a kidney stone because she had a similar episode of 6 months ago when she passed a stone. At that time she was treated with narcotics and, following passage of the stone, was told that she did not need any intervention because in the absence of a family history and a normal laboratory workup her risk of recurrence was low. She was advised to increase her fluid intake. Other than a history of back pain for which she takes an occasional Ibuprofen she is otherwise healthy. In the ED, her vital signs are stable, and examination is unrevealing except for a young woman in mild distress.

Her laboratory results show: hemoglobin, 12 g/dL; leukocyte count, 11.4×10^9 cells/μL; S[Cr] 0.7 mg/dL; S[Na], 144 mmol/L; S[K], 3.9 mmol/L; serum chloride, 106 mmol/L; serum bicarbonate, 23 mmol/L; S[Ca] 10.8 mg/dL; serum phosphorus, 2.2 mg/dL; urinalysis: pH, 6.0, specific gravity, 1.020, lots of blood, and 1+ protein on dip.

Her renal ultrasound reveals right-sided hydronephrosis and a 4 mm-stone in her left renal pelvis.

Which of the following tests is likely to reveal the cause of her recurrent stone formation?

A. Review of her adherence to dietary and fluid recommendations
B. Spiral CT of the abdomen after a pregnancy test
C. Intact PTH and urinary calcium excretion
D. Urine examination for crystals

Answer: C

Recurrent stone formation in a patient should raise the suspicion for metabolic abnormalities that predispose patients to multiple stones. In this patient, the mild hypercalcemia and hypophosphatemia are clues that she has primary hyperparathyroidism. Although dietary and fluid recommendations should be reviewed and reinforced, that by itself, is not likely to prevent recurrence of stones. The renal ultrasound reveals a stone and hydronephrosis, and hence a urine examination for crystals or a spiral CT is not likely to add to the diagnosis or therapy.

Question 5

A 74-year-old patient, a resident of a nursing home, is sent to the renal clinic for evaluation of an elevated S[Cr]. She had a stroke 3 years ago and since then has been mostly bed bound. The nursing home reports that she had many urine infections in the past that were treated with antibiotics.

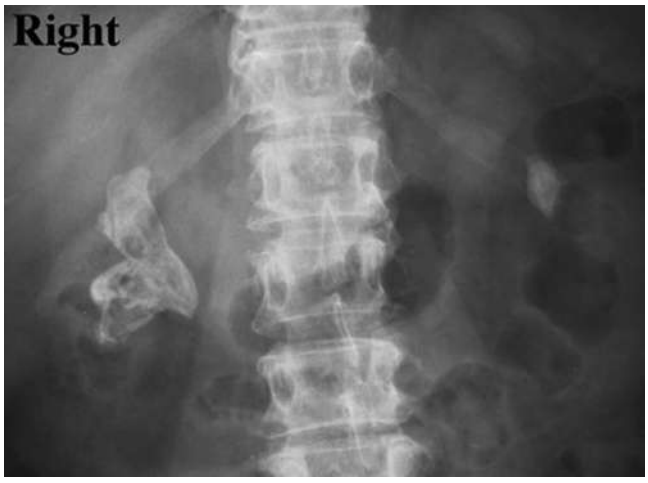
Further history is limited because the patient is nonverbal. Vital signs are stable except for a temperature of 38°C, and examination elicits some tenderness on deep palpation over the right flank. Labs are within normal limits except for a S[Cr] of 2.0 g/dL. Her urine analysis in the clinic shows specific gravity of 1028, pH of 8.4, blood ++, leukocyte esterase ++, nitrite +. Her urine microscopy shows many coffin lid−shaped crystals. X-ray KUB is shown below. She is started on antibiotics and her urine is sent for culture.

Which of the following organism is least likely to grow in her urine?

A. Proteus
B. E coli
C. Klebsiella
D. Serratia
E. Pseudomonas

Answer B

With a history of recurrent infections, high urine pH, struvite crystals in urine, and the appearance of a staghorn calculus on KUB, the patient has struvite stones. These are composed of magnesium ammonium phosphate and form when urease-producing bacterial infections split urea and generate ammonia in alkaline urine. Of all the bacteria *E. coli* does not produce urease.



KUB X-ray.

CHAPTER

68

Treatment of Psychiatric Disorders in Chronic Kidney Disease Patients

L. Parker Gregg[a], *S. Susan Hedayati*[b]

[a]University of Texas Southwestern and Veterans Affairs North Texas Health Care System, Dallas, TX, United States; [b]University of Texas Southwestern, Dallas, TX, United States

Abstract

Patients with chronic kidney disease (CKD) have a high rate of comorbid psychiatric conditions, including mood and anxiety disorders, substance use disorders, and eating disorders. Treatment of psychiatric disorders in CKD patients can be complicated by altered pharmacokinetics, unclear safety and efficacy of treatments, and lack of supporting evidence to guide treatment decisions. Furthermore, some psychiatric interventions may lead to renal complications, such as fluid and electrolyte disorders or worsening CKD. We review the evidence base regarding treatment of psychiatric disorders in CKD patients. We also present practical considerations regarding the management of psychiatric disorders in patients with CKD, including identifying candidates for therapy or mental health referral, the evidence for pharmacologic and nonpharmacologic therapy in CKD patients, the effects of CKD on psychiatric treatment, and consequences of these interventions that may prompt nephrology consultation.

INTRODUCTION

Increasing evidence shows a high rate of comorbid psychiatric disorders in patients with chronic kidney disease (CKD). Patients with CKD and psychiatric disorders are at risk for poor outcomes, including progression of CKD, hospitalization, cardiovascular events, and death. Unfortunately, symptoms of uremia often overlap with psychiatric symptom profiles (Table 68.1), which can complicate identification of appropriate candidates for psychiatric therapies. Furthermore, recent studies call into question the effectiveness and safety of some standard treatments for psychiatric disorders in CKD patients, or whether treatment affects long-term outcomes such as death. We review the literature and discuss practical concerns important to the nephrologist regarding the treatment of psychiatric disorders in patients with kidney disease.

GENERAL CONSIDERATIONS IN THERAPY

Pharmacologic and Nonpharmacologic Options

CKD patients are medically complex, often with multiple comorbid illnesses, receive polypharmacy, and have frequent healthcare contacts. Therapies for psychiatric disorders frequently include pharmacologic and nonpharmacologic interventions, either alone or in combination. Individual patients may have different preferences in seeking treatment. Some may prioritize avoiding additional pill burden, while others may find frequent healthcare appointments onerous. There is limited available evidence to compare the safety and efficacy of pharmacologic and nonpharmacologic interventions to placebo or to each other in CKD patients. In general, treatment should be guided by individual patient preference and available resources where evidence is lacking.

Drug–Drug Interactions

CKD patients often have a high pill burden due to the illness, its multiple sequelae, and comorbid medical conditions such as hypertension, diabetes, and cardiovascular disease. Psychotropic medications such as certain antidepressant medication classes and lithium carbonate can lead to harmful drug–drug interactions, increased risk of bleeding, cardiovascular toxicity, and central nervous system effects (Table 68.2).[1]

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00068-1

TABLE 68.1 Symptoms Associated with DSM-5 Disorders Common in Chronic Kidney Disease Patients

Disorder	Symptoms
Major depressive disorder	Depressed mood, decreased pleasure, weight changes, sleep disturbance, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, decreased concentration, recurrent thoughts of death or suicide.
Generalized anxiety disorder	Excessive, difficult to control worry associated with restlessness, fatigue, difficulty concentrating, irritability, muscle tension, or sleep disturbance.
Panic disorder	Recurrent, unexpected panic attacks associated with persistent worry about or maladaptive response to the attacks.
Posttraumatic stress disorder	Reexperiencing a trauma through flashbacks, intrusive thoughts, or nightmares; avoidance of stimuli associated with the trauma; irritability, anger, or hypervigilance.
Bipolar affective disorder I	At least one lifetime manic episode, defined as $\geq$1 week of elevated or irritable mood associated with grandiosity, decreased sleep, talkativeness, flight of ideas, distractibility, increased goal-directed activity, or activities with high potential for adverse consequences. Patients often also have intermittent depressive symptoms.
Substance use disorder	Problematic substance use involving greater intake than intended, difficulty decreasing use, large time commitment to obtaining/using/recovering, craving, failure to fulfill obligations, interpersonal problems, use in hazardous situations, tolerance, or withdrawal.
Anorexia nervosa	Caloric restriction leading to low body weight, associated with intense fear of weight gain. May be associated with purging.
Bulimia nervosa	Recurrent episodic binge eating associated with inappropriate compensatory behaviors (i.e. purging).

Consequently, treatment individualization and adjustments in nonpsychotropic medications when initiating or adjusting pharmacotherapy for a psychiatric condition is required. In addition, dose adjustment in the setting of reduced estimated glomerular filtration rate (eGFR) is needed for drugs that are cleared by the kidneys to avoid increased risk of toxicity.

Pharmacokinetics in CKD

The kidneys play a key role in drug metabolism. CKD can significantly affect pharmacokinetics by altering absorption, volume of distribution, and excretion of medications and their metabolites (Table 68.2). For example, urea is secreted into the gut, where it is hydrolyzed to ammonia. This may increase gastric pH and alter the oral bioavailability of medications.[2] Nausea and vomiting or increased gastric emptying time due to gastroparesis may also alter enteral medication absorption. Once absorbed, a drug's volume of distribution can be altered by fluid overload, hypoalbuminemia, or malnutrition in CKD patients.[2] Protein binding of drugs can be affected by nephrotic-range proteinuria and hypoalbuminemia. Accumulated organic acids and uremic toxins can compete with drugs for binding sites on albumin and other proteins.[3] Decreased protein binding increases the concentration of unbound circulating drug, leaving more drug available for activity at its receptor and decreasing the dose necessary for both therapeutic and adverse effects.[3] Drugs and their metabolites may also have decreased renal excretion, due to abnormalities of glomerular filtration, tubular secretion, and passive tubular reabsorption. Altered hepatic drug metabolism may occur due to downregulation of the cytochrome P450 enzymes in CKD.[4,5] In patients with end-stage renal disease (ESRD), consideration must be given to the intermittent removal of some medications by dialysis.

CKD clearly has far-reaching effects on multiple aspects of pharmacokinetics, extending beyond decreased renal clearance in the setting of low glomerular filtration rate (GFR). Because of these varied effects, drug pharmacokinetics can be difficult to predict in individuals with CKD. Few studies have investigated the pharmacokinetics of psychotropic medications in CKD patients. Generally, in the absence of specific recommendations to guide dosing, it is advisable to start at a low dose and gradually uptitrate, with careful, frequent monitoring for adverse effects in patients with CKD. Use the lowest effective but tolerable dose of psychotropic medications in CKD patients.

Treatment Nonadherence

Between 34% and 60% of patients with CKD demonstrate poor adherence to prescribed pharmacologic therapy.[6,7] Total pill burden, regimen complexity, lack of social support, side effects, and concern about drug interactions have been identified as primary factors associated with poor adherence, whereas studies vary as to whether older or younger age is more strongly associated with nonadherence.[8,9] Nephrologists and mental health providers should consider polypharmacy and the patient's likelihood of adherence when initiating treatment for psychiatric disorders, and routinely reassess adherence.

TABLE 68.2 General Considerations for the Prescription of Psychotropic Medications in CKD Patients

Drug–Drug Interactions
Bleeding risk with SSRIs, antiplatelet agents, and anticoagulants
Prolonged QTc and arrhythmias with SSRIs, TCAs, and antipsychotics exacerbated by hypomagnesemia due to diuretics
Hyponatremia with SSRIs and thiazide diuretics
Thiazide and loop diuretics can increase lithium carbonate levels
Pharmacokinetic Derangements in CKD
Medication absorption
Increased gastric pH due to uremia
Nausea and vomiting
Chelation due to concurrent medications such as phosphate binders
Gastroparesis
Decreased protein binding
Hypoalbuminemia
Competitive protein binding by uremic toxins
Volume of distribution
Volume overload leading to increased volume of distribution
Muscle wasting leading to decreased volume of distribution
Metabolism and excretion
Decreased renal clearance of drugs and metabolites
Decreased hepatic drug clearance by cytochrome P450 enzymes
Other than lithium carbonate, most psychotropic medications are protein bound and not significantly dialyzable
Medication Nonadherence
High total pill burden due to CKD and its sequelae
Lack of social support
Significant adverse effects of psychotropic medications

Abbreviations: *CKD*, chronic kidney disease; *SSRIs*, selective serotonin reuptake inhibitors; *TCAs*, tricyclic antidepressants.

MOOD AND ANXIETY DISORDERS

Major Depressive Disorder

Identifying Candidates for Treatment

Major depressive disorder (MDD), prevalent in approximately 7% of the general population, is disproportionately common in patients with kidney disease, with up to 20–25% of both nondialysis- and dialysis-dependent CKD patients meeting *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) criteria.[10–15] Diagnostic criteria for MDD include the presence, for at least 2 weeks, of at least 5 of 9 symptoms of depression (Table 68.1, Figure 68.1), one of which has to be sadness or anhedonia. Some of the physical symptoms (fatigue, weight or appetite changes, and insomnia) can also be attributed to uremia (Figure 68.1).[16] CKD patients may experience psychosocial stressors associated with their disease process, such as pain and fear or dislike of dialysis.[17,18] The symptom overlap between CKD and MDD can present a challenge to the clinician in identifying patients who may benefit from treatment for depression.

Identifying candidates for treatment requires initial screening and subsequent evaluation to confirm the diagnosis of MDD or other psychiatric disorders such as psychosis or bipolar disorder. Recognizing important symptoms such as suicidal ideation that may require urgent intervention is also critical (Figure 68.2). There is currently no consensus about which measurement tool is the best to screen for and diagnose MDD. In CKD patients, cutoffs of the Beck Depression Inventory (BDI) $\geq$11 and the Quick Inventory of Depressive Symptomatology Self-Reported Questionnaire (QIDS-SR) $\geq$10 have been validated as sensitive and specific screening tools for MDD.[19,20] In dialysis patients, cutoffs of BDI $\geq$14–16, Center for Epidemiologic Studies Depression Scale (CESD) $\geq$18, and Patient Health Questionnaire (PHQ) $\geq$10 are associated with MDD.[14,15,21,22] However, in addition to the significant symptom overlap between CKD and MDD, self-report measures may lack scoring criteria for the inclusion of depressed mood or anhedonia to diagnose depression. Consequently, the prevalence of MDD is generally higher when estimated by self-report screening tools than by interview-based DSM-5 criteria.[14,23] Although the use of structured psychiatric interview tools, such as the Mini International Neuropsychiatric Interview (MINI),[24] can verify the diagnosis of MDD, these tools are generally not widely available for clinical use by a nephrologist and require special training for administration. Therefore, a diagnosis of MDD can be more feasibly confirmed by inquiring whether the patient endorses depressed mood or anhedonia after identifying a patient with a positive self-report screening measure.[20] Finally, clinical suspicion for other complex psychiatric conditions such as psychosis or bipolar disorder may require different management and referral to mental health specialists. Clinicians can then consider initiation of treatment for patients with uncomplicated MDD.[20]

Traditional Pharmacologic Therapy

Treatment of MDD can involve both pharmacologic and nonpharmacologic interventions (Figure 68.2). Although several classes of antidepressant medications have been developed and proven effective for MDD in the general population, clinicians must prescribe these medications cautiously for CKD patients, due to decreased drug clearance, drug–drug interactions, and higher potential for adverse side effects (Table 68.3). Most studies of these drugs excluded patients with CKD and ESRD, so dose recommendations and pharmacokinetic information are often based on little evidence. Because of the lack of data supporting safe and effective

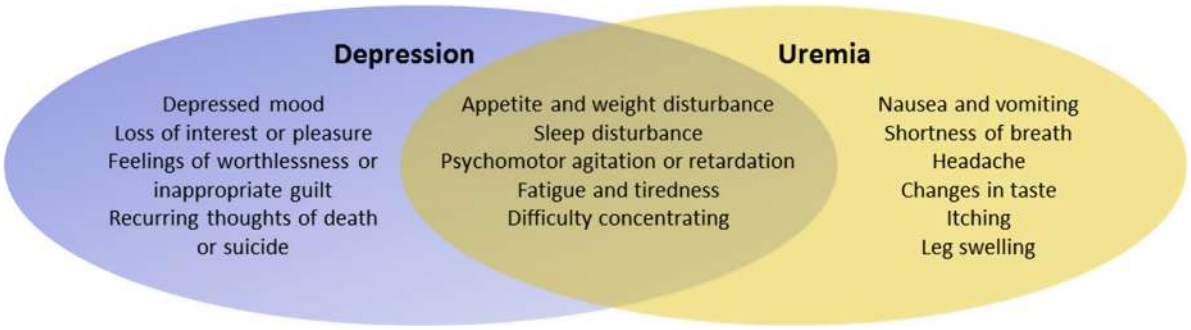


FIGURE 68.1 Similarities and differences in symptoms of depression and uremia.

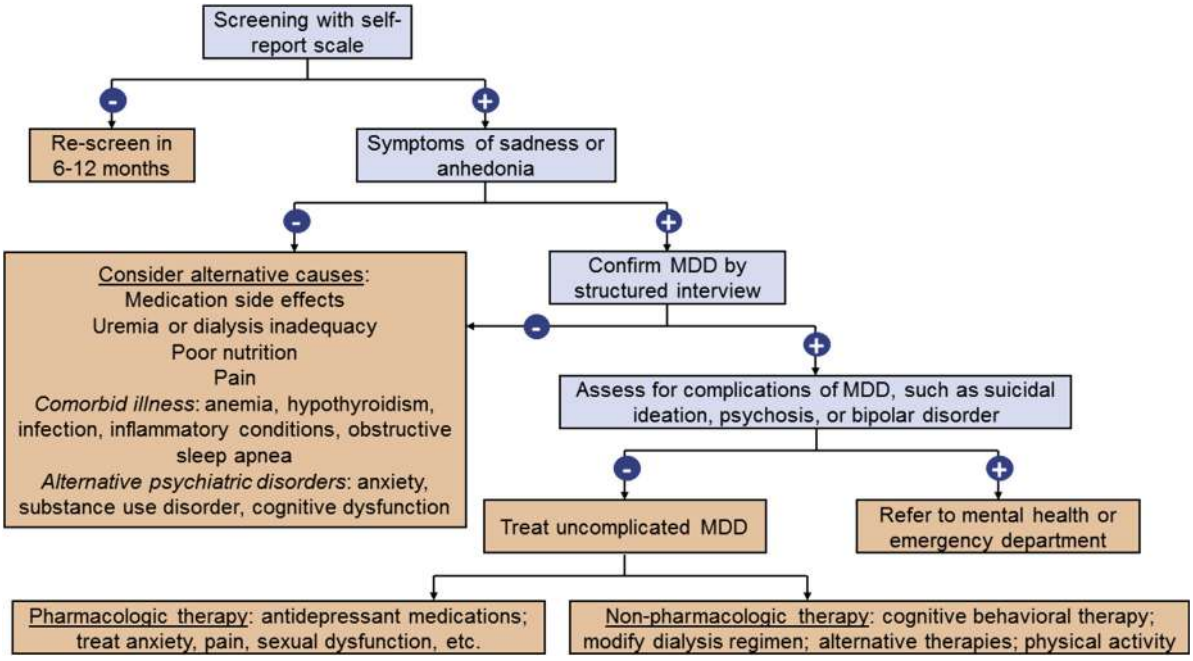


FIGURE 68.2 Identification of chronic kidney disease patients who may benefit from treatment of major depressive disorder (MDD).

dosing in these populations, underdosing of antidepressant medications is a major concern in both clinical care and existing studies of these medications in CKD patients.

In addition to the safety concerns regarding traditional antidepressant medications in CKD patients, several studies indicate that they may be less effective for treating MDD associated with chronic medical comorbidities, such as CKD or heart failure, than in the treatment of primary MDD in the general population. Most prior trials of antidepressant medications in CKD or ESRD patients were limited by small sample sizes,[25–30] nonstandard diagnostic criteria for MDD,[26,30,31] absence of a placebo control group,[27–32] or possible inadequate exposure to the drug by either low dose or short treatment duration.[25–27,30,31] The Chronic Kidney Disease Antidepressant Sertraline Trial (CAST) is the only adequately powered double-blind, randomized, placebo-controlled clinical trial that evaluated the effectiveness of a commonly prescribed antidepressant, sertraline, compared with placebo for the short-term treatment of depression in CKD patients.[33] In this trial, there was some improvement in depressive symptoms from baseline to study exit in both groups after 12 weeks of treatment, but there was no benefit of sertraline over placebo.[33] These results were similar to other trials showing no benefit of selective serotonin reuptake inhibitors (SSRIs) compared with placebo for the treatment of depression in patients with other chronic diseases such as heart failure, coronary artery disease, or asthma.[34–37] In addition, sertraline resulted in a higher incidence of gastrointestinal side effects (nausea and diarrhea) compared with placebo in CKD patients.[33]

Clinicians must consider the lack of efficacy data for traditional antidepressant medications in CKD patients, unclear dosing, and increased risk of side effects when

TABLE 68.3 Antidepressant Medication Dosing and Toxicities in CKD and ESRD

Medication	Non-CKD Dose	Manufacturer-Recommended Dose in CKD and ESRD	Potential Class and Individual Toxicities
SSRIs			Increased bleeding risk; GI symptoms such as nausea and diarrhea; CNS effects; sexual dysfunction; hyponatremia
Citalopram	20–40 mg once daily	Initial dose: 10 mg once daily Not recommended for eGFR <20 mL/min/1.73 m^2	Higher doses associated with QTc prolongation, torsades de pointes
Escitalopram	10–20 mg once daily	Use with caution in severe renal impairment	
Fluoxetine	20–80 mg once daily	No dose adjustment recommended; use with caution due to long half-life	
Paroxetine immediate release	20–50 mg once daily	Initial dose: 10 mg once daily Max dose: 40 mg once daily	
Paroxetine controlled release	25–62.5 mg once daily	Initial dose: 12.5 mg once daily Max dose: 50 mg once daily	
Sertraline	50–200 mg once daily	No dose adjustment recommended, but active metabolite is renally excreted	
TCAs		Generally avoid TCAs given cardiac side effects	QTc prolongation, arrhythmias, orthostatic hypotension; CNS and anticholinergic effects
Amitriptyline	75–150 mg per day in 1–3 divided doses	No dose adjustment recommended	
Desipramine	100–300 mg once daily or in divided doses	Caution advised in eGFR <15 mL/min/1.73m^2	
Doxepin	25–300 mg once daily or in divided doses	No dose adjustment recommended	
Nortriptyline	25 mg in 3–4 divided doses; max 150 mg daily	No dose adjustment recommended	
MAOIs		Avoid MAOIs in CKD due to drug–drug interactions	Significant drug–drug interactions, risk of hypertensive emergency with tyramine-rich foods, orthostatic hypotension
Phenelzine	45–90 mg daily in 3–5 divided doses	No dose adjustment advised for mild to moderate renal impairment	
Selegiline	6 mg per 24 hours *via* transdermal patch		
Serotonin Modulators			
Nefazodone	100–600 mg/day in 2 divided doses	Generally avoid in cardiovascular or liver disease, increase dose carefully	Cardiac dysrhythmias, Stevens Johnson syndrome, liver failure, serotonin syndrome, priapism
Trazodone immediate-release	150–400 mg/day, divided	Increase dose carefully, use divided dose in the elderly	
Trazodone extended-release	150–375 mg once daily at night		
Other			
Bupropion	100 mg twice daily; max 450 mg per day in 3–4 divided doses	Active metabolite; reduce frequency and/or dose	Accumulation of toxic metabolites; cardiac dysrhythmia; wide QRS complex; nausea; insomnia; dizziness

Continued

TABLE 68.3 Antidepressant Medication Dosing and Toxicities in CKD and ESRD—cont'd

Medication	Non-CKD Dose	Manufacturer-Recommended Dose in CKD and ESRD	Potential Class and Individual Toxicities
Mirtazapine	15–45 mg daily at bedtime	Reduce dose; clearance reduced by 30% if CrCl 11–39 mL/min, and by 50% if CrCl <10 mL/min	CNS effects including somnolence, weight gain
Venlafaxine immediate release	75–225 mg/day in 2–3 divided doses	Reduce dose by 25–50% in patients with mild to moderate renal impairment	Hypertension, sexual dysfunction, neuroleptic malignant syndrome, serotonin syndrome, accumulation of toxic metabolite O-desmethylvenlafaxine
Venlafaxine extended release	37.5–225 mg once daily		

Abbreviations: *CNS*, central nervous system; *CrCl*, creatinine clearance; *eGFR*, estimated glomerular filtration rate; *GI*, gastrointestinal; *MAOIs*, monoamine oxidase inhibitors; *SSRIs*, selective serotonin reuptake inhibitors; *TCAs*, tricyclic antidepressants.

prescribing pharmacologic therapies to treat MDD. If pharmacologic treatment is being considered, an SSRI such as sertraline, which currently has the best safety profile in CKD patients, may be initiated at a low dose while monitoring the patient closely for side effects during gradual dose uptitration every 1–2 weeks. Finally, consideration should be given to early withdrawal of the SSRI if the patient develops intolerable side effects or the drug proves to be ineffective. Adequately powered placebo-controlled clinical trials of alternative SSRIs and other classes of antidepressant medications in CKD patients are needed to guide pharmacologic treatment of MDD.

Nontraditional Pharmacologic Therapy

St. John's Wort is a popular herbal supplement advertised for the treatment of depression, but this approach is fraught with drug–drug interactions important in patients with CKD.[38] St. John's Wort is known to alter hepatic metabolism by inducing the cytochrome P450 system and gastrointestinal P-glycoprotein.[39,40] This becomes particularly important in patients who require immunosuppressive therapy with calcineurin inhibitors for diseases such as focal segmental glomerulosclerosis, or who go on to receive a kidney transplant, as St. John's Wort can decrease cyclosporine and tacrolimus levels.[41] When given in combination with SSRIs, St. John's Wort can also cause serotonin syndrome.[42] There are no data to suggest safety or efficacy of this supplement in CKD patients.

Limited evidence also suggests possible utility of antiinflammatory therapies to treat depressive symptoms. In the general population, inflammatory biomarkers including interleukin-6 (IL-6), high sensitivity C-reactive protein (hsCRP), and tumor necrosis factor-α (TNF-α) are elevated in people with depressive symptoms.[43–47] Given the connection between MDD and immune activation, it is thought that elevated baseline inflammation associated with chronic medical illnesses may account for the high prevalence of MDD in patients with comorbidities such as CKD,[12,13] heart failure,[48,49] and diabetes.[50] Some studies demonstrated improvement in depressive symptoms in patients with other chronic diseases such as rheumatoid arthritis, psoriasis, or Crohn's disease treated with anticytokine or anti-TNF-α therapies.[51,52] No trials have studied these interventions in CKD or ESRD patients, who are at high risk of side effects from such treatments. Despite this potentially promising preliminary data, further studies are needed to determine whether antiinflammatory therapies may be useful in the treatment of depressive symptoms in CKD patients.

Nonpharmacologic Therapy

Nonpharmacologic therapies avoid the risks and toxicities associated with antidepressant medications. However, other barriers may limit access to these treatments, particularly in resource-limited settings, or they may be undesirable due to increased patient time spent on disease management. Cognitive behavioral therapy (CBT) is an evidence-based treatment targeting a patient's "automatic thoughts" in response to negative emotions, to improve distorted thinking, behavior, and communication.[53] Four small randomized trials in hemodialysis patients showed significantly greater improvement of depressive symptoms in the CBT group compared with controls.[54–57] However, no studies have investigated the effectiveness of CBT in nondialysis-dependent CKD patients. Nonetheless, CBT may be a promising nonpharmacologic intervention to treat MDD in individuals with CKD.

A recent randomized trial, A Trial of Sertraline vs. CBT for End-Stage Renal Disease Patients with Depression (ASCEND), compared nonpharmacologic to pharmacologic therapy. This multicenter trial randomized 120 hemodialysis patients with MDD to sertraline or CBT.[58] Depressive symptoms ascertained by the QIDS-Clinician Rated scale improved from baseline with both treatments, with a modestly greater improvement with sertraline than with CBT, effect estimate (95% CI), −1.84 (−3.54, −0.13).[59] Because an active control arm was not included, conclusions regarding the efficacy of either treatment compared with no active treatment were not possible. In addition, there was a greater frequency of mild to moderate nonserious adverse events with sertraline than with CBT.

Physical activity also improves mental health in various populations.[60,61] Low physical activity is associated with depression in CKD and ESRD patients.[62,63] Several studies have demonstrated a benefit of aerobic activity on depressive symptoms in dialysis patients.[64–69] Although these studies were limited by sample size[65–69] or absence of a control group,[64,67] nephrologists should recommend an exercise regimen to their patients due to other potential benefits such as improved cardiovascular health, with the assumption that it may also improve their depressive symptoms.

Recommendations

In summary, little is known about the safest and most effective way to treat MDD in CKD patients, and whether treatment impacts long-term outcomes such as cardiovascular events and survival. Existing data do not support the indiscriminate use of sertraline or other medications to treat MDD in CKD patients, due to lack of efficacy and increased side effects, but sertraline can still be considered in select individuals who tolerate the medication and show a treatment response. Studies of other antidepressant medications are needed. Limited data suggest that nonpharmacologic therapies, such as CBT, may be effective for and better tolerated by motivated individuals.

Anxiety

Identifying Candidates for Treatment

Most studies of dialysis patients measured anxiety symptoms such as uncertainty, fear, restlessness, disordered sleep, shortness of breath, and palpitations, rather than specific DSM-5-based anxiety disorders.[70] Anxiety was reported in 12−52% of patients with CKD or ESRD.[71,72] As with MDD, overlap between symptoms of anxiety, depression, and CKD can thwart clinicians in recognizing candidates for treatment. In dialysis patients, these symptoms can manifest as the patient shortening dialysis treatments, dizziness, palpitations, nausea, sweating, chest pain, shortness of breath, numbness, tremors, or disruptive behaviors.[71] Similar to MDD, there is no consensus about which screening tools should be used to identify anxiety disorders in CKD and ESRD patients. Studies have used the Structured Clinical Interview for DSM-IV,[72–74] Hospital Anxiety and Depression score,[64,73] Beck Anxiety Inventory,[56] State-Trait Anxiety Inventory,[65,75,76] and the Hemodialysis Stressor Scale.[75] The 7-item Generalized Anxiety Disorder Scale (GADS-7) is a short and simple self-report tool that can be easily administered that is being used in ongoing trials in ESRD patients.[58]

Pharmacologic Therapy

SSRIs are now considered first line for chronic outpatient therapy of anxiety disorders. Unfortunately, no randomized trials have investigated their effectiveness compared with placebo for the treatment of anxiety in CKD or ESRD patients. The CAST study showed sertraline had an increased risk of gastrointestinal side effects compared with placebo in CKD patients.[33] Therefore, treatment should be individualized based on response and tolerability (Table 68.2).

Benzodiazepines are prescribed in the general population for use on an as-needed basis for acute anxiety symptoms. The addictive potential of these medications, as well as the accumulation of active metabolites,[3] limits their use in the CKD population.

Nonpharmacologic Therapy

CBT has the largest evidence base supporting its effectiveness for the treatment of anxiety disorders in the general population and has been demonstrated to be effective in hemodialysis patients.[55,56] In dialysis patients, physical activity[65] and music therapy[75–78] may also decrease anxiety symptoms. Although not systematically studied, individualization of dialysis therapy such as switching dialysis modality, short frequent dialysis treatments, or consistent assignment to the same dialysis nurses, technicians, and physicians may also alleviate anxiety for selected patients. There are no studies of nonpharmacologic interventions for anxiety in nondialysis CKD patients.

Recommendations

Although symptoms of anxiety are common in CKD patients, evidence-based screening, diagnosis, and treatment options for anxiety disorders are lacking in this population.[71] Limited existing evidence favors a nonpharmacologic approach, although a trial of SSRI therapy while monitoring for efficacy is reasonable. CBT, physical activity, and individualization of dialysis therapy may alleviate anxiety.

Bipolar Affective Disorder

Bipolar affective disorder appears to have a strong connection with CKD, which may be largely driven by nephrotoxic effects of chronic lithium therapy.[79,80] Close communication between nephrology and psychiatry specialists is critical to ensure safe and effective treatment of this serious psychiatric condition.

Pharmacologic Therapy

Maintenance pharmacologic therapy is the mainstay of treatment of bipolar disorder (Table 68.4). Lithium carbonate, one of the first-line therapies for bipolar affective disorder, has multiple known nephrotoxic adverse effects such as nephrotic syndrome resulting from minimal change or membranous nephropathy, as well as tubulointerstitial disease and nephrogenic diabetes insipidus with chronic use. In individuals with CKD stage 3 (eGFR 30–59 mL/min/1.73 m^2), it is recommended to measure eGFR every 3 months and urine albumin:creatinine ratio annually.[81] Because lithium is 89–98% renally cleared, lithium should be avoided in patients with eGFR <30 mL/min/1.73 m^2.[81] Medications commonly prescribed to CKD patients may affect lithium pharmacokinetics. Thiazide and loop diuretics can raise lithium concentrations by inducing reabsorption of lithium along with sodium in the proximal tubule.[82] Initiation or dose increase of angiotensin-converting enzyme inhibitors may lead to a decline in GFR that can raise lithium levels.[81] Because lithium is a small molecule that is not protein bound, it is easily removed by hemodialysis. Therefore, lithium can be safely prescribed in hemodialysis patients with dosing after dialysis sessions.[3]

Other first-line agents for bipolar affective disorder include anticonvulsants such as divalproex and lamotrigine, and atypical antipsychotics such as quetiapine. Manufacturers do not recommend dose adjustment of

TABLE 68.4 Commonly Used Mood Stabilizer Medication Dosing and Toxicities in CKD and ESRD

Medication	Non-CKD Dose	Manufacturer-Recommended Dose in CKD and ESRD	Potential Toxicities
Lithium carbonate immediate release	900–1200 mg daily in 3–4 divided doses (goal serum lithium level 0.6–1.2 mmol/L)	No dose adjustment for GFR >50 mL/min; give 50–75% of dose for GFR 10–50 mL/min; give 25–50% of the dose at the usual dosing interval for GFR <10 mL/min. For dialysis patients, give 600–900 mg maintenance dose three times weekly after HD	Nephrotoxicity including nephrogenic diabetes insipidus, progressive CKD; nausea; weight gain; cardiovascular effects including bradycardia and sinus node dysfunction
Lithium carbonate extended release	900–1200 mg daily in 2–3 divided doses (goal serum lithium level 0.6–1.2 mmol/L)		
Divalproex	Maximum 60 mg/kg/day in divided doses	No dose adjustment recommended in CKD or ESRD. Monitoring total concentrations can be misleading due to decreased protein binding	Nausea, diarrhea, and other GI side effects; increased bleeding risk; CNS effects; cardiovascular effects including chest pain, hypertension or hypotension, tachycardia, and edema
Lamotrigine	200 mg once daily, with adjustment based on drug–drug interactions	No dose adjustment in CKD, but reduced dose may be effective. Unknown if removed by dialysis	Nausea, diarrhea, and other GI side effects; DRESS; CNS effects; rarely can cause hematuria and AKI
Quetiapine regular release	400–800 mg daily in two divided doses, generally used in combination with lithium or divalproex	No dose adjustment recommended. For geriatric patients initiate at 50 mg daily and increase slowly based on response and tolerance	Increased appetite and other GI side effects; anemia; tachycardia; rare but serious cardiovascular effects such as prolonged QTc, syncope, and bradycardia; CNS effects are common
Quetiapine extended release	400–800 mg once daily, generally used in combination with lithium or divalproex		

Abbreviations: *AKI*, acute kidney injury; *CKD*, chronic kidney disease; *CNS*, central nervous system; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *ESRD*, end-stage renal disease; *GFR*, glomerular filtration rate; *GI*, gastrointestinal; *HD*, hemodialysis.

divalproex in CKD or ESRD patients. Similarly, manufacturers do not recommend decreased lamotrigine dose for those with CKD, but they note that a lower dose may be effective in those with low eGFR. Although there are no dose adjustments for quetiapine in CKD patients, it is recommended starting at a dose of 50 mg daily, and increasing the dose carefully in the elderly. Because of significant treatment heterogeneity, in general, the best therapy for bipolar disorder is the one that works for the patient. However, given the nephrotoxicity of lithium carbonate, other agents should be used preferentially in individuals with CKD and ESRD, if possible.

Nonpharmacologic Therapy

Therapy for bipolar affective disorder is primarily pharmacologic, as few nonpharmacologic therapies have been proven effective in bipolar disorder in the general population. Despite this, many psychiatrists recommend concurrent psychotherapy and pharmacologic therapy to prevent relapse. The only nonpharmacologic therapy substantiated by evidence is electroconvulsive therapy, an intervention reserved for those who fail medical therapy.[83] Electroconvulsive therapy has been successfully administered to individuals with CKD and ESRD, but possible complications include hyperkalemia due to succinylcholine, altered pharmacokinetics of anesthetic agents, fractures during the procedure due to secondary hyperparathyroidism and poor bone mineralization, and alteration of the seizure threshold due to hypocalcemia and acidosis.[84,85]

Recommendations

Nephrologists should carefully monitor CKD patients treated with lithium, particularly when adjusting their dose of diuretics or renin–angiotensin–aldosterone system blocking agents. In patients with advanced CKD, nephrologists may recommend changing to alternative pharmacologic therapies due to the nephrotoxicity of lithium. In cases of severe bipolar affective disorder, electroconvulsive therapy has been safely conducted in CKD and ESRD patients, but nephrologists should be aware of the potential complications of this treatment.

SUBSTANCE USE DISORDERS

Substance use disorders are serious psychiatric conditions requiring involvement of a mental health or addiction specialist to manage pharmacologic and nonpharmacologic therapies. Existing data are inconsistent regarding the association of substance abuse with CKD.[86,87] Such a potential association may be in part due to direct relationships between various substances of abuse and causes of kidney disease. For example, intravenous drug use is associated with hepatitis B and C and human immunodeficiency virus infections, cocaine and methamphetamines are associated with hypertension, levamisole-adulterated cocaine is associated with pauci-immune vasculitis, and alcohol abuse is linked to the development of cirrhosis. There are nearly no data regarding treatment of substance use disorders in individuals with CKD, so treatment decisions must be guided by studies done in the general population. For the nephrologist, appropriate management of substance use disorders is particularly important, as they are associated with nonadherence with medical therapy, which becomes problematic in patients' adherence to pharmacologic and dialytic therapies.

Alcohol Use Disorder

Pharmacologic Therapy

Naltrexone is an opioid antagonist used to treat alcohol and opioid use disorders and is sometimes used off-label to treat generalized pruritus in hemodialysis patients. Naltrexone is thought to act by blocking the mu-opioid receptor, thus decreasing expression of the reinforcing effects of alcohol.[88] According to the manufacturer's label, there is no recommended dose adjustment for those with creatinine clearance of 50–80 mL/min, but naltrexone has not been studied in those with more advanced CKD. Only one study of naltrexone used to treat pruritus in hemodialysis patients reported that there is no need to modify the starting dose, but blood levels were higher in dialysis patients than in healthy controls.[89] Importantly, prescription of opioids for pain is a contraindication to therapy with naltrexone for substance use disorder.

Acamprosate is another first-line pharmacologic option to treat alcohol use disorder, thought to work by normalizing neurotransmitter activity that can be altered in the setting of frequent alcohol use.[90] Almost half of acamprosate is excreted in the urine, and in individuals with CKD the total and renal clearance of acamprosate are decreased.[90,91] Thus, acamprosate requires a dose decrease in those with a creatinine clearance of 30–50 mL/min and is contraindicated for those with a creatinine clearance less than 30 mL/min.

Nonpharmacologic Therapy

There are no specific data or recommendations about the effectiveness of nonpharmacologic therapies for addiction, such as 12-step programs or inpatient rehabilitation, in patients with CKD. Referral for psychiatric evaluation to determine the timing and duration of these interventions is key. As with other nonpharmacologic psychiatric treatments, the time commitment may be a

barrier for patients burdened by frequent medical visits and physical symptoms such as fatigue.

Opioid Use Disorder

The alarming epidemic of opioid use, and consequent rise in deaths due to opioid overdose, has prompted nationwide interest in increasing access to treatment of this serious condition.[92] As chronic pain is common in patients with CKD, as many as 31.8% of CKD patients are prescribed opioids, with higher rates of prescription in those with more advanced CKD stages.[93] Nephrologists should be aware of available treatments for opioid use disorder and have a low threshold to refer such patients to mental health or addiction specialists.

Pharmacologic Therapy

Supervised treatment with opioid receptor antagonists has remained the cornerstone of treatment of opioid use disorder for decades.[92] Methadone, a long-acting opioid receptor agonist, is often prescribed to opioid users to decrease both the highs and withdrawal symptoms of shorter-acting opioids such as heroin. Methadone is primarily hepatically metabolized and excreted in the stool, but up to 20% of the active drug and metabolites are also excreted in the urine.[94] When used in anuric dialysis patients, it is excreted entirely in the stool and does not accumulate systemically despite being poorly removed by hemodialysis.[95,96] Manufacturers recommend lower initial dose, longer dosing intervals, and slower titration in patients with CKD.

Buprenorphine is another partial opioid receptor antagonist, most commonly prescribed in combination with naloxone to treat opioid use disorder. Although few data exist to guide the use of buprenorphine/naloxone in patients with CKD, some studies show that the pharmacokinetics of buprenorphine are unaltered in hemodialysis patients, likely due to its primarily hepatic metabolism.[97,98] There are no manufacturer recommendations for dose adjustment in patients with decreased renal clearance.

EATING DISORDERS

Eating disorders are underdiagnosed, and such patients may present to nephrologists with acute kidney injury, CKD, nephrolithiasis, or electrolyte disturbances.[99] It is important for nephrologists to recognize patients with eating disorders and refer them for appropriate management. Serious electrolyte disturbances are common in patients undergoing therapy for eating disorders, so nephrologists should understand the implications of eating disorders on the management of CKD and fluid and electrolyte disorders.

Anorexia Nervosa

Patients with anorexia nervosa, characterized by pathologic dieting, exercise, or purging, have a high rate of kidney complications. Severe caloric restriction and purging behaviors such as vomiting and diuretic or laxative abuse in patients with anorexia nervosa can lead to the development of hypokalemia, kidney stones, and chronic volume depletion, which are thought to contribute to an increased risk of developing CKD.[99,100] The prevalence of hypokalemic CKD in patients with anorexia nervosa is 15–20%.[99,101] One study showed that 5.2% of individuals with anorexia nervosa developed ESRD over 21 years of follow-up.[102] Diagnosis of anorexia nervosa can be challenging in patients with CKD due to the loss of appetite that occurs with uremia. Prevalence of low appetite using self-report measures is as high as 47% in hemodialysis patients and correlates with poor quality of life and depression.[103,104] There are no specific recommendations for the screening and diagnosis of anorexia nervosa in CKD patients. A clinician who suspects this diagnosis can screen using tools validated in the general population, such as the SCOFF or Screen for Disordered Eating questionnaires (Table 68.5).[105,106] These screening questions distinguish uremic anorexia from anorexia nervosa by focusing on the patient's psychologic relationship to food.

Pharmacologic Therapy

No pharmacologic therapies have been proven effective for anorexia nervosa in adults, although open-label nonrandomized preliminary data suggest that olanzapine may be useful to help patients gain weight.[107] Mental health providers will frequently treat comorbid anxiety and depression with pharmacologic therapy,[108] but these interventions have serious limitations in CKD patients as detailed above.

Nonpharmacologic Therapy

Anorexia nervosa is a psychiatric illness notoriously difficult to treat. Patients with suspected eating disorders should be referred to psychiatry for management. The cornerstone of therapy is weight gain *via* restoration of normal nutrition by focusing on eating behaviors, including high-protein intake and regular meals.[109] Dietary restrictions in CKD can complicate this treatment by limiting intake of protein, phosphate, and potassium. Importantly, patients undergoing nutritional rehabilitation after prolonged malnutrition are at risk for refeeding syndrome, which is a potentially fatal complication associated with severe electrolyte disturbances.

TABLE 68.5 Screening for Eating Disorders

Item	SCOFF Screening Questionnaire	Screen for Disordered Eating
1	Do you make yourself sick because you feel uncomfortably full?	Do you often feel the desire to eat when you are emotionally upset or stressed?
2	Do you worry that you have lost control over how much you eat?	Do you often feel that you cannot control what or how much you eat?
3	Have you recently lost more than one stone (14 lb) in a 3-month period?	Do you sometimes make yourself throw up (vomit) to control your weight?
4	Do you believe yourself to be fat when others say you are too thin?	Are you often preoccupied with a desire to be thinner?
5	Would you say that food dominates your life?	Do you believe yourself to be fat when others say you are thin?
Scoring	1 point for each yes answer; a score of ≥2 points total should increase suspicion for anorexia nervosa	1 point for each yes answer; a score of ≥2 points total should increase suspicion for any eating disorder

Refeeding syndrome can be prevented in these patients by repleting electrolytes before the gradual reintroduction of caloric intake.[110] Management of refeeding syndrome includes limiting caloric intake and close monitoring and correction of hypophosphatemia, hypomagnesemia, and hypokalemia.[110,111] CBT, with the goal to affect attitudes and behaviors related to food, in conjunction with nutritional rehabilitation has been shown to prevent relapse of anorexia nervosa.[112]

Bulimia Nervosa

Like anorexia nervosa, this disorder is also characterized by unhealthy compensatory behaviors such as vomiting, diuretic or laxative abuse, or enema abuse to avoid weight gain. Such patients may present to nephrologists with acute kidney injury, CKD, or electrolyte abnormalities resulting from these behaviors. Bulimia nervosa can be distinguished from anorexia nervosa by the presence of binge eating and generally a normal or high total body weight. The Screen for Disordered Eating can be used to identify patients with bulimia nervosa, with a sensitivity of 100% and a specificity of 51%.[106]

Pharmacologic Therapy

Pharmacologic therapy with fluoxetine or other SSRIs in conjunction with nonpharmacologic interventions is more effective for the treatment of bulimia nervosa than psychotherapy or pharmacologic therapy alone.[113,114] However, no studies have examined the efficacy of these treatment modalities in individuals with CKD, particularly regarding safe and effective dosing of SSRIs, leaving clinicians with only vague recommendations to start at a low dose and gradually uptitrate while monitoring for adverse effects.

Nonpharmacologic Therapy

Treatment hinges on nutritional rehabilitation focused on addressing binge eating and purging behaviors. Psychiatry involvement is critical to manage CBT, which has been demonstrated as an effective treatment modality for this disorder.[115]

Management of Pseudo-Bartter Syndrome

Purging cessation can lead to Pseudo-Bartter syndrome. Purging behaviors lead to chronic volume depletion, which stimulates the secretion of renin. The consequent secondary hyperaldosteronism causes hypokalemia, hypochloremia, and metabolic alkalosis, and plasma aldosterone does not normalize for up to 3 weeks after cessation of purging behaviors.[116] Patients who abruptly cease chronic purging, often in a medical setting, will maintain an ongoing aldosterone-induced sodium avidity. Administering intravenous fluid boluses to such patients can cause net positive fluid balance, third spacing of fluid, and edema that can be remarkably severe.[117,118] Intravenous fluids should be administered at a slow continuous rate for a total administration no greater than 1−2 L over 24−48 hours, with the goal to normalize metabolic alkialosis.[116] Hypokalemia should be corrected.[119] Aldosterone antagonists such as spironolactone (25−200 mg once daily) can be used to prevent or manage edema and hypokalemia for 2−3 weeks after cessation of purging, but this should be done cautiously in those with CKD to avoid the development of hyperkalemia.[116]

CONCLUSIONS

Psychiatric disorders are common in CKD patients, likely due to concomitant burden of chronic medical illnesses, renal complications of psychiatric disorders or

treatments, and inflammation or other risk factors in CKD patients that may lead to psychiatric disorders. Despite this, few data exist to guide safe and effective treatment of these disorders in this large group of patients at risk for significant adverse effects, unpredictable pharmacokinetics, and unclear efficacy for some standard first-line therapies. Studies are needed to determine the most appropriate therapies for psychiatric disorders in CKD patients, with a focus on safety and dosing of pharmacologic interventions, as well as the efficacy and feasibility of nonpharmacologic interventions.

Acknowledgments

Parts of Table 68.1 are adapted from Cukor D. *Seminars Dial* 2013;**26**(3): 265–8.

References

1. Dumbreck S, Flynn A, Nairn M, et al. Drug-disease and drug-drug interactions: systematic examination of recommendations in 12 UK national clinical guidelines. *BMJ* 2015;**350**:h949.
2. Velenosi TJ, Urquhart BL. Pharmacokinetic considerations in chronic kidney disease and patients requiring dialysis. *Expert Opin Drug Metabol Toxicol* 2014;**10**(8):1131–43.
3. Levy NB. Psychopharmacology in patients with renal failure. *Int J Psychiatry Med* 1990;**20**(4):325–34.
4. Velenosi TJ, Fu AY, Luo S, Wang H, Urquhart BL. Down-regulation of hepatic CYP3A and CYP2C mediated metabolism in rats with moderate chronic kidney disease. *Drug Metab Dispos* 2012;**40**(8):1508–14.
5. Sun H, Huang Y, Frassetto L, Benet LZ. Effects of uremic toxins on hepatic uptake and metabolism of erythromycin. *Drug Metab Dispos* 2004;**32**(11):1239–46.
6. Sontakke S, Budania R, Bajait C, Jaiswal K, Pimpalkhute S. Evaluation of adherence to therapy in patients of chronic kidney disease. *Indian J Pharmacol* 2015;**47**(6):668–71.
7. Williams AF, Manias E, Walker R. Adherence to multiple, prescribed medications in diabetic kidney disease: a qualitative study of consumers' and health professionals' perspectives. *Int J Nurs Stud* 2008;**45**(12):1742–56.
8. Ghimire S, Castelino RL, Lioufas NM, Peterson GM, Zaidi ST. Nonadherence to medication therapy in haemodialysis patients: a systematic review. *PLoS One* 2015;**10**(12):e0144119.
9. McKillop G, Joy J. Patients' experience and perceptions of polypharmacy in chronic kidney disease and its impact on adherent behaviour. *J Ren Care* 2013;**39**(4):200–7.
10. Association AP. *Diagnostic and statistical manual of mental disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
11. Waraich P, Goldner EM, Somers JM, Hsu L. Prevalence and incidence studies of mood disorders: a systematic review of the literature. *Can J Psychiatr* 2004;**49**(2):124–38.
12. Hedayati SS, Minhajuddin AT, Toto RD, Morris DW, Rush AJ. Prevalence of major depressive episode in CKD. *Am J Kidney Dis* 2009;**54**(3):424–32.
13. Palmer S, Vecchio M, Craig JC, et al. Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. *Kidney Int* 2013;**84**(1):179–91.
14. Hedayati SS, Bosworth HB, Kuchibhatla M, Kimmel PL, Szczech LA. The predictive value of self-report scales compared with physician diagnosis of depression in hemodialysis patients. *Kidney Int* 2006;**69**(9):1662–8.
15. Watnick S, Wang PL, Demadura T, Ganzini L. Validation of 2 depression screening tools in dialysis patients. *Am J Kidney Dis* 2005;**46**(5):919–24.
16. Hedayati SS, Finkelstein FO. Epidemiology, diagnosis, and management of depression in patients with CKD. *Am J Kidney Dis* 2009;**54**(4):741–52.
17. Unruh ML, Cohen LM. Sleep and pain management are key components of patient care in ESRD. *Nephrol Dial Transplant* 2012; **27**(7):2618–20.
18. Zalai D, Szeifert L, Novak M. Psychological distress and depression in patients with chronic kidney disease. *Semin Dial* 2012; **25**(4):428–38.
19. Hedayati SS, Minhajuddin AT, Toto RD, Morris DW, Rush AJ. Validation of depression screening scales in patients with CKD. *Am J Kidney Dis* 2009;**54**(3):433–9.
20. Hedayati SS, Yalamanchili V, Finkelstein FO. A practical approach to the treatment of depression in patients with chronic kidney disease and end-stage renal disease. *Kidney Int* 2012;**81**(3):247–55.
21. Cohen SD, Norris L, Acquaviva K, Peterson RA, Kimmel PL. Screening, diagnosis, and treatment of depression in patients with end-stage renal disease. *Clin J Am Soc Nephrol* 2007;**2**(6):1332–42.
22. Craven JL, Rodin GM, Littlefield C. The Beck Depression Inventory as a screening device for major depression in renal dialysis patients. *Int J Psychiatry Med* 1988;**18**(4):365–74.
23. Kimmel PL, Weihs K, Peterson RA. Survival in hemodialysis patients: the role of depression. *J Am Soc Nephrol* 1993;**4**(1):12–27.
24. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;**59**(Suppl. 20):22–33. quiz 34-57.
25. Friedli K, Guirguis A, Almond M, et al. Sertraline versus placebo in patients with major depressive disorder undergoing hemodialysis: a randomized, controlled feasibility trial. *Clin J Am Soc Nephrol* 2017;**12**(2):280–6.
26. Blumenfield M, Levy NB, Spinowitz B, et al. Fluoxetine in depressed patients on dialysis. *Int J Psychiatry Med* 1997;**27**(1): 71–80.
27. Koo JR, Yoon JY, Joo MH, et al. Treatment of depression and effect of antidepression treatment on nutritional status in chronic hemodialysis patients. *Am J Med Sci* 2005;**329**(1):1–5.
28. Wuerth D, Finkelstein SH, Ciarcia J, Peterson R, Kliger AS, Finkelstein FO. Identification and treatment of depression in a cohort of patients maintained on chronic peritoneal dialysis. *Am J Kidney Dis* 2001;**37**(5):1011–7.
29. Kennedy SH, Craven JL, Rodin GM. Major depression in renal dialysis patients: an open trial of antidepressant therapy. *J Clin Psychiatry* 1989;**50**(2):60–3.
30. Levy NB, Blumenfield M, Beasley Jr CM, et al. Fluoxetine in depressed patients with renal failure and in depressed patients with normal kidney function. *Gen Hosp Psychiatry* 1996;**18**(1):8–13.
31. Turk S, Atalay H, Altintepe L, et al. Treatment with antidepressive drugs improved quality of life in chronic hemodialysis patients. *Clin Nephrol* 2006;**65**(2):113–8.
32. Wuerth D, Finkelstein SH, Kliger AS, Finkelstein FO. Chronic peritoneal dialysis patients diagnosed with clinical depression: results of pharmacologic therapy. *Semin Dial* 2003;**16**(6):424–7.
33. Hedayati SS, Gregg LP, Carmody T, et al. Effect of sertraline on depressive symptoms in patients with chronic kidney disease without dialysis dependence: the CAST randomized clinical trial. *J Am Med Assoc* 2017;**318**(19):1876–90.
34. O'Connor CM, Jiang W, Kuchibhatla M, et al. Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline against Depression and Heart Disease in Chronic Heart Failure) trial. *J Am Coll Cardiol* 2010; **56**(9):692–9.

35. Angermann CE, Gelbrich G, Stork S, et al. Effect of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression: the MOOD-HF randomized clinical trial. *J Am Med Assoc* 2016;**315**(24):2683–93.
36. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. *J Am Med Assoc* 2002;**288**(6):701–9.
37. Brown ES, Vigil L, Khan DA, Liggin JD, Carmody TJ, Rush AJ. A randomized trial of citalopram versus placebo in outpatients with asthma and major depressive disorder: a proof of concept study. *Biol Psychiatry* 2005;**58**(11):865–70.
38. Brown AC. Kidney toxicity related to herbs and dietary supplements: online table of case reports. Part 3 of 5 series. *Food Chem Toxicol* 2017;**107**(Pt A):502–19.
39. Weber CC, Kressmann S, Fricker G, Muller WE. Modulation of P-glycoprotein function by St John's wort extract and its major constituents. *Pharmacopsychiatry* 2004;**37**(6):292–8.
40. Kober M, Pohl K, Efferth T. Molecular mechanisms underlying St. John's wort drug interactions. *Curr Drug Metabol* 2008;**9**(10): 1027–37.
41. Alscher DM, Klotz U. Drug interaction of herbal tea containing St. John's wort with cyclosporine. *Transpl Int* 2003;**16**(7):543–4.
42. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: an updated systematic review. *Drugs* 2009;**69**(13): 1777–98.
43. van Dooren FE, Schram MT, Schalkwijk CG, et al. Associations of low grade inflammation and endothelial dysfunction with depression - the Maastricht Study. *Brain Behav Immun* 2016;**56**: 390–6.
44. Haapakoski R, Mathieu J, Ebmeier KP, Alenius H, Kivimaki M. Cumulative meta-analysis of interleukins 6 and 1beta, tumour necrosis factor alpha and C-reactive protein in patients with major depressive disorder. *Brain Behav Immun* 2015;**49**:206–15.
45. Fan N, Luo Y, Ou Y, He H. Altered serum levels of TNF-alpha, IL-6, and IL-18 in depressive disorder patients. *Hum Psychopharmacol* 2017;**32**(4).
46. Bob P, Raboch J, Maes M, et al. Depression, traumatic stress and interleukin-6. *J Affect Disord* 2010;**120**(1–3):231–4.
47. Wium-Andersen MK, Orsted DD, Nielsen SF, Nordestgaard BG. Elevated C-reactive protein levels, psychological distress, and depression in 73, 131 individuals. *JAMA Psychiatry* 2013;**70**(2): 176–84.
48. Havranek EP, Ware MG, Lowes BD. Prevalence of depression in congestive heart failure. *Am J Cardiol* 1999;**84**(3):348–50. A349.
49. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol* 2006;**48**(8):1527–37.
50. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001;**24**(6):1069–78.
51. Kappelmann N, Lewis G, Dantzer R, Jones PB, Khandaker GM. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Mol Psychiatr* 2018;**23**(2):335–43.
52. Kohler O, Benros ME, Nordentoft M, et al. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* 2014;**71**(12):1381–91.
53. Beck AT. The current state of cognitive therapy: a 40-year retrospective. *Arch Gen Psychiatr* 2005;**62**(9):953–9.
54. Cukor D, Ver Halen N, Asher DR, et al. Psychosocial intervention improves depression, quality of life, and fluid adherence in hemodialysis. *J Am Soc Nephrol* 2014;**25**(1):196–206.
55. Valsaraj BP, Bhat SM, Latha KS. Cognitive behaviour therapy for anxiety and depression among people undergoing haemodialysis: a randomized control trial. *J Clin Diagn Res* 2016;**10**(8):VC06–10.
56. Lerma A, Perez-Grovas H, Bermudez L, Peralta-Pedrero ML, Robles-Garcia R, Lerma C. Brief cognitive behavioural intervention for depression and anxiety symptoms improves quality of life in chronic haemodialysis patients. *Psychol Psychother* 2017; **90**(1):105–23.
57. Duarte PS, Miyazaki MC, Blay SL, Sesso R. Cognitive-behavioral group therapy is an effective treatment for major depression in hemodialysis patients. *Kidney Int* 2009;**76**(4):414–21.
58. Hedayati SS, Daniel DM, Cohen S, et al. Rationale and design of A trial of sertraline vs. Cognitive behavioral therapy for end-stage renal disease patients with depression (ASCEND). *Contemp Clin Trials* 2016;**47**:1–11.
59. Mehrotra R, Cukor D, Unruh M, Rue T, Heagerty P, Cohen SD, Dember LM, Diaz-Linhart Y, Dubovsky A, Greene T, Grote N, Kutner N, Trivedi MH, ver Helan N, Weisbord SD, Young BA, Kimmel PL, Hedayati SS. Comparative efficacy of therapies for treatment of depression for patients undergoing maintenance hemodialysis. A randomized clinical trial. *Ann Intern Med* 2019. https://doi.org/10.7326/M18-2229.
60. Gerber M, Brand S, Herrmann C, Colledge F, Holsboer-Trachsler E, Puhse U. Increased objectively assessed vigorous-intensity exercise is associated with reduced stress, increased mental health and good objective and subjective sleep in young adults. *Physiol Behav* 2014;**135**:17–24.
61. Telenius EW, Engedal K, Bergland A. Long-term effects of a 12 weeks high-intensity functional exercise program on physical function and mental health in nursing home residents with dementia: a single blinded randomized controlled trial. *BMC Geriatr* 2015;**15**:158.
62. Lopes AA, Lantz B, Morgenstern H, et al. Associations of self-reported physical activity types and levels with quality of life, depression symptoms, and mortality in hemodialysis patients: the DOPPS. *Clin J Am Soc Nephrol* 2014;**9**(10):1702–12.
63. Anand S, Johansen KL, Grimes B, et al. Physical activity and self-reported symptoms of insomnia, restless legs syndrome, and depression: the comprehensive dialysis study. *Hemodial Int* 2013; **17**(1):50–8.
64. Greenwood SA, Lindup H, Taylor K, et al. Evaluation of a pragmatic exercise rehabilitation programme in chronic kidney disease. *Nephrol Dial Transplant* 2012;**27**(Suppl. 3):iii126–134.
65. Dziubek W, Kowalska J, Kusztal M, et al. The level of anxiety and depression in dialysis patients undertaking regular physical exercise training–a preliminary study. *Kidney Blood Pres Res* 2016;**41**(1): 86–98.
66. Kouidi E, Karagiannis V, Grekas D, et al. Depression, heart rate variability, and exercise training in dialysis patients. *Eur J Cardiovasc Prev Rehabil* 2010;**17**(2):160–7.
67. Suh MR, Jung HH, Kim SB, Park JS, Yang WS. Effects of regular exercise on anxiety, depression, and quality of life in maintenance hemodialysis patients. *Ren Fail* 2002;**24**(3):337–45.
68. Ouzouni S, Kouidi E, Sioulis A, Grekas D, Deligiannis A. Effects of intradialytic exercise training on health-related quality of life indices in haemodialysis patients. *Clin Rehabil* 2009;**23**(1):53–63.
69. Levendoglu F, Altintepe L, Okudan N, et al. A twelve week exercise program improves the psychological status, quality of life and work capacity in hemodialysis patients. *J Nephrol* 2004; **17**(6):826–32.
70. Cukor D, Ver Halen N, Fruchter Y. Anxiety and quality of life in ESRD. *Semin Dial* 2013;**26**(3):265–8.
71. Cohen SD, Cukor D, Kimmel PL. Anxiety in patients treated with hemodialysis. *Clin J Am Soc Nephrol* 2016;**11**(12):2250–5.

72. Cukor D, Coplan J, Brown C, Peterson RA, Kimmel PL. Course of depression and anxiety diagnosis in patients treated with hemodialysis: a 16-month follow-up. *Clin J Am Soc Nephrol* 2008;**3**(6): 1752–8.
73. Cukor D, Coplan J, Brown C, et al. Anxiety disorders in adults treated by hemodialysis: a single-center study. *Am J Kidney Dis* 2008;**52**(1):128–36.
74. Cukor D, Coplan J, Brown C, et al. Depression and anxiety in urban hemodialysis patients. *Clin J Am Soc Nephrol* 2007;**2**(3):484–90.
75. Cantekin I, Tan M. The influence of music therapy on perceived stressors and anxiety levels of hemodialysis patients. *Ren Fail* 2013;**35**(1):105–9.
76. Melo GAA, Rodrigues AB, Firmeza MA, Grangeiro ASM, Oliveira PP, Caetano JA. Musical intervention on anxiety and vital parameters of chronic renal patients: a randomized clinical trial. *Rev Lat Am Enfermagem* 2018;**26**:e2978.
77. Pothoulaki M, Macdonald RA, Flowers P, et al. An investigation of the effects of music on anxiety and pain perception in patients undergoing haemodialysis treatment. *J Health Psychol* 2008;**13**(7): 912–20.
78. Kim Y, Evangelista LS, Park YG. Anxiolytic effects of music interventions in patients receiving incenter hemodialysis: a systematic review and meta-analysis. *Nephrol Nurs J* 2015;**42**(4):339–47. quiz 348.
79. Iwagami M, Mansfield KE, Hayes JF, et al. Severe mental illness and chronic kidney disease: a cross-sectional study in the United Kingdom. *Clin Epidemiol* 2018;**10**:421–9.
80. Kessing LV, Gerds TA, Feldt-Rasmussen B, Andersen PK, Licht RW. Use of lithium and anticonvulsants and the rate of chronic kidney disease: a nationwide population-based study. *JAMA Psychiatry* 2015;**72**(12):1182–91.
81. Kripalani M, Shawcross J, Reilly J, Main J. Lithium and chronic kidney disease. *BMJ* 2009;**339**:b2452.
82. Handler J. Lithium and antihypertensive medication: a potentially dangerous interaction. *J Clin Hypertens* 2009;**11**(12):738–42.
83. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: acute and long-term treatment of mixed states in bipolar disorder. *World J Biol Psychiatr* 2018;**19**(1):2–58.
84. Williams S, Ostroff R. Chronic renal failure, hemodialysis, and electroconvulsive therapy: a case report. *J ECT* 2005;**21**(1):41–2.
85. Varghese ST, Sagar R, Jhanjee S. Chronic renal failure and electroconvulsive therapy. *Indian J Med Sci* 2006;**60**(3):114–5.
86. Novick T, Liu Y, Alvanzo A, Zonderman AB, Evans MK, Crews DC. Lifetime cocaine and opiate use and chronic kidney disease. *Am J Nephrol* 2016;**44**(6):447–53.
87. Akkina SK, Ricardo AC, Patel A, et al. Illicit drug use, hypertension, and chronic kidney disease in the US adult population. *Transl Res* 2012;**160**(6):391–8.
88. Lee YK, Park SW, Kim YK, et al. Effects of naltrexone on the ethanol-induced changes in the rat central dopaminergic system. *Alcohol Alcohol* 2005;**40**(4):297–301.
89. Kambia NK, Dine T, Odou P, et al. Pharmacokinetics and dialysability of naltrexone in patients undergoing hemodialysis. *Eur J Drug Metab Pharmacokinet* 2004;**29**(4):225–30.
90. Overman GP, Teter CJ, Guthrie SK. Acamprosate for the adjunctive treatment of alcohol dependence. *Ann Pharmacother* 2003; **37**(7–8):1090–9.
91. Antonelli M, Ferrulli A, Sestito L, et al. Alcohol addiction - the safety of available approved treatment options. *Expert Opin Drug Saf* 2018;**17**(2):169–77.
92. Volkow ND, Frieden TR, Hyde PS, Cha SS. Medication-assisted therapies–tackling the opioid-overdose epidemic. *N Engl J Med* 2014;**370**(22):2063–6.
93. Novick TK, Surapaneni A, Shin JI, et al. Prevalence of opioid, gabapentinoid, and NSAID use in patients with CKD. *Clin J Am Soc Nephrol* 2018;**13**(12):1886–8.
94. Pohland A, Boaz HE, Sullivan HR. Synthesis and identification of metabolites resulting from the biotransformation of DL-methadone in man and in the rat. *J Med Chem* 1971;**14**(3):194–7.
95. Kreek MJ, Schecter AJ, Gutjahr CL, Hecht M. Methadone use in patients with chronic renal disease. *Drug Alcohol Depend* 1980; **5**(3):197–205.
96. Furlan V, Hafi A, Dessalles MC, Bouchez J, Charpentier B, Taburet AM. Methadone is poorly removed by haemodialysis. *Nephrol Dial Transplant* 1999;**14**(1):254–5.
97. Summerfield RJ, Allen MC, Moore RA, Sear JW, McQuay HJ. Buprenorphine in end stage renal failure. *Anaesthesia* 1985;**40**(9): 914.
98. Boger RH. Renal impairment: a challenge for opioid treatment? The role of buprenorphine. *Palliat Med* 2006;**20**(Suppl. 1):s17–23.
99. Bouquegneau A, Dubois BE, Krzesinski JM, Delanaye P. Anorexia nervosa and the kidney. *Am J Kidney Dis* 2012;**60**(2):299–307.
100. Palla B, Litt IF. Medical complications of eating disorders in adolescents. *Pediatrics* 1988;**81**(5):613–23.
101. Riemenschneider T, Bohle A. Morphologic aspects of low-potassium and low-sodium nephropathy. *Clin Nephrol* 1983; **19**(6):271–9.
102. Zipfel S, Lowe B, Reas DL, Deter HC, Herzog W. Long-term prognosis in anorexia nervosa: lessons from a 21-year follow-up study. *Lancet* 2000;**355**(9205):721–2.
103. Burrowes JD, Larive B, Chertow GM, et al. Self-reported appetite, hospitalization and death in haemodialysis patients: findings from the Hemodialysis (HEMO) Study. *Nephrol Dial Transplant* 2005;**20**(12):2765–74.
104. Lopes AA, Elder SJ, Ginsberg N, et al. Lack of appetite in haemodialysis patients–associations with patient characteristics, indicators of nutritional status and outcomes in the international DOPPS. *Nephrol Dial Transplant* 2007;**22**(12):3538–46.
105. Morgan JF, Reid F, Lacey JH. The SCOFF questionnaire: assessment of a new screening tool for eating disorders. *BMJ* 1999; **319**(7223):1467–8.
106. Maguen S, Hebenstreit C, Li Y, et al. Screen for disordered eating: improving the accuracy of eating disorder screening in primary care. *Gen Hosp Psychiatry* 2018;**50**:20–5.
107. Spettigue W, Norris ML, Maras D, et al. Evaluation of the effectiveness and safety of olanzapine as an adjunctive treatment for anorexia nervosa in adolescents: an open-label trial. *J Can Acad Child Adolesc Psychiatry* 2018;**27**(3):197–208.
108. Marvanova M, Gramith K. Role of antidepressants in the treatment of adults with anorexia nervosa. *Ment Health Clin* 2018; **8**(3):127–37.
109. Marzola E, Nasser JA, Hashim SA, Shih PA, Kaye WH. Nutritional rehabilitation in anorexia nervosa: review of the literature and implications for treatment. *BMC Psychiatry* 2013;**13**:290.
110. Fuentebella J, Kerner JA. Refeeding syndrome. *Pediatr Clin N Am* 2009;**56**(5):1201–10.
111. Mehler PS, Winkelman AB, Andersen DM, Gaudiani JL. Nutritional rehabilitation: practical guidelines for refeeding the anorectic patient. *J Nutr Metab* 2010;**2010**.
112. Pike KM, Walsh BT, Vitousek K, Wilson GT, Bauer J. Cognitive behavior therapy in the posthospitalization treatment of anorexia nervosa. *Am J Psychiatry* 2003;**160**(11):2046–9.

113. Bacaltchuk J, Hay P, Trefiglio R. Antidepressants versus psychological treatments and their combination for bulimia nervosa. *Cochrane Database Syst Rev* 2001;(4):CD003385.
114. Bacaltchuk J, Trefiglio RP, Oliveira IR, Hay P, Lima MS, Mari JJ. Combination of antidepressants and psychological treatments for bulimia nervosa: a systematic review. *Acta Psychiatr Scand* 2000;**101**(4):256–64.
115. Poulsen S, Lunn S, Daniel SI, et al. A randomized controlled trial of psychoanalytic psychotherapy or cognitive-behavioral therapy for bulimia nervosa. *Am J Psychiatry* 2014; **171**(1):109–16.
116. Mascolo M, McBride J, Mehler PS. Effective medical treatment strategies to help cessation of purging behaviors. *Int J Eat Disord* 2016;**49**(3):324–30.
117. Mascolo M, Trent S, Colwell C, Mehler PS. What the emergency department needs to know when caring for your patients with eating disorders. *Int J Eat Disord* 2012;**45**(8):977–81.
118. Trent SA, Moreira ME, Colwell CB, Mehler PS. ED management of patients with eating disorders. *Am J Emerg Med* 2013;**31**(5):859–65.
119. Mitchell JE, Pyle RL, Eckert ED, Hatsukami D, Lentz R. Electrolyte and other physiological abnormalities in patients with bulimia. *Psychol Med* 1983;**13**(2):273–8.

QUESTIONS AND ANSWERS

Question 1

In addition to decreased renal clearance of drugs in the setting of reduced GFR, which of the following consequences of CKD can affect medication pharmacokinetics?

A. Increased gastric pH
B. Nausea and vomiting
C. Hypoalbuminemia
D. Fluid overload
E. All of the above

Answer: E

The correct answer is E. CKD has multiple effects on drug pharmacokinetics beyond decreased renal clearance, such that anticipating the net effect of CKD on the clinical properties of medications can be challenging. Elevated blood urea nitrogen levels lead to increased secretion of urea into the stomach, where it is hydrolyzed to ammonia. Ammonia can pick up a proton and increase gastric pH, which can either increase or decrease oral medication bioavailability, depending on the properties of the medication in question. Nausea and vomiting are common symptoms in advanced CKD and can decrease oral bioavailability for those unable to retain medications in the stomach. Urinary protein loss in patients with nephrotic syndrome leads to hypoalbuminemia. Decreased available sites for medication protein binding can increase the fraction of unbound drug, which alters the amount of drug available for action at receptor sites. Fluid overload, even in the absence of overt peripheral edema, can alter medication pharmacokinetics by increasing volume of distribution, leading to lower than expected drug concentrations.

Question 2

A 56-year-old woman with CKD stage 4 due to diabetes mellitus and hypertension presents for a follow-up visit. She has lost 5 pounds since her last visit 3 months ago. She also mentions that she has been sleeping much less than usual lately. On further questioning, she notes that she has felt fatigued and has had a difficult time concentrating. She denies itching and metallic taste. On physical examination, blood pressure is 135/72 mm Hg, heart rate is 84 beats per minute, and oxygen saturation is 99% on room air. Auscultation of the chest reveals a regular heart rhythm with no pericardial friction rub. She has trace lower extremity pitting edema. Laboratory tests reveal a hemoglobin of 9 g/dL. Which of the following is the most appropriate next step?

A. Have the patient complete a screening questionnaire for MDD
B. Refer to psychiatry for CBT
C. Begin treatment with an erythropoiesis-stimulating agent
D. Start sertraline 50 mg daily
E. Initiate dialysis for uremic symptoms

Answer: A

The correct answer is A. This patient presents with several symptoms that could be consistent with either MDD or uremia, including changes in weight, sleep disturbance, fatigue, and difficulty concentrating. To distinguish between uremia and MDD, clinicians should first screen patients with a self-report questionnaire and confirm the presence of anhedonia or sadness. If the patient's screening questionnaire is positive, clinicians should then confirm the diagnosis by a structured clinical interview. Answers B and D are incorrect because the diagnosis of uncomplicated MDD must be established before considering the patient's preference for treatment with either pharmacologic or nonpharmacologic therapy. Distinguishing between uremic symptoms and MDD is critical, because dialysis initiation would not address the underlying problem if the patient's symptoms are caused by MDD, so Answer E is incorrect. Answer C is incorrect because although anemia can result in fatigue symptoms, beginning treatment for anemia with an erythropoiesis-stimulating agent is not the next best step.

Question 3

A 48-year-old man with CKD stage 3b presents for follow-up. He notes loss of interest in going for walks in his neighborhood, which he previously enjoyed. He also states that he has been having a difficult time sleeping and feels tired all the time. You suspect that he may have MDD. Screening questionnaire with the Quick Inventory of Depressive Symptomatology revealed a score of 14. Structured clinical interview confirms MDD. He denies any episodes of psychosis or mania. He asks about initiating pharmacologic treatment.

Compared with placebo, sertraline has been shown to have which of the following effects in patients with nondialysis CKD stages 3–5 and MDD?

A. Improvement in depressive symptoms and no increased side effects
B. Improvement in depressive symptoms and increase in neurologic side effects such as somnolence
C. No improvement in depressive symptoms and greater gastrointestinal side effects such as nausea and diarrhea

D. Improvement in depressive symptoms and increased gastrointestinal side effects
E. No improvement in depressive symptoms and neurologic side effects

Answer: C

The correct answer is C. Only one clinical trial has compared a SSRI to placebo for the treatment of MDD in patients with nondialysis CKD. The Chronic Kidney Disease Antidepressant Sertraline Trial (CAST) was a double-blind, randomized, placebo-controlled trial evaluating the efficacy and tolerability of sertraline for the treatment of MDD. In this trial, participants in both the placebo and sertraline groups demonstrated some improvement in depressive symptoms from baseline to study exit, but there was no benefit of sertraline over placebo. Furthermore, participants randomized to sertraline experienced greater side effects of nausea and diarrhea compared with the placebo group. Given the lack of data to support efficacy of treatments for MDD in patients with CKD, it is reasonable to initiate a cautious trial of sertraline in patients who are interested in pharmacologic therapy, with close monitoring of depressive symptoms and side effects.[33]

Question 4

A 42-year-old woman with bipolar affective disorder I and hypertension is referred to you for management of CKD stage 3a. She takes lithium and amlodipine. On physical examination, blood pressure is 152/94 mm Hg, heart rate is 74 beats per minute, and oxygen saturation is 98% on room air. Cardiopulmonary and abdominal examinations are unremarkable. She has trace lower extremity edema. You start chlorthalidone 25 mg once daily to treat her hypertension. She returns two weeks later for follow-up. Laboratory values from her initial and follow-up visit are as follows:

Laboratory Value	Initial Visit	Follow-Up Visit
S[Na]	142 mEq/L	139 mEq/L
S[K]	4.2 mEq/L	4.1 mEq/L
tCO2	23 mEq/L	25 mEq/L
S[Cr]	1.41 mg/dL	1.38 mg/dL
eGFR	52 mL/min/1.73 m^2	53 mL/min/1.73 m^2
Lithium level	1.1 mEq/L	1.5 mEq/L (target range 0.6−1.2 mmol/L)

Which of the following is the most likely mechanism of the elevated lithium level?

A. Intentional lithium overdose
B. Increased lithium reabsorption in the proximal tubule
C. Prerenal acute kidney injury due to starting a diuretic
D. Alteration in lithium protein binding due to inhibition by the thiazide diuretic
E. Development of lithium-induced tubulointerstitial kidney disease

Answer: B

The correct answer is B. Lithium is filtered at the glomerulus and reabsorbed in a manner similar to sodium in the proximal tubule, so states associated with increased proximal tubular sodium reabsorption also increase lithium reabsorption. Thiazide and loop diuretics augment natriuresis, generating a state of mild volume depletion that increases sodium and lithium reabsorption in the proximal tubule. Answer A is incorrect because known medication interactions should be considered before making a diagnosis of intentional lithium overdose. Answer C is incorrect because her eGFR was unchanged from the initial visit to her follow-up visit 2 weeks later. Answer D is incorrect because thiazide diuretics are not known to alter protein binding. Answer E is incorrect because tubulointerstitial disease is a potential chronic complication of lithium therapy and would not develop as an acute complication.

Question 5

You are called to evaluate a 19-year-old woman admitted to the hospital for the management of anorexia nervosa. On physical examination, blood pressure is 106/72 mm Hg, heart rate is 90 beats per minute, respiratory rate is 16 per minute, and oxygen saturation is 100% on room air. Her body mass index is 16 kg/m^2. She has increased risk of which of the following?

A. Kidney stones
B. Chronic kidney disease
C. Refeeding syndrome
D. Metabolic alkalosis
E. All of the above

Answer: E

The correct answer is E. Kidney stone risk is thought to be increased in patients with anorexia nervosa due to chronic volume depletion and low urinary output, as well as renal homeostatic alterations in response to hypophosphatemia and chronic hypochloremic alkalosis that can develop in the setting of chronic purging behaviors. Patients with anorexia nervosa have a high rate of CKD, thought to be related to chronic volume depletion, hypokalemia, and nephrolithiasis. Refeeding syndrome is an important complication of nutritional therapy and weight gain for patients with anorexia

nervosa. Patients admitted to the hospital for weight gain require careful monitoring and correction of electrolyte disturbances, and gradual reintroduction of caloric intake. Metabolic alkalosis can develop in the setting of chronic purging behaviors, such as laxative or diuretic abuse.

Question 6

During hemodialysis rounds, you are called to evaluate a 50-year old woman with ESRD secondary to lupus nephritis. She is trying to sign off early again. She also has a history of chronic back pain, migraine headaches, and irritable bowel syndrome. Today she complains of left arm tingling and cramps and states that "Maxine was not here to cannulate me. The rest don't know what they're doing." The dialysis staff have voiced frustration about this patient's hemodialysis shortening and skipping behavior.

Which of the following is the next best step in management?

A. Prescribe temazepam to take orally 2 hours before dialysis treatments
B. Start treatment with sertraline 100 mg once daily
C. Assign the same dialysis nurse to the patient during hemodialysis treatments
D. Change dialysis prescription to frequent daily hemodialysis
E. Refer to psychiatry for further management

Answer: C

The correct answer is C. The patient manifests symptoms of a generalized anxiety disorder often encountered in hemodialysis patients, such as somatic symptoms, hemodialysis shortening and skipping behavior, and fear of losing control by asking for the same caretaker. One approach, therefore, is to assign the same hemodialysis nursing staff to take care of the patient, which could lessen or alleviate anxiety symptoms during the hemodialysis procedure. Options B, D, and E could be considered if conservative measures do not address the patient's anxiety symptoms but are not the next best options. Benzodiazepines should be avoided in dialysis patients due to adverse effects such as psychomotor retardation and cognitive dysfunction, so option A is incorrect.

CHAPTER

69

Preparing for Transplantation

Alexander C. Wiseman, Scott Davis, Erik Stites, James E. Cooper

Division of Nephrology, University of Colorado Anschutz Medical Campus, Aurora, CO, United States

Abstract

Individuals with progressive advanced chronic kidney disease (CKD) have a number of treatment modalities to consider before reaching end-stage renal disease. As CKD reaches stage 4, and particularly as glomerular filtration rate approaches 20 mL/min, patients should be informed of kidney transplantation as a treatment option, provided education regarding the transplant process, and be referred to a transplant center unless there are clear contraindications or comorbidities that preclude consideration. There is an unfortunate and dramatic disparity between those who are eligible for transplantation and those who receive a transplant, due in part to referral biases, the comparative shortage of deceased donors, and a lack of acceptance or awareness of living kidney donation as an option. This chapter reviews the transplant landscape, discusses the procedural and pathophysiological considerations for kidney transplantation, and outlines the transplant evaluation process, including inclusion and exclusion criteria.

KIDNEY TRANSPLANTATION VERSUS DIALYSIS: SCOPE OF THE PROBLEM AND PUBLIC HEALTH IMPLICATIONS

After over a century in development, kidney transplantation is well established as the preferred treatment modality for patients with severe chronic kidney disease (CKD). As Alexis Carrel, a pioneering figure who developed vascular suturing techniques and contributed to the invention of the first perfusion pump, wrote in 1914, "The surgical side of transplantation of organs is now completed, as we are now able to perform transplantation of organs with perfect ease and with excellent results from an anatomical standpoint…all our efforts must now be directed toward the biological methods which will prevent the reaction of the body against foreign tissue and allow the adapting of homoplastic organs to their hosts."[1] Our evolving understanding of the immunologic barriers has resulted in critical discoveries involving the major histocompatibility complex (MHC), tissue typing, and immunosuppressive drugs and advanced transplantation as the standard of care. Although dialysis has developed alongside kidney transplantation as an important alternative for patients with end-stage renal disease (ESRD), transplantation can now offer more years of life that are of higher quality and often at less cost to society when performed in appropriately selected individuals.

Patients undergoing kidney transplantation have higher mortality shortly after surgery compared with patients still awaiting transplant on dialysis, related to the surgical procedure and the associated induction immunosuppression. In a landmark study performed in 1999, Wolfe et al. reported an early risk of death that was 2.8-fold higher 2 weeks after surgery, which importantly became equal at 106 days after transplantation, with improved survival by 244 days. Similar analyses have been performed in many different subgroups and in contemporary cohorts of patients.[2,3] In a low cardiovascular risk elderly patient, living donor transplantation confers an immediate survival advantage, while even a high cardiovascular risk elderly patient undergoing transplantation with a deceased donor kidney with comorbidities (termed expanded criteria donor, ECD) enjoys a survival benefit of transplantation over dialysis after 528 days (Figure 69.1).[2] This survival benefit can represent many more years of life, particularly for younger patients. A 37-year-old woman might be expected to gain 21.2 more years of life through kidney transplantation compared with dialysis, although this is still several years less than the expected lifetime of a person who is of the same age and sex in the general population.[4] Longer duration of pretransplant dialysis exposure decreases posttransplant survival, emphasizing the critical importance of early referral to transplant, identification of living donors, and performing preemptive kidney transplantation.[5–7]

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00069-3

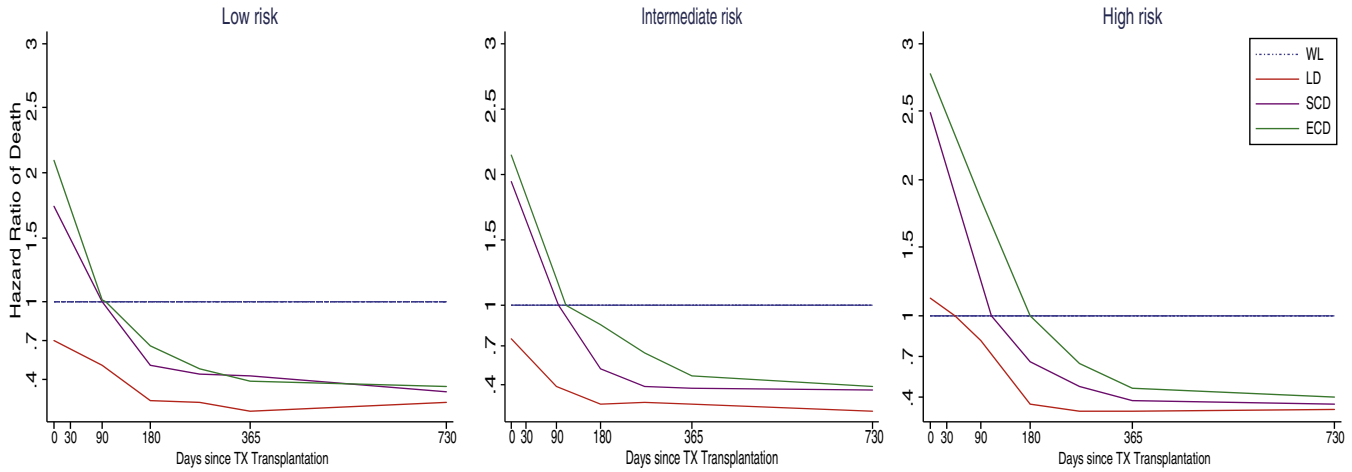


FIGURE 69.1 Quantification of the Early Risk of Death in Elderly Kidney Transplant Recipients. The multivariate adjusted relative risk of death in low (first panel), intermediate (second panel), and high (third panel) cardiovascular risk patients. In each panel, the multivariate adjusted risk of death in living donor (LD, shown in red), standard criteria deceased donor (SCD, shown in purple), or expanded criteria deceased donor (ECD, shown in green) transplant recipients is compared with that in waitlisted patients of similar cardiovascular risk (shown in blue) who had been on dialysis for equal lengths of time but who had not yet received a kidney transplant. In all cardiovascular risk groups, the risk of death immediately after SCD and ECD transplantation was higher than that among waitlisted patients of similar cardiovascular risk. In contrast, the risk of death in low and intermediate cardiovascular risk recipients was immediately lower than that in similar risk patients who remained on the waiting list. The long-term risk of death was lower with transplantation in all risk groups and with all donor types. *J. S. Gill, E. Schaeffner, S. Chadban, et al, Quantification of the Early Risk of Death in Elderly Kidney Transplant Recipients, American Journal of Transplantation, John Wiley and Sons, November 21, 2012.*

In addition to improved survival, patients undergoing transplantation enjoy improvements in quality of life. ESRD is commonly marked by physical symptoms and impairments, an increasing burden of lifestyle restrictions, medications, and procedures, as well as psychological distress and depression, all of which can impose stress on personal and professional relationships. Several different instruments have been used to measure health-related quality of life in kidney transplant recipients. The vast majority demonstrate significant improvements in physical, emotional, and social well-being compared with responses in those treated with multiple different renal replacement modalities and throughout many different healthcare systems.[8,9] Many of these benefits extend to several different subgroups of patients, including the elderly, the morbidly obese, and patients with significant comorbid medical conditions.[10,11]

Kidney transplantation can also be cost-saving or more cost-effective compared with dialysis therapy. In 2015, the US spent $88,195 per patient per year for hemodialysis care, compared with $34,084 per patient per year for transplant care.[4] A study in 2003 found that living donor kidney transplantation saved $94,579 and with the added value of 3.5 quality-adjusted life years gained per recipient, a total savings of $269,319 compared with remaining on dialysis was achieved.[12] A more recent study estimated the monetary savings of improved survival and health of the recipient at $1.3 million.[13] Even practices designed to increase access to transplantation that are often associated with more resource utilization, including the use of kidneys from deceased donors with increased comorbidities and transplantation across ABO- or human leukocyte antigen (HLA)-incompatibility with enhanced immunosuppressive strategies, may be cost-effective compared with continued dialysis therapy.[13]

Despite these striking clinical and social benefits of kidney transplantation, transplant rates have only incrementally increased relative to those in need.[14–16] There are myriad factors that limit transplantation rates, with organ availability often paramount. Although preemptive living donor kidney transplantation currently represents the optimal treatment for ESRD, living donor rates have decreased over the past decade in the US, with 6436 in 2006 and 5630 in 2016. Barriers to living donation include cultural or religious beliefs, help in identifying donors, and lack of effective education, costs, and transplant center processes, much of which can be manifestations of socioeconomic, racial, and geographic differences.[17,18]

Although approximately 2.4 million people die every year in the US, only a fraction of these deaths occur in absence of comorbid conditions and in a manner that allows effective procurement and subsequent kidney utilization, excluding them from donation. In 2016, the potential deceased donor pool was estimated to be around 38,500 donors, much larger than the 14,229 deceased donor kidneys actually transplanted, yet still dwarfed by the 95,456 patients on the transplant waitlist that same year.[14,19] As a result, 20% of patients on the kidney transplantation waiting list in 2016 had been on dialysis for at least 6 years, placing them at continued

risk of developing health complications that ultimately exclude them from transplantation.[14,20] 50% of patients listed in 2013 were still waiting for transplantation by 2016, whereas only 20% and 15% had undergone deceased or living donor transplant. 11% were removed from the list, and 8% died while awaiting transplantation.[14]

Long waiting times make it imperative to maximize the utilization of the potential deceased donor pool, yet barriers exist for organ procurement organizations in obtaining donor consent and procuring organs. Many countries have enacted "opt-out" laws for donor consent to expand the donor pool.[21] Additionally, many kidney offers are turned down by transplant centers or patients because of perceptions of poorer organ quality. Various categories have been designed to capture the variables of a given organ to estimate graft survival and aid appropriate allocation, including standard criteria donor (SCD) vs. ECD, the latter encompassing donors >60 years of age or donors age 50–59 years who have at least two of the following: hypertension, terminal S[Cr] > 1.5 mg/dL, or death from a cerebrovascular accident. Recently, the US adopted the Kidney Donor Profile Index (KDPI), which combines ten variables to predict the likelihood of graft failure relative to all donor kidneys recovered the prior year to aid in organ allocation. There have been several efforts to increase use of marginal organs and reduce discard rates, including ECD or high KDPI kidneys, those with acute kidney injury, and kidneys with hepatitis C, human immunodeficiency virus (HIV), or increased risk for infectious disease transmission. Importantly, all of these practices have shown better outcomes for patients who receive these organs compared with the competing risk of continued dialysis while waiting for a better organ offer.[22–25]

There are also several factors associated with the recipient that limit access to transplantation. A number of barriers other than medical conditions include appropriate insurance coverage and financial means, a social support system to help patients through the posttransplant period, and the ability to stay in the area of the transplant center the first several weeks after surgery. All these factors can introduce socioeconomic, racial, and geographic disparities in patient access to transplantation.[26,27]

KIDNEY TRANSPLANTATION: PATHOPHYSIOLOGY AND IMMUNOBIOLOGY

Kidney transplantation is now highly successful, due to advances in understanding the immunological response to transplanted tissue and in the development of pharmaceutical agents that inhibit this response. The discovery of the HLA gene complex on chromosome 6 that encodes a highly polymorphic group of MHC proteins responsible for antigen presentation to T cells was critical in identifying the major factors in host recognition of donor tissue. Transplantation between two non-HLA identical individuals results in a recipient alloimmune response to donor HLA proteins (or "antigens"), necessitating the use of posttransplantation immunosuppression to minimize the risk of allograft rejection. The following section provides an overview of the mechanisms underlying alloimmune responses to kidney grafts and the immunosuppressive therapies used to prevent these processes from occurring.

The HLA antigens most relevant to transplant immunobiology are organized into two classes. Each class has a common function of antigen presentation to lymphocytes. Class I HLA molecules are present on all nucleated cells, consist of a polymorphic α-chain and a nonvariable β2 microglobulin molecule, and include HLA-A, B, and C peptides. Class II HLA molecules are found on antigen-presenting cells (APCs), consist of two polymorphic α and β chains, and include HLA DR, DQ, and DP peptides. Both HLA antigen classes are codominantly expressed, such that individuals express two copies of each protein, one from each parent.

Because these highly polymorphic HLA proteins represent the major antigenic stimuli in host recognition of donor tissue, it stands to reason that improved HLA matching between donor and recipient would equate to less alloimmune response following transplantation, with improved longer-term allograft outcomes. This is indeed the case, with better HLA-matched transplant recipients experiencing longer average graft survival[28]; however, the relative importance of HLA matching has been lessened over time with the development of more effective "modern day" immunosuppression.[29] Traditional HLA matching between kidney donors and recipients takes into consideration antigen alleles at the A, B, and DR loci. Accounting for two codominant antigens at each of these loci on each copy of chromosome 6, a total of six HLA loci are considered for each transplant pair (2 A, 2 B, and 2 DR HLA). Although not historically factored into traditional match/mismatch calculations, the degree of matching at other HLA loci, namely DQ, has also been shown to correlate with graft outcomes.[30] The decision to proceed with kidney transplantation between a particular donor/recipient pair is not typically contingent on the degree of HLA match/mismatch. However, this information does influence deceased donor organ allocation, may be used if multiple potential living kidney donors are available for a particular recipient, and may influence posttransplant immunosuppression goals (e.g. less aggressive immunosuppression for better HLA-matched donor/recipient pairs).

Preexisting antibodies directed against HLA antigens represent a significant barrier to transplantation for many individuals. These anti-HLA antibodies develop as a result of exposure to another individual's HLA antigens, usually by way of blood transfusions, pregnancies, or prior organ transplants. A landmark study in the 1960s by Paul Terasaki demonstrated transplantation in the presence of high levels of donor-specific anti-HLA antibodies (DSAs) often leads to catastrophic hyperacute graft rejection.[31] His subsequent development of pretransplant cross-match assays revolutionized transplantation by allowing clinicians to identify and avoid dangerous levels of donor-specific anti-HLA antibody (DSA) between a particular donor–recipient pair.

The total burden of an individual's anti-HLA antibodies is quantified as a panel reactive antibody, or PRA, and represents the population frequency to which an individual will be incompatible due to their current level of circulating anti-HLA antibodies. PRA is calculated as a percent ranging from 0 to 100, such that an individual with a PRA of 50% would be expected to have transplant-limiting anti-HLA antibodies directed toward approximately 50% of the population. Higher degrees of PRA increasingly limit the available population of kidney donors for a particular individual, resulting in increased average waiting times for patients with high PRA values (Figure 69.2). Given this disadvantage, allocation policies attempt to prioritize organs to highly sensitized patients regardless of region of donor origin.[32]

Following transplantation, immunosuppression is used to prevent allorecognition of the donor organ and subsequent graft rejection; however, insufficient immunosuppression may allow an alloimmune response to occur. This begins with recipient T-cell recognition of donor HLA antigens, presented either intact on donor-derived APCs (direct pathway) or as allopeptides presented by recipient APCs (indirect pathway). T-cell activation proceeds *via* several overlapping pathways that can be organized into three separate signals.

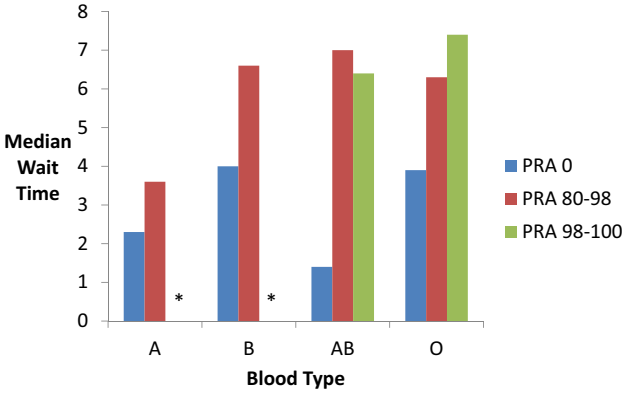


FIGURE 69.2 Median wait times for patients with 0%, 80–98%, and 98–100% PRA by blood type. *Median wait time cannot be calculated due to estimated time to transplant probability has not reached 50%. *Adapted from the* USRDS 2017 annual data report, *vol. 2, Chapter 6.*

Signal 1 follows T-cell receptor recognition of antigen. It includes calmodulin activation of calcineurin, subsequent dephosphorylation of the nuclear factor of activated T cells and its translocation to the nucleus, eventually leading to transcription of growth signals.

Signal 2 is a costimulatory event that, together with signal 1, is required for T-cell activation to occur. In one of the better-characterized pathways, the CD80/86 complex on APCs binds to CD28 on T cells, providing a costimulatory signal resulting in T-cell cytokine production, including IL-2, inducing further T-cell development. This signaling pathway is inhibited by the T-cell surface protein CTLA-4, which competitively binds to CD80/86, effectively acting as an "off" switch. CTLA-4 expression is upregulated when foreign antigen is less abundant.

Signal 3 is initiated with IL-2 binding to its receptor on T cells, leading to activation of proliferative signals, such as the mammalian target of rapamycin (mTOR) pathway, and subsequent cell cycle progression, resulting in lymphocyte proliferation.

The more commonly prescribed immunosuppressive agents used to prevent and treat allograft rejection in transplant recipients can be described in terms of their mechanisms of action (Figure 69.3). Induction therapy given in the perioperative phase includes T-cell depleting rabbit-derived anti-thymocyte globulin (rATG) or the IL-2 receptor antagonist basiliximab. rATG is more effective at preventing acute rejection compared with basiliximab, especially in higher immunologic risk transplant recipients,[33,34] and is used in the majority of US transplants.[14]

Maintenance immunosuppression regimens most commonly include a combination of a calcineurin inhibitor (CNI) with an antiproliferative agent, with or without prednisone. The CNIs cyclosporine (CsA) and tacrolimus inhibit calcineurin activity (signal 1), and the purine analogues azathioprine and mycophenolate mofetil (MMF) inhibit lymphocyte cell cycle progression (signal 3), preventing subsequent T-cell proliferation. Tacrolimus and MMF have largely replaced CsA and azathioprine, respectively, due to their increased efficacy in preventing acute allograft rejection.[14,35–38] Indeed, over 93% of all US transplant recipients are prescribed tacrolimus and MMF, with or without prednisone, at the time of transplantation.[14]

Despite the well-documented superior efficacy of CNIs in preventing acute allograft rejection, considerable effort has focused on minimizing posttransplant CNI exposure due to concerns over potential long-term nephrotoxicity. Inhibitors of the signal 3

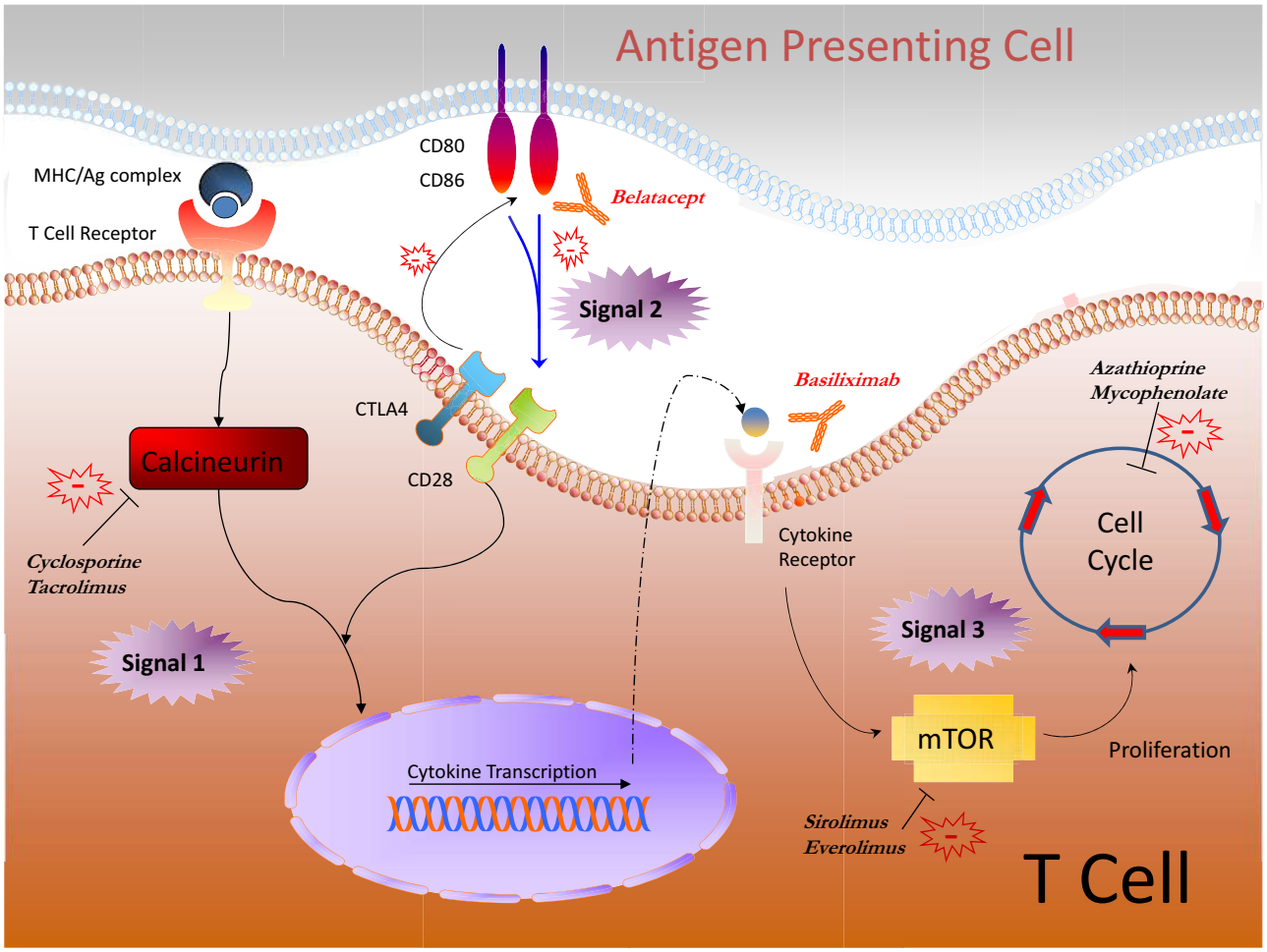


FIGURE 69.3 Schematic cartoon depicting a simplified schematic of T-cell activation with sites of action for common immunosuppressive agents.

proliferative mTOR pathway (mTORis) sirolimus and everolimus have been used in several CNI-minimization strategies, including CNI withdrawal, CNI conversion, reduced CNI exposure, and complete CNI avoidance.[37–41] Higher rates of acute rejection, unfavorable side effect profiles, and a lack of data showing improvement in longer-term outcomes such as graft or patient survival compared with CNI-containing regimens has tempered enthusiasm for these agents. The costimulation inhibitor belatacept has been studied as an alternative to CNI-based therapy with more promising results. Belatacept is a humanized monoclonal antibody containing the extracellular portion of human CTLA-4, which inhibits signal 2 costimulation by providing a negative signal to the CD80/86 complex on APCs. When compared with CsA and combined with MMF and prednisone, improved graft and patient survival was reported in those receiving belatacept despite higher early acute rejection rates.[42] Recent data suggest introducing belatacept while tapering CNI for several months after transplantation may reduce the higher rejection rates seen when used in complete CNI-avoidance regimens.[43]

The evolution of posttransplant immunosuppression protocols over the last 5 decades has resulted in a significant reduction in allograft rejection rates. Nevertheless, allograft rejection continues to occur in approximately 10–15% of transplant recipients during the first year following transplantation, conveying inferior graft outcomes.[44] Following T-cell activation events, the surrounding cytokine milieu further influences T-cell differentiation into various effector subtypes, each with the ability to damage allograft tissue *via* distinct mechanisms. These patterns of immune-mediated allograft damage, or graft rejection, are broadly characterized as "cell-mediated" (T-cell) and "antibody-mediated" (B-cell, or AMR) rejection. Cell-mediated rejection is driven mainly by CD8+ and CD4+ T-cell activity. Cytotoxic CD8+ T cells can cause direct tissue toxicity by way of the fas-fas ligand complex and perforin/granzyme B

mechanism. Proliferative signals from CD4+ helper T cells can augment further CD8+ T-cell activation, macrophage activation, and subsequent delayed-type hypersensitivity reaction within the graft, as well as B-cell activation. Activated B cells, in turn, when differentiated into antibody-producing plasma cells, produce antibodies directed against donor HLA-antigens (DSA). Antibody–antigen binding can then lead to complement-dependent graft damage, or AMR.

Allograft rejection is diagnosed histologically using allograft biopsy samples. Rejection is characterized by the Banff criteria,[45] and this information is used to direct appropriate treatment. Milder forms of T cell–mediated rejection include lymphocytic infiltration of tubules and the interstitium and are usually treated with 3–5 days of intravenous (IV) steroids. More severe forms of T-cell mediated rejection involve lymphocytic infiltration of large vessel endothelium, requiring treatment with lymphocyte depleting therapies such as rATG. In contrast, AMR is characterized by microvascular (capillary) inflammation with or without complement split-product C4d deposition in the presence of circulating DSA. Treatment of AMR is directed at removal of DSA with methods such as plasma exchange or immune absorption, and various combinations of therapies to suppress further antibody development, such as the immunomodulatory agent intravenous immunoglobulin (IVIG), the anti-B-cell CD20 monoclonal antibody rituximab, and the anti-plasma cell proteasome inhibitor bortezomib.[46] Recently, several groups have studied terminal complement inhibition with the anti-C5 humanized monoclonal antibody eculizumab in the treatment of more severe forms of AMR.[47]

DIAGNOSIS: DETERMINING ELIGIBILITY FOR KIDNEY TRANSPLANTATION

While kidney transplantation is the optimal mode of treatment for patients with severe CKD, the surgical procedure and the attendant risks of chronic immunosuppressive therapy require that screening processes are in place to ensure successful posttransplant outcomes. There are few absolute contraindications for kidney transplantation (Table 69.1).

Beyond these considerations, there are a number of medical conditions that may represent relative contraindications, including hypotension, pulmonary hypertension, morbid obesity, frailty, asymptomatic cardiovascular disease, and moderate-severe pulmonary disease.[3,48–50] While these factors may not be exclusionary in isolation, a combination of these factors may lead to the consideration of risk/reward of transplantation favoring risk rather than reward. These conditions may have treatment options or rehabilitation potential that may mitigate these risks. Many patients therefore should be referred and evaluated for transplantation despite these potentially hazardous conditions.

TABLE 69.1 Contraindications to Kidney Transplantation

Recent or metastatic malignancy
Severe, irreversible vascular disease
Active/uncontrolled infection
Severe, irreversible organ disease such as severe chronic obstructive or restrictive lung disease, cirrhosis, or heart failure (although in certain cases combined lung–kidney, liver–kidney, or heart–kidney transplant could be considered)
Severe debilitation
Persistent nonadherence
Uncontrolled psychiatric disease
Persistent substance abuse

The evaluation is a multidisciplinary process that takes into consideration the potential candidate's medical, surgical, and psychosocial circumstances, ultimately leading to a determination by both the candidate and the transplant center of the potential advantages and disadvantages of transplantation compared with other treatment options. Highlights of this process include specific considerations and resulting assessments.

Medical

Mortality after transplantation is driven by infections, malignancy, and cardiovascular disease. Effort to mitigate these risks is a goal of the evaluation process. Patients with a history of coronary artery disease (CAD) or congestive heart failure (CHF) and patients with risk factors for CAD/CHF are typically screened for the presence of ongoing disease by an echocardiogram and cardiac stress testing. Recent guidelines suggest that screening for CAD may be considered for asymptomatic patients without prior history of CAD if greater than three or more of the following risk factors are present: (a) diabetes mellitus, (b) prior cardiovascular disease, (c) more than 1 year on dialysis, (d) left ventricular hypertrophy, (e) age greater than 60 years, (f) smoking, (g) hypertension, and (h) dyslipidemia (Class IIb; Level of Evidence C).[51] Positive findings often lead to evaluation by coronary angiography. Intervention once disease is characterized remains a topic of controversy. In general, critical lesions (e.g. proximal left main CAD) should be revascularized. Noncritical disease should not arbitrarily lead to revascularization. The physician and patient should balance the risk of revascularization and the potential (but perhaps unproven) benefits.

The prognosis and the response to immunosuppressive therapy of patients with a history of malignancy influence the candidacy for and the timing of transplantation. In general, those with a history of treated malignancy with >95% 5-year estimated disease progression-free survival (DPFS) may proceed with transplantation. Those with 85–95% DPFS may be best served by a 2-year waiting period before transplantation. Those with <85% DPFS may be asked to wait 5 years before transplantation, to avoid the risk of recurrence and accelerated progression once receiving immunosuppression.[52] Oncology consultation is necessary to assist in predicting expected disease remission and risk of recurrence, as well as the likelihood of progression and the potential response to additional treatments following transplantation.

Routine screening for infections before transplantation includes a chest radiograph, dental assessment, urinalysis, screening for mycobacterium tuberculosis, and serologic testing for cytomegalovirus (CMV), Epstein–Barr virus, hepatitis B and C virus, HIV, and syphilis. Additional screening based on regional risk factors (e.g. coccidioides, histoplasma) may also be considered. These tests assist in guiding pretransplant treatment, assessing for risk of reactivation of disease, and planning for appropriate antibiotic prophylaxis and monitoring following transplantation. Patients with controlled HIV infection and those with chronic hepatitis C virus infection in the absence of cirrhosis may still successfully undergo transplantation with appropriate monitoring and treatment following transplant.[53,54] Active bacterial infections must be treated successfully before transplantation. Vaccinations should be up to date and should include vaccination for hepatitis A and B virus, influenza, varicella zoster, and pneumococcus. Live vaccines and live attenuated vaccines are contraindicated in immunosuppressed candidates, candidates within one month of transplantation, and in recipients following transplantation.

Surgical

Urologic evaluation entails assessment of adequate bladder structure and function. Patients with known neurologic or structural concerns including congenital anomalies, neurologic diseases, and bladder or ureteral obstruction will typically require evaluation of bladder integrity *via* urodynamic studies and cystoscopy.

Vascular issues pertinent to transplantation include identification of healthy vasculature to facilitate vascular anastomosis. Imaging of the aortoiliac system typically entails computed tomography to evaluate for vascular calcification, with IV contrast as needed if significant concern is raised on initial imaging.

Psychosocial

A key component in determining transplant candidacy is the assessment of potential barriers to success either from a psychological or social perspective. Nonadherence is a primary cause of chronic rejection and graft loss following transplantation. Efforts to identify potential barriers to adherence (whether physical, emotional, financial, or educational) are important at an early stage of referral. Screening for untreated/undertreated mental health disorders, a history of nonadherence, substance abuse, and financial or physical/geographic barriers to appropriate medical care, is performed as part of the transplant evaluation process, typically by a social worker. These may include referral for psychological, psychiatric, or neurocognitive testing.

Risk Factor-Specific Considerations

Elderly Patients

There is no defined age at which one is deemed no longer a transplant candidate, but age does serve as a framework for discussing associated risks as well as a more broad understanding of the relative benefits of transplantation compared with dialysis, which diminish with increasing age and comorbidities. Elderly patients with a history of cardiovascular disease may still derive benefit from transplantation. They may particularly benefit from the lower-risk procedure of living donor transplantation rather than deceased donor transplant (Figure 69.1).[2] Given the lack of an absolute "age cutoff" for transplant eligibility, measures of frailty are more commonly employed to assist in determining differences in "biological age" vs. "chronological age."[50,55,56]

Obesity

Similar to age, there is not a clear body mass index (BMI) cutoff at which point transplant is demonstrably inferior to remaining on dialysis; however, obesity contributes to posttransplant recovery/morbidity including wound healing, infections, delayed graft function (DGF), increased risk of posttransplant diabetes, and cardiovascular disease.[57] Given these concerns most transplant centers request weight loss interventions pretransplant to minimize complications and untoward outcomes following transplant.

Risk for Recurrent Renal Disease

A number of renal diseases leading to CKD will recur in the allograft but are variable in their presentation and

TABLE 69.2 Estimated Risks for Recurrent Disease Following Transplant and Risk for Graft Loss Related to Recurrence

Disease	Approximate Recurrence Rate (%)	Graft Loss due to Recurrence
FSGS	30–60	Common
Atypical HUS	20–50	Common
Immune complex–mediated MPGN	30–50	Common
Complement-mediated MPGN	60–100	Common
ANCA-associated Vasculitis	10–20	Common
Membranous	10–30	Uncommon
Henoch Schonlein Purpura (HSP)	15–50	Uncommon
IgA nephropathy	30–50	Uncommon
Anti-glomerular basement membrane (GBM)	Rare	Uncommon

severity following transplant.[58–60] In general, there is no primary renal disease that recurs with such frequency or severity that poses a contraindication for transplantation. If disease recurrence does occur and leads to early or rapid graft loss, future retransplantation may be deferred until a different therapeutic intervention emerges. Table 69.2 delineates a number of diseases that recur in the transplanted kidney, and the risk of subsequent graft loss related to disease recurrence.

TREATMENT: THE KIDNEY TRANSPLANTATION PROCEDURE

Organ Procurement

Deceased Donor Organ Procurement

Procurement of organs from deceased donors occurs following declaration of patient death (either brain death or cardiac death). The kidneys are typically removed *en bloc* to ensure preservation of the vasculature. Special attention is given to avoid stripping the adventitial tissue surrounding the ureters and potentially compromising their blood supply. The kidneys are prepared on the back table with further dissection and isolation of vessels, flushed with cold preservation fluid, and then placed in cold storage for transportation and preservation until the transplantation procedure.

A number of preservation solutions are available. There is no consensus evidence to support the use of one solution over another. Use patterns therefore vary by region.[61] Cold storage can either be static or with machine-driven pulsatile perfusion ("pumped"). Prolonged cold storage (cold ischemia time) is one of several factors that has a strong association with the risk for developing DGF, commonly defined as the need for renal replacement therapy within seven days after transplantation. DGF results in higher posttransplantation costs due to the cost of dialysis and higher rates of readmission.[62] DGF is associated with decreased 1- and 5-year graft survival.[63] Machine perfusion has been associated with reduced rates of DGF[64] and has become increasingly prevalent, but its widespread use continues to be controversial due to increased procurement costs and unclear impact on long-term patient and graft outcomes.[65]

Living Donor Surgical Procedure and Kidney Procurement

Open surgery for living donor nephrectomy has largely been replaced by less-invasive laparoscopic approaches, due to several advantages including reduced morbidity, shorter length of stay, and better cosmetic results. Laparoscopic nephrectomy accounts for greater than 97% of living donor nephrectomies in the US.[14] There are multiple technical variations of laparoscopic donor nephrectomy. Hand-assisted laparoscopic nephrectomy in which one of the laparoscopic ports is large enough for the surgeon to manually manipulate intraabdominal structures is twice as common in the US compared with unassisted methods. Newer approaches on the horizon include single-site laparoendoscopic nephrectomy and robotic nephrectomy.

The Transplantation Procedure

The kidney graft is typically placed extraperitoneally in the recipient right or left iliac fossa, with venous and arterial anastomoses to the ipsilateral external iliac vein and artery, respectively. The ureter is preferably anastamosed to the bladder, but can also be connected to the

ipsilateral native ureter if needed. A double-J ureteral stent is commonly placed at the time of transplant to reduce the risk of major urologic complications, such as urine leak and ureteral obstruction, but at the cost of an increased risk of urinary tract infection and BK virus activation (see below, complications).[66] The ureteral stent is typically retrieved by cystoscopy 2–6 weeks after transplantation.

Surgical complications of transplantation typically manifest with graft dysfunction within the first few days to months after transplantation. They can be generally divided into vascular complications, urologic complications, and extrinsic compression by fluid collections.[67] Prompt imaging of the graft with duplex ultrasound is crucial to diagnosis and management. Arterial or venous thromboses are rare, but can be catastrophic, and often require urgent surgical reexploration. Dilation of the ureter or collecting system may suggest ureteral obstruction or bladder dysfunction that must be relieved with placement of a ureteral stent, percutaneous nephrostomy, or bladder catheter. Fluid collections due to hematomas, seromas, and lymphocoeles are common after transplantation and are often benign and need only be monitored. However, collections may lead to graft dysfunction *via* compression of vascular structures, renal parenchyma, or urine outflow and require intervention. Urinary leak, commonly from the ureteral anastomosis, manifests as a fluid collection and is diagnosed by measuring the fluid creatinine concentration, which will be higher than the S[Cr] in the setting of a urine leak, but will be similar/equivalent to S[Cr] in the setting of a lymphocoele.

Short-Term and Long-Term Outcomes

Unadjusted patient and graft survival for both living donor and deceased donor kidney transplantation has steadily improved over the past several decades. In the US, 1- and 5-year patient survival is 97% and 87% for deceased donor kidney transplantation and 98% and 92% for living donor kidney transplantation, respectively. Graft survival at 1 and 5 years is 93% and 75% for deceased donor kidney transplantation and 98% and 85% for living donor kidney transplantation, respectively.[14] Reported registry outcomes from other regions of the world such as Europe, the United Kingdom, Australia, and New Zealand are very similar to US outcomes.

Among the most important donor factors predicting outcomes is whether the donor is a living donor or a deceased donor. Many risk factors for deceased donor transplantation are captured by a Kidney Donor Risk Index,[68] that is then translated to a KDPI that stratifies and estimates expected graft longevity on a percentile scale. A higher score on a scale of 1–100% is associated with an increased risk of graft failure. For example, the predicted median graft survival of a deceased donor kidney with a KDPI >85% is 5.6 years, compared with a median graft survival of over 11 years for a deceased donor kidney with a KDPI <20%. Despite the associated increased risk of graft failure, patients with higher predicted waitlist mortality (i.e. older, diabetic, or on renal replacement therapy) still derive benefit from accepting higher risk transplants rather than remaining on dialysis.[24]

Preemptive Transplantation

Early access to transplantation is important to optimize posttransplant outcomes. Receiving a transplant before initiating dialysis, termed preemptive transplantation, is associated with a substantial improvement in patient and graft survival. Recipients of preemptive deceased donor transplants experience an 18% reduced risk of death and a 25% reduced risk of graft failure. Preemptive living donor recipients experience a 31% reduced risk of death and a 27% reduced risk of graft failure compared with those treated with dialysis before transplantation.[69] This only encapsulates posttransplant advantages and neglects the additional morbidity and mortality benefits of avoiding initiation of and maintenance on dialysis.

Common Complications Following Transplantation

Immunologic injury due to graft rejection is a primary focus when considering potential complications after transplantation leading to early and late graft loss. Other complications, often related to immunosuppression, also have important implications for patient morbidity and mortality and graft loss. Over 40% of renal graft failures are due to patient death with a functioning graft (DWFG). Rates of DWFG have remained constant over the past 20 years.[14,70] Recurrent or *de novo* glomerular disease leads to graft loss in 18% to 22% of renal transplants, with particularly high rates of recurrence for patients with focal segmental glomerulosclerosis and some complement-mediated diseases such as dense deposit disease (Table 69.2).[70,71]

Cardiovascular disease is the leading cause of death in renal transplant recipients, accounting for about 25% of graft loss due to DWFG.[70,72] This is due to the high burden of preexisting disease in the advanced

CKD/ESRD population and traditional risk factors such as hypertension, dyslipidemia, diabetes, and obesity. Other contributing factors include the increased risk of development of diabetes after transplantation due to adverse effects of immunosuppression medications, particularly attributed to CNIs and corticosteroids. Patients developing diabetes after transplantation have a threefold increased risk of major cardiac events compared with patients without diabetes.[73]

The second leading cause of death after transplantation is infection, accounting for about 15% of graft loss from DWFG.[70,72] The source and type of infection is influenced by recipient characteristics, immunosuppression regimen, and time since transplantation.[74] Donor-derived and nosocomial infections must be considered within the first few weeks after transplantation. Reactivation of latent infections occurs within the first few months after transplantation. Beyond six months after transplantation, community-acquired infections are the most prevalent. Infections of particular importance after kidney transplant include CMV and BK virus infection.

CMV is a member of the human herpesvirus family, with 60–70% seroprevalence in adults. CMV infection after transplantation is associated with increased mortality and death-censored graft failure after transplant, and is common in high-risk recipients (CMV-seropositive donor to CMV-seronegative recipient).[75,76] Prophylactic antiviral therapy is often prescribed for 3–6 months following transplantation, but after discontinuation of prophylaxis, a high index of suspicion must be maintained because late-onset infection is not uncommon.[77]

BK virus is a polyomavirus with 80–90% seroprevalence in the population. It remains dormant in the uroepithelium. The virus may reactivate after transplantation in the setting of immunosuppression, leading to allograft nephropathy, characterized by tubulointerstitial inflammation. BK viruria and viremia typically precede nephropathy by 2–3 months and 2–6 weeks, respectively, offering an opportunity to screen for BK virus during periods of increased risk (e.g. the first 1–2 years following transplantation). Most BK viremia occurs in the first 3–6 months after transplantation. While not a life-threatening infection, nephropathy can result in graft loss in 15–40% of cases.[78]

Malignancy accounts for 12–14% of DWFG and is the third leading cause of death after kidney transplantation.[70,72] Several cancers have higher incidence in renal transplant recipients compared with the general population, particularly nonmelanoma skin cancer, lymphoma, kidney cancer, melanoma, leukemia, and cervical and vulvovaginal cancers.[79] Posttransplant lymphoproliferative disorder (PTLD) is a spectrum of disorders ranging from localized polymorphic B-cell proliferation to B-cell and rarely T-cell lymphomas. It is relatively rare, with an incidence of 0.1–0.2% per year overall, but EBV-seronegative transplant recipients (approximately 5% of the US population) have a significantly higher risk of early PTLD than EBV-seropositive recipients.[80]

TABLE 69.3 Important Drug–Drug Interactions with Immunosuppressive Agents and Commonly Used Medications

Drug Class (Examples)	Causes of Increased Blood Levels	Causes of Decreased Blood Levels
Calcineurin inhibitors* (tacrolimus, cyclosporine)	Azole antifungals (i.e. fluconazole) Protease inhibitors (i.e. atazanavir, nelfinavir) Calcium channel blockers (nondihydropyridine > dihydropyridine) Macrolide antibiotics Antiretroviral-boosting agent (i.e. ritonavir) Amiodarone Grapefruit Other CYP3A4 inhibitors	Antiepileptics (i.e. carbamazepine, phenytoin) Rifampin Efavirenz St. John's Wort Other CYP3A4 inducers
mTOR inhibitors (sirolimus, everolimus)	Azole antifungals (i.e. fluconazole)	Antiepileptics (i.e. carbamazepine, phenytoin)
	Macrolide antibiotics	Rifampin
	Grapefruit	St. John's Wort
	Other CYP3A4 and P-glycoprotein/ABCB1 inhibitors	Other CYP3A4 and P-glycoprotein/ABCB1 inducers
Antimetabolites (azathioprine, mycophenolate)	Allopurinol or febuxostat (only for azathioprine)	Antacids (mycophenolate)

** Calcineurin inhibitors (cyclosporine > tacrolimus) inhibit metabolism of statins and increase risk of myopathy.*

Treatment depends on the morphology, location, and EBV status of the lesion but involves immunosuppression reduction and potentially chemotherapy, radiation, and surgical resection.

Drug Interactions

Immunosuppression medications have narrow therapeutic windows to achieve the desired effect of reducing the risk of graft rejection while minimizing the risk of toxicities. Therefore, it is important to understand the impact that other medications and substances can have on their metabolism that may perturb this balance, particularly by affecting the cytochrome P450 (CYP3A4) metabolism of CNIs.[81] Table 69.3 provides a list of interactions with the most common immunosuppression therapies in kidney transplant patients.

CONCLUSIONS

Early consideration of transplantation and referral for transplant evaluation for appropriate candidates with stage 4 CKD is essential. This priority is necessary to determine candidacy and begin the discussion of the waitlist process and living kidney donation options. Education regarding the surgical procedure and immunosuppressive agents is important to balance the potential risks vs. the rewards of transplantation. With few exceptions, transplantation is the treatment of choice for eligible individuals. When proactively considered (particularly in the context of potential living kidney donation) transplantation can be performed preemptively and dialysis treatment can be avoided.

References

1. Hamilton D. *A history of organ transplantation : ancient legends to modern practice*. Pittsburgh, PA: University of Pittsburgh Press; 2012.
2. Gill JS, Schaeffner E, Chadban S, Dong J, Rose C, Johnston O, et al. Quantification of the early risk of death in elderly kidney transplant recipients. *Am J Transplant* 2013;**13**(2):427–32.
3. Gill JS, Lan J, Dong J, Rose C, Hendren E, Johnston O, et al. The survival benefit of kidney transplantation in obese patients. *Am J Transplant* 2013;**13**(8):2083–90.
4. System USRD. *2017 USRDS annual data report: epidemiology of kidney disease in the United States*. Bethesda, 2017. June 8, 2018.
5. Meier-Kriesche HU, Port FK, Ojo AO, Rudich SM, Hanson JA, Cibrik DM, et al. Effect of waiting time on renal transplant outcome. *Kidney Int* 2000;**58**(3):1311–7.
6. Wiseman AC, Huang E, Kamgar M, Bunnapradist S. The impact of pre-transplant dialysis on simultaneous pancreas-kidney versus living donor kidney transplant outcomes. *Nephrol Dial Transplant* 2013;**28**(4):1047–58.
7. Goldfarb-Rumyantzev A, Hurdle JF, Scandling J, Wang Z, Baird B, Barenbaum L, et al. Duration of end-stage renal disease and kidney transplant outcome. *Nephrol Dial Transplant* 2005;**20**(1):167–75.
8. Tonelli M, Wiebe N, Knoll G, Bello A, Browne S, Jadhav D, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant* 2011;**11**(10):2093–109.
9. Butt Z, Yount SE, Caicedo JC, Abecassis MM, Cella D. Quality of life assessment in renal transplant: review and future directions. *Clin Transplant* 2008;**22**(3):292–303.
10. Cornella C, Brustia M, Lazzarich E, Cofano F, Ceruso A, Barbe MC, et al. Quality of life in renal transplant patients over 60 years of age. *Transplant Proc* 2008;**40**(6):1865–6.
11. Zaydfudim V, Feurer ID, Moore DR, Moore DE, Pinson CW, Shaffer D. Pre-transplant overweight and obesity do not affect physical quality of life after kidney transplantation. *J Am Coll Surg* 2010;**210**(3):336–44.
12. Matas AJ, Schnitzler M. Payment for living donor (vendor) kidneys: a cost-effectiveness analysis. *Am J Transplant* 2004;**4**(2):216–21.
13. Axelrod DA, Schnitzler MA, Xiao H, Irish W, Tuttle-Newhall E, Chang SH, et al. An economic assessment of contemporary kidney transplant practice. *Am J Transplant* 2018;**18**(5):1168–76.
14. Hart A, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Robinson A, et al. OPTN/SRTR 2016 annual data report: kidney. *Am J Transplant* 2018;**18**(Suppl. 1):18–113.
15. *ERA-EDTA registry annual report 2016*, vol. 27. Amsterdam; 2018. p. 1–182.
16. *Brazilian transplantation registry*. 2017. p. 1–34.
17. Wu DA, Robb ML, Watson CJE, Forsythe JLR, Tomson CRV, Cairns J, et al. Barriers to living donor kidney transplantation in the United Kingdom: a national observational study. *Nephrol Dial Transplant* 2017;**32**(5):890–900.
18. Purnell TS, Hall YN, Boulware LE. Understanding and overcoming barriers to living kidney donation among racial and ethnic minorities in the United States. *Adv Chron Kidney Dis* 2012;**19**(4):244–51.
19. Klassen DK, Edwards LB, Stewart DE, Glazier AK, Orlowski JP, Berg CL. The OPTN deceased donor potential study: implications for policy and practice. *Am J Transplant* 2016;**16**(6):1707–14.
20. Schold J, Srinivas TR, Sehgal AR, Meier-Kriesche HU. Half of kidney transplant candidates who are older than 60 years now placed on the waiting list will die before receiving a deceased-donor transplant. *Clin J Am Soc Nephrol* 2009;**4**(7):1239–45.
21. Shepherd L, O'Carroll RE, Ferguson E. An international comparison of deceased and living organ donation/transplant rates in opt-in and opt-out systems: a panel study. *BMC Med* 2014;**12**:131.
22. Bae S, Massie AB, Luo X, Anjum S, Desai NM, Segev DL. Changes in discard rate after the introduction of the kidney donor profile index (KDPI). *Am J Transplant* 2016;**16**(7):2202–7.
23. Bowring MG, Holscher CM, Zhou S, Massie AB, Garonzik-Wang J, Kucirka LM, et al. Turn down for what? Patient outcomes associated with declining increased infectious risk kidneys. *Am J Transplant* 2018;**18**(3):617–24.
24. Massie AB, Luo X, Chow EK, Alejo JL, Desai NM, Segev DL. Survival benefit of primary deceased donor transplantation with high-KDPI kidneys. *Am J Transplant* 2014;**14**(10):2310–6.
25. Cohen JB, Eddinger KC, Locke JE, Forde KA, Reese PP, Sawinski DL. Survival benefit of transplantation with a deceased diabetic donor kidney compared with remaining on the waitlist. *Clin J Am Soc Nephrol* 2017;**12**(6):974–82.
26. Patzer RE, Perryman JP, Schrager JD, Pastan S, Amaral S, Gazmararian JA, et al. The role of race and poverty on steps to kidney transplantation in the Southeastern United States. *Am J Transplant* 2012;**12**(2):358–68.
27. Joshi S, Gaynor JJ, Bayers S, Guerra G, Eldefrawy A, Chediak Z, et al. Disparities among Blacks, Hispanics, and Whites in time from starting dialysis to kidney transplant waitlisting. *Transplantation* 2013;**95**(2):309–18.

28. Report: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/.
29. Opelz G, Dohler B. Effect of human leukocyte antigen compatibility on kidney graft survival: comparative analysis of two decades. *Transplantation* 2007;**84**(2):137–43.
30. Lim WH, Chapman JR, Coates PT, Lewis JR, Russ GR, Watson N, et al. HLA-DQ mismatches and rejection in kidney transplant recipients. *Clin J Am Soc Nephrol* 2016;**11**(5):875–83.
31. Patel R, Terasaki PI. Significance of the positive crossmatch test in kidney transplantation. *N Engl J Med* 1969;**280**(14):735–9.
32. Stewart DE, Kucheryavaya AY, Klassen DK, Turgeon NA, Formica RN, Aeder MI. Changes in deceased donor kidney transplantation one year after KAS implementation. *Am J Transplant* 2016;**16**(6):1834–47.
33. Brennan DC, Daller JA, Lake KD, Cibrik D, Del Castillo D, Thymoglobulin Induction Study G. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 2006;**355**(19):1967–77.
34. Gralla J, Wiseman AC. The impact of IL2ra induction therapy in kidney transplantation using tacrolimus- and mycophenolate-based immunosuppression. *Transplantation* 2010;**90**(6):639–44.
35. Wagner M, Earley AK, Webster AC, Schmid CH, Balk EM, Uhlig K. Mycophenolic acid versus azathioprine as primary immunosuppression for kidney transplant recipients. *Cochrane Database Syst Rev* 2015;(12):CD007746.
36. Webster AC, Woodroffe RC, Taylor RS, Chapman JR, Craig JC. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. *BMJ* 2005;**331**(7520):810.
37. Ekberg H, Tedesco-Silva H, Demirbas A, Vitko S, Nashan B, Gurkan A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007;**357**(25):2562–75.
38. Sawinski D, Trofe-Clark J, Leas B, Uhl S, Tuteja S, Kaczmarek JL, et al. Calcineurin inhibitor minimization, conversion, withdrawal, and avoidance strategies in renal transplantation: a systematic review and meta-analysis. *Am J Transplant* 2016;**16**(7):2117–38.
39. Flechner SM. mTOR inhibition and clinical transplantation: kidney. *Transplantation* 2018;**102**(2S Suppl. 1):S17–8.
40. Oberbauer R. Protocol conversion from a calcineurin inhibitor based therapy to sirolimus. *Transplantation* 2009;**87**(8 Suppl.):S7–10.
41. Pascual J, Berger SP, Witzke O, Tedesco H, Mulgaonkar S, Qazi Y, et al. Everolimus with reduced calcineurin inhibitor exposure in renal transplantation. *J Am Soc Nephrol* 2018;**29**(7):1979–91.
42. Vincenti F, Rostaing L, Grinyo J, Rice K, Steinberg S, Gaite L, et al. Belatacept and long-term outcomes in kidney transplantation. *N Engl J Med* 2016;**374**(4):333–43.
43. Adams AB, Goldstein J, Garrett C, Zhang R, Patzer RE, Newell KA, et al. Belatacept combined with transient calcineurin inhibitor therapy prevents rejection and promotes improved long-term renal allograft function. *Am J Transplant* 2017;**17**(11):2922–36.
44. Lefaucheur C, Loupy A, Vernerey D, Duong-Van-Huyen JP, Suberbielle C, Anglicheau D, et al. Antibody-mediated vascular rejection of kidney allografts: a population-based study. *Lancet* 2013;**381**(9863):313–9.
45. Haas M. The relationship between pathologic lesions of active and chronic antibody-mediated rejection in renal allografts. *Am J Transplant* 2018;**18**(12):2849–56.
46. Wan SS, Ying TD, Wyburn K, Roberts DM, Wyld M, Chadban SJ. The treatment of antibody-mediated rejection in kidney transplantation: an updated systematic review and meta-analysis. *Transplantation* 2018;**102**(4):557–68.
47. Orandi BJ, Zachary AA, Dagher NN, Bagnasco SM, Garonzik-Wang JM, Van Arendonk KJ, et al. Eculizumab and splenectomy as salvage therapy for severe antibody-mediated rejection after HLA-incompatible kidney transplantation. *Transplantation* 2014;**98**(8):857–63.
48. Alhamad T, Brennan DC, Brifkani Z, Xiao H, Schnitzler MA, Dharnidharka VR, et al. Pretransplant midodrine use: a newly identified risk marker for complications after kidney transplantation. *Transplantation* 2016;**100**(5):1086–93.
49. Lentine KL, Villines TC, Axelrod D, Kaviratne S, Weir MR, Costa SP. Evaluation and management of pulmonary hypertension in kidney transplant candidates and recipients: concepts and controversies. *Transplantation* 2017;**101**(1):166–81.
50. McAdams-DeMarco MA, Law A, King E, Orandi B, Salter M, Gupta N, et al. Frailty and mortality in kidney transplant recipients. *Am J Transplant* 2015;**15**(1):149–54.
51. Lentine KL, Costa SP, Weir MR, Robb JF, Fleisher LA, Kasiske BL, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *J Am Coll Cardiol* 2012;**60**(5):434–80.
52. Knoll G, Cockfield S, Blydt-Hansen T, Baran D, Kiberd B, Landsberg D, et al. Canadian Society of Transplantation consensus guidelines on eligibility for kidney transplantation. *CMAJ* 2005;**173**(10):1181–4.
53. Stock PG, Barin B, Murphy B, Hanto D, Diego JM, Light J, et al. Outcomes of kidney transplantation in HIV-infected recipients. *N Engl J Med* 2010;**363**(21):2004–14.
54. Sawinski D, Kaur N, Ajeti A, Trofe-Clark J, Lim M, Bleicher M, et al. Successful treatment of hepatitis C in renal transplant recipients with direct-acting antiviral agents. *Am J Transplant* 2016;**16**(5):1588–95.
55. McAdams-DeMarco MA, Law A, Salter ML, Chow E, Grams M, Walston J, et al. Frailty and early hospital readmission after kidney transplantation. *Am J Transplant* 2013;**13**(8):2091–5.
56. Reese PP, Cappola AR, Shults J, Townsend RR, Gadegbeku CA, Anderson C, et al. Physical performance and frailty in chronic kidney disease. *Am J Nephrol* 2013;**38**(4):307–15.
57. Nicoletto BB, Fonseca NK, Manfro RC, Goncalves LF, Leitao CB, Souza GC. Effects of obesity on kidney transplantation outcomes: a systematic review and meta-analysis. *Transplantation* 2014;**98**(2):167–76.
58. Fairhead T, Knoll G. Recurrent glomerular disease after kidney transplantation. *Curr Opin Nephrol Hypertens* 2010;**19**(6):578–85.
59. O'Shaughnessy MM, Liu S, Montez-Rath ME, Lenihan CR, Lafayette RA, Winkelmayer WC. Kidney transplantation outcomes across GN subtypes in the United States. *J Am Soc Nephrol* 2017;**28**(2):632–44.
60. Stegall MD, Cornell LD, Park WD, Smith BH, Cosio FG. Renal allograft histology at 10 Years after transplantation in the tacrolimus era: evidence of pervasive chronic injury. *Am J Transplant* 2018;**18**(1):180–8.
61. O'Callaghan JM, Knight SR, Morgan RD, Morris PJ. Preservation solutions for static cold storage of kidney allografts: a systematic review and meta-analysis. *Am J Transplant* 2012;**12**(4):896–906.
62. Groen H, Moers C, Smits JM, Treckmann J, Monbaliu D, Rahmel A, et al. Cost-effectiveness of hypothermic machine preservation versus static cold storage in renal transplantation. *Am J Transplant* 2012;**12**(7):1824–30.
63. Butala NM, Reese PP, Doshi MD, Parikh CR. Is delayed graft function causally associated with long-term outcomes after kidney

transplantation? Instrumental variable analysis. *Transplantation* 2013;**95**(8):1008–14.
64. O'Callaghan JM, Morgan RD, Knight SR, Morris PJ. Systematic review and meta-analysis of hypothermic machine perfusion versus static cold storage of kidney allografts on transplant outcomes. *Br J Surg* 2013;**100**(8):991–1001.
65. Sandal S, Luo X, Massie AB, Paraskevas S, Cantarovich M, Segev DL. Machine perfusion and long-term kidney transplant recipient outcomes across allograft risk strata. *Nephrol Dial Transplant* 2018;**33**(7):1251–9.
66. Wilson CH, Rix DA, Manas DM. Routine intraoperative ureteric stenting for kidney transplant recipients. *Cochrane Database Syst Rev* 2013;(6):CD004925.
67. Humar A, Matas AJ. Surgical complications after kidney transplantation. *Semin Dial* 2005;**18**(6):505–10.
68. Rao PS, Schaubel DE, Guidinger MK, Andreoni KA, Wolfe RA, Merion RM, et al. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. *Transplantation* 2009;**88**(2):231–6.
69. Kasiske BL, Snyder JJ, Matas AJ, Ellison MD, Gill JS, Kausz AT. Preemptive kidney transplantation: the advantage and the advantaged. *J Am Soc Nephrol* 2002;**13**(5):1358–64.
70. El-Zoghby ZM SM, Lager DJ, Kremers WK, Amer H, Gloor JM, Cosio FG. Identifying specific causes of kidney allograft loss. *Am J Transplant* 2009;**9**(3):527–35.
71. Sellares J, de Freitas DG, Mengel M, Reeve J, Einecke G, Sis B, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant* 2012;**12**(2):388–99.
72. Kahwaji J, Bunnapradist S, Hsu JW, Idroos ML, Dudek R. Cause of death with graft function among renal transplant recipients in an integrated healthcare system. *Transplantation* 2011;**91**(2): 225–30.
73. Hjelmesaeth J, Hartmann A, Leivestad T, Holdaas H, Sagedal S, Olstad M, et al. The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. *Kidney Int* 2006;**69**(3):588–95.
74. Karuthu S, Blumberg EA. Common infections in kidney transplant recipients. *Clin J Am Soc Nephrol* 2012;**7**(12):2058–70.
75. Sagedal S, Hartmann A, Nordal KP, Osnes K, Leivestad T, Foss A, et al. Impact of early cytomegalovirus infection and disease on long-term recipient and kidney graft survival. *Kidney Int* 2004; **66**(1):329–37.
76. Schnitzler MA, Lowell JA, Hardinger KL, Boxerman SB, Bailey TC, Brennan DC. The association of cytomegalovirus sero-pairing with outcomes and costs following cadaveric renal transplantation prior to the introduction of oral ganciclovir CMV prophylaxis. *Am J Transplant* 2003;**3**(4):445–51.
77. Humar A, Lebranchu Y, Vincenti F, Blumberg EA, Punch JD, Limaye AP, et al. The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Am J Transplant* 2010;**10**(5):1228–37.
78. Brennan DC, Agha I, Bohl DL, Schnitzler MA, Hardinger KL, Lockwood M, et al. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. *Am J Transplant* 2005;**5**(3):582–94.
79. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. *Am J Transplant* 2004;**4**(6): 905–13.
80. Caillard S, Lamy FX, Quelen C, Dantal J, Lebranchu Y, Lang P, et al. Epidemiology of posttransplant lymphoproliferative disorders in adult kidney and kidney pancreas recipients: report of the French registry and analysis of subgroups of lymphomas. *Am J Transplant* 2012;**12**(3):682–93.
81. Menon MC, Murphy B. Maintenance immunosuppression in renal transplantation. *Curr Opin Pharmacol* 2013;**13**(4):662–71.

QUESTIONS AND ANSWERS

Question 1

What factors contribute most to the variability in expected wait time among patients waiting for a deceased donor kidney transplant in the US?

A. Blood type, prior transplantation
B. Age, PRAs
C. PRAs, blood type
D. PRAs, insurance type
E. Blood type, age

Answer: C

Blood type and tissue matching play roles in the allocation of kidneys for transplantation. A patient's "sensitization" or burden of preformed antibodies to human tissue, often generated through prior exposures such as pregnancy, blood transfusions, or past transplants, is measured by a PRA test, representing the estimated percentage of people in the general population against whom a recipient might have HLA antibodies. It can often be very difficult to find an acceptable match for patients with very high PRAs. Priority is given to blood type matching between donor and recipient, with patients with blood type AB and A having the shortest time until transplantation, and those with blood types B and O with longer wait times. Recipient age and insurance type do not influence matching but could be relative barriers in gaining access to the waiting list.

Question 2

A 53-year-old woman with stage 4 CKD due to diabetic nephropathy presents to a transplant center for transplant evaluation. She has a history of three pregnancies and two blood transfusions. HLA testing reveals a calculated PRA of 73%. Which of the following statements pertaining to her PRA is accurate?

A. The patient carries a 73% risk of antibody-mediated graft rejection following transplant due to circulating anti-HLA antibodies
B. The patient would be expected to have a positive cross-match against 73% of the population due to circulating anti-HLA antibodies
C. 73% of the patient's circulating anti-HLA antibodies would be expected to react with a particular kidney donor organ
D. The patient is expected to have 0 of 6 HLA matches (six mismatches) with 73% of the population

Answer: B

The PRA test is a quantitative assessment of anti-HLA antibody burden in terms of likelihood of a positive cross-match with any other individual within the population. In this example, this patient has developed anti-HLA antibodies throughout her lifetime that, when taken as a whole, would be expected to cross-react with the tissue of another individual within the population approximately 73% of the time. The PRA is calculated using known frequencies of individual HLA alleles throughout a given population. Antibodies against common HLA antigens will add significantly to an individual's PRA, whereas antibodies against rare HLA antigens may not add to the PRA at all. The PRA is calculated using the sum of all anti-HLA antibodies detected by screening methods.

Because the pool of available kidney donors for a given patient in need of transplantation becomes increasingly restricted as the PRA level rises, patients with high PRA levels suffer from longer wait times for donor kidneys.

Answer A is incorrect because PRA does not necessarily correlate with risk of acute rejection. Rejection risk stems from DSA as opposed to the overall PRA level. Answer C is incorrect as PRA is a measure of total anti-HLA antibodies, not a percentage of antibody burden. Answer D is incorrect as PRA level does not necessarily correlate with the degree of HLA-antigen matching between a recipient and a particular donor. Rather it is a measurement of the likelihood that an individual's total antibody load may react with another individual within the population.

Question 3

A 69-year-old man with CKD stage 4 due to type 2 diabetes undergoes kidney transplant evaluation. His past medical history is significant for stable CAD, status-post a drug-eluting stent to his left circumflex artery 3 years ago. A stress echocardiogram demonstrates no wall motion defects. Ejection fraction is 40%. His BMI is 35.5 kg/m^2. During evaluation, he is noted to be frail due to slow walk speed, weakness as assessed by grip strength, self-reported exhaustion, and low physical activity. Which risk factor will be of greatest concern regarding his posttransplant graft loss and death?

A. His age
B. His cardiovascular history
C. His obesity
D. His risk of recurrent disease
E. His functional status

Answer: E

Chronological age is not a contraindication to kidney transplantation. While increasing age may lead to increase in associated morbidities that influence successful transplantation, age alone is not a risk factor. Similarly, patients with appropriately treated cardiovascular

disease are transplant candidates and demonstrate significant survival benefit particularly when receiving a living donor kidney transplant. Diabetic nephropathy commonly occurs following transplantation but is typically indolent and not clinically significant until late (~10 years) into the posttransplant period. Diabetic nephropathy is not a contraindication for transplant. Obesity is a risk factor for DGF and graft loss but not increased mortality following transplantation. However, this patient's functional status (assessed by objective measures of frailty) is associated with DGF, early hospital readmission, graft loss, and mortality and is the primary risk factor from the above choices that would deserve attention. Dedicated physical therapy with longitudinal assessments may improve outcomes after transplantation.

Question 4

A 61-year-old male with a history of CKD due to lupus nephritis, status-post deceased donor kidney transplant 15 months ago presents for routine follow-up. His graft function has been stable with S[Cr] 1.5 mg/dL. His immunosuppression regimen consists of tacrolimus, mycophenolate, and prednisone. He has had no rejection, *de novo* DSA, BK virus reactivation, or infection. He denies any complaints other than having gained 15 pounds since transplantation. He now has a BMI of 34. His blood pressure is 142/89 mm Hg. Physical examination is otherwise unremarkable. Relevant laboratory values are below:

S[Cr] 1.6 mg/dL
Fasting glucose 150 mg/dL
Tacrolimus trough 9.8 ng/mL
Urine protein:creatinine ratio 0.5 g/g

Which of the following steps will address the most likely cause of his eventual graft failure?

A. Stop tacrolimus and replace with an mTOR inhibitor
B. Check serum ANA titer, anti-dsDNA titer, and complement levels
C. Kidney biopsy to assess for acute rejection
D. Check hemoglobin A1c, encourage weight loss, and optimize blood pressure control
E. Check BK virus PCR

Answer: D

Forty percent of renal graft failures are due to DWFG. Cardiovascular disease is the leading cause of death. The patient has multiple risk factors for cardiovascular disease including obesity, hypertension, and now likely posttransplant diabetes based on an elevated fasting glucose. He needs aggressive management of his cardiovascular risk factors. Isolated CNI toxicity is now thought to be a rare cause of graft failure. Lupus nephritis can recur after transplantation, but this is relatively rare. Stable graft function would be inconsistent with lupus recurrence or acute rejection. BK nephropathy is more commonly diagnosed within 3–6 months after transplantation.

Question 5

A 62-year-old man with chronic glomerulonephritis due to hepatitis C virus infection is referred for kidney transplant evaluation. His estimated glomerular filtration rate is 19 mL/min/1.73 m^2. During the evaluation, he is noted to have anti-HCV antibodies. HCV RNA is 680,000 copies/mL. The detected HCV is genotype 1a. He has no stigmata of liver disease on physical examination. His liver function panel, prothrombin time, serum albumin concentration, and platelet count are all within normal range. A liver ultrasound is normal. With respect to his transplant candidacy and renal replacement therapy planning, which of the following is true?

A. He is not eligible for transplantation due to chronic HCV infection
B. He should be treated to clear HCV before transplantation because the direct-acting antiviral agents are ineffective following transplantation
C. If approved for transplant, he should undergo combined liver–kidney transplantation
D. His waiting time for transplant will be shorter because he can be transplanted with organs from HCV positive donors without increased risk
E. He should undergo transplantation with a kidney from an HCV Ab-negative donor to prevent potential complications related to HCV coinfection and reactivation.

Answer: D

Chronic HCV infection is not an exclusion to kidney transplantation. The survival benefit of transplantation over dialysis still prevails, despite the potential for HCV-related complications such as worsening liver disease and recurrence of glomerulonephritis. Understanding the degree of liver injury before transplantation is important, as advanced cirrhosis is a contraindication to kidney transplantation. Patients should be considered for combined liver–kidney transplantation under these circumstances. The direct-acting antivirals are effective in both the pre- and posttransplant settings, despite the theoretical impact of immunosuppression on viral clearance, and drug–drug interactions that exist with some DAA and CNIs. Patients with chronic viremic HCV infection can receive organs from HCV-positive kidney donors. Because the pool of HCV positive donors is much larger than the pool of HCV positive candidates,

waiting time for transplantation is dramatically shorter for HCV positive candidates. (Transplantation with less than 6 months waiting time is not unusual in the US.) This should be taken into consideration when caring for the HCV-positive patient with stage 4–5 CKD. DAA therapy should be withheld in many circumstances if the patient is determined to be transplant-eligible due to this tremendous advantage.

Question 6

A 26-year-old patient is admitted with acute kidney injury of his kidney transplant, now 4 years after transplantation. He has missed a number of clinic appointments recently. His most recent visit to the transplant center the month prior had identified fluctuating and downtrending tacrolimus trough concentrations, as well as the presence of new-onset donor-specific antibody to DR7 (class II HLA). S[Cr] is 2.4 mg/dL, increased from a baseline of 1.5 mg/dL with no explanation after initial evaluation. You obtain a kidney transplant biopsy that demonstrates microvascular inflammation in the peritubular capillaries without tubulitis. Immunohistochemical stain for C4d staining is positive. In addition to high-dose corticosteroids, initial therapy should include which of the following?

A. Belatacept
B. Thymoglobulin
C. High-dose IVIG
D. Plasmapheresis/low-dose IVIG
E. Basiliximab

Answer: D

The biopsy and accompanying circulating donor-specific antibody results are consistent with AMR. Antibody-directed therapy should be used. Basiliximab, belatacept, and thymoglobulin act on T cells, not B cells or plasma cells. Belatacept acts by inhibiting activation of T cells, thymoglobulin by binding to and depleting T cells, and basiliximab binds to IL-2 receptors and inhibits T-cell proliferation. Therefore, A, B, and C are incorrect. IVIG is a useful therapy for inhibiting antibodies and antibody production but has not been shown to be adequate alone in treating AMR. Plasmapheresis together with IVIG is more effective than IVIG alone in inhibiting alloantibody responses, albeit proven in small, uncontrolled studies. Answer D is correct.

CHAPTER

70

Preparing for Hemodialysis

Robert T. Isom, Glenn M. Chertow

Stanford University School of Medicine, Division of Nephrology, Palo Alto, CA, United States

Abstract

Decisions regarding the initiation of renal replacement therapy (RRT)—whether hemodialysis (HD), peritoneal dialysis, kidney transplantation, or palliative care is chosen—are critical when considering combined efforts among nephrologists, patients, family members, and nonphysician health care personnel. The transition from management of progressive chronic kidney disease (CKD) to that of end-stage renal disease (ESRD) requires the nephrologist to have a clear understanding of the disease trajectory in the individual patient and to function as a teacher for the patient and members of the patient's family, as well as for their professional and social networks. These functions involve an understanding of the patient both as an individual and as a member of a social milieu and require an appreciation of the patient's culture, spirit, and belief systems. Although all therapeutic choices facing patients with advanced CKD have advantages and disadvantages, many of the steps in the transition to ESRD care are common to all the choices. In particular, recent advances in clinical science (based on evidence derived from observational studies and clinical trials) allow the nephrologist to advise patients regarding appropriate timing of initiation of RRT and factors related to successful creation of vascular access, which will promote the best health outcomes. The nephrologist, while delivering complex care at the time of a crucial transition, plays a key role in determining whether the start of RRT with HD will be characterized by a "smooth landing" or a "crash landing," ultimately by serving as a coordinator of education and multidisciplinary consultation.

INTRODUCTION

Patients with all forms of progressive chronic kidney disease (CKD) whose glomerular filtration rate (GFR) is expected to decline within their lifetime, to the point where life-threatening manifestations of advanced uremia are expected to develop, have a number of treatment and management options to consider. The different forms of renal replacement therapy (RRT) include hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation (KTx). The choice of RRT modality should be tailored to the individual patient. The choice is generally based on a combination of medical and surgical comorbidities, anticipated life expectancy, psychosocial factors, and patient preference. KTx, when possible, remains the preferred treatment modality for almost all patients with end-stage renal disease (ESRD). Kidney transplant recipients, in aggregate, enjoy prolonged life expectancy and enhanced quality of life relative to patients undergoing either HD or PD.[1] However, when transplantation is not an option for an individual patient, or if not available preemptively (before the initiation of dialysis), the patient and his or her nephrologist must decide between planning for PD, HD, or, in selected circumstances, emphasizing a more conservative, nondialytic approach. Palliative nephrology implies nonprovision of RRT in situations where, because of a patient's cumulative comorbidities (or less commonly due to patient choice), dialysis of any type tends to provide only limited prolongation of life or functional rehabilitation, such that symptom-based, comfort-directed measures may be more appropriate.[2,3] For most younger (and healthier) patients with ESRD, goals of dialysis include prolongation of life expectancy and service as a bridge to KTx. For many older patients, however, dialysis itself is palliative care, in that its principal objective is to relieve symptoms rather than to necessarily prolong life.

Planning for dialysis requires convincing a patient that he or she will derive meaningful quality and prolongation of life by submitting him or herself to an intrusive, mechanical form of support for a failing organ system, without which uremic symptoms and eventually death would ensue. The first step in this process involves educating the patient about the role of the kidneys in maintaining health and the anticipated effects on the patient's health and survival associated with different degrees of impaired kidney function. The nephrologist cannot assume that the patient understands the roles of the kidneys in maintaining health or

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00070-X

what signs and symptoms might develop in an individual patient as kidney function declines. (Indeed, even an experienced nephrologist may be fooled by patient-to-patient variation in the expression and timing of symptoms.) The nephrologist must tailor his or her information delivery based on the patient's intellectual capacity, educational background, culture, hopes for and fears about the future, and fixed beliefs, to integrate complex medical concepts. Not all patients, for example, can grasp the concept of estimated glomerular filtration rate (eGFR), although this parameter is increasingly noted on laboratory reports, and many patients will present for nephrology consultation with the chief complaint of having been told of a "low eGFR" by their referring internal medicine or family medicine physician, physician assistant, or nurse practitioner. Confusion surrounding parameters of kidney function, whether eGFR or serum creatinine concentration (S[Cr]), can place the nephrologist in an awkward position because the terms "glomerular" and "filtration" are foreign to most laypersons, and addressing the concern of a "low eGFR" to a patient's full satisfaction may compel the nephrologist into a discussion of renal microanatomy, including details on the structure and function of the glomerulus. How else might a patient be able to understand what "eGFR" means? Understandably, without even a cursory discussion of this concept, patients may leave the consultation room still wondering, "What does my low eGFR actually mean?" Or, they may question "What is a glomerulus?" Some patients may be able to integrate this degree of physiologic discussion, if communicated skillfully by the nephrologist. For others, it may be more helpful to tell them to disregard the term "eGFR" and focus instead on something more tangible, such as "the kidneys' percent ability to filter waste products" (conveniently, because an eGFR of 100 mL/min is not far off an expected, "normal" value for a young to middle-aged person). Ultimately, in terms that he or she can understand, the patient needs to learn that progressive CKD is associated with substantial morbidity and symptomatology, and if untreated in its most advanced form, is a lethal condition.

Bearing in mind the patient's cognitive function, capacity to understand, attention, cultural background, and ability to integrate medical terminology, the nephrologist must explain the different forms of RRT, emphasizing that these are treatments, not cures, for ESRD. Indeed, it is not unusual for a patient with ESRD to arrive for his or her first HD session and ask how long it will take for his or her kidneys to get better. Or he or she may ask, understandably, "Is there anything I can do to make my creatinine go down?"

Many patients are understandably reluctant to go along with the recommended planning phases in preparation for dialysis initiation. Patients may repeatedly delay or outright refuse dialysis planning. The idea of being tethered to a machine several times a week for necessary life support may seem painful, unnatural, overly time-consuming, and unacceptable. Although they may already have advanced CKD, patients are often free of the typical signs and symptoms of uremia, such that the stated benefits of dialysis (prolonging life and relieving symptoms), when viewed against the perspective of the hardships of the planned dialysis modality, remain abstract and difficult for a layperson to embrace.

The first step in planning for HD, therefore, involves educating the patient and his or her sources of social support regarding the role of the kidneys in maintaining health and the anticipated impact of a progressive decline in kidney function on the patient's health status and life expectancy. If the patient's CKD is expected to progress to end-stage, he or she must be educated regarding the potential health benefits that would realistically be expected from dialysis. Patients should also have a good understanding of the trade-offs that would be encountered after they have started dialysis, in terms of dietary restriction, time commitment to the procedure, and subsequent impact on the lifestyle and occupation they may currently enjoy, as well as the physiologic limitations of what dialysis is and is not able to correct. The concept of "RRT" must be carefully explained to the patient, because HD and PD, strictly speaking, do not replace kidney function in its entirety. Although dialysis may diminish high serum levels of potassium, acid and by-products of nitrogenous (ingested protein) and muscle metabolism, it fails to correct a variety of reabsorptive, excretory, secretory, endocrine, metabolic, anti-inflammatory, and other functions of the kidneys. As a result, even when patients are fully adherent with their prescribed dialysis regimen, they typically do not experience the comprehensive physiologic and lifestyle rehabilitation that only transplantation affords. In other words, although dialysis sustains life, it typically fails to restore health.

When caregiver and patient agree on eventual provision of dialysis, a choice must be made between HD and PD. Although long-term survival among patients receiving HD and PD are generally similar, the argument has been made that when possible from the technical and psychosocial points of view, the initial modality of choice for most patients should be PD.[4,5] This view is based on the observation that PD is associated with improved quality of life and patient independence, is less costly on an annual basis than HD, and is associated with longer preservation of residual kidney function. This is important because as is well known to nephrologists, maintenance of residual kidney function is associated with improved fluid and blood pressure control, phosphate and middle molecule clearance,

nutritional status, left ventricular hypertrophy and cardiovascular (CV) risk, decreased inflammatory markers, and prolonged survival.[6–8]

When the nephrologist and patient do agree on future implementation of HD as the optimal and preferred RRT modality, many factors must be addressed during the course of the patient's declining kidney function, to allow optimization of outcomes at the time of initiation of HD, as well as during the ensuing months and years of maintenance therapy. We make the distinction to patients between a "smooth landing" and a "crash landing," where crash landing may involve emergency hospitalization of the patient with decompensated uremic symptoms, severe metabolic disarray, pulmonary edema, possibly uremic pericarditis, and without preexisting vascular access, necessitating placement of a temporary vascular catheter, often in a critical care setting by less-experienced personnel. Outcomes under these circumstances are generally poor—hospitalizations may be lengthy and costly, infection rates from emergency catheter placement are high, and long-term patient rehabilitation from having started dialysis *in extremis*, with globally decompensated signs and symptoms of uremia, may be suboptimal. Causes of a crash landing may include (a) lack of primary medical care and/or the patient being unaware of his or her disease until it becomes symptomatic, (b) late referral to nephrology services from the patient's primary care provider, (c) the patient's inability to come to terms with the progressive nature of his or her disease, leading to failure to follow the nephrologist's recommendations, or (d) failure by the nephrologist and his or her treatment team to have a structured, guideline-based approach to management of the pre-ESRD patient.

Ideally, preparation of the patient for HD should result in meeting several conditions.

From the educational point of view, patients and families should have a reasonable understanding of the functional and symptomatic consequences of progressive kidney failure. They should also have a good understanding of the various modalities of RRT, with the eventual modality choice being tailored to the individual circumstances, taking into account medical and surgical comorbidities, age and projected life expectancy, lifestyle and occupation, social support system, and personal choice. Patients should have a reasonable set of expectations regarding what HD can and cannot replace for the failing kidneys. Patients should have a clear understanding of the scheduling and logistic requirements that will be expected of them and how new dietary restrictions will be imposed on them. For selected patients, because of either advanced age or other significant comorbid conditions, there should be an understanding that a palliative, conservative, symptom-based, and comfort-based approach may be reasonable.

Appropriate measures to slow the progression of the patient's CKD should be in place, targeting the underlying etiology of the patient's CKD, potential implementation of a protein-restricted diet, and ongoing use (or *de novo* implementation) of inhibitors of the renin–angiotensin–aldosterone system (RAAS), even in late stage CKD. Importantly, with the newer generation potassium-binding agents now available, nephrologists should feel more emboldened to continue RAAS blockade further into the trajectory of a given patient's CKD, without the fear of encountering critically significant hyperkalemia.[9–12]

The patient's nutritional and functional status should be optimized.

Guidelines regarding treatment of the anemia of CKD should be adhered to, with the goal of avoiding blood product administration before or at the time of dialysis initiation, particularly if patients are deemed to be (or will likely be considered) acceptable kidney transplant recipients.

Because of the heightened risk of CV morbidity and mortality associated with moderate to advanced CKD and ESRD, modifiable risk factors for CV disease should be optimized, including coronary revascularization if significant, reversible ischemic heart disease is present.

For those patients deemed to be medically and otherwise suitable for transplantation, they should, ideally, be seen and evaluated by a local transplant center and listed for eventual transplantation as soon as feasible. This should occur well before the actual time of dialysis initiation because an eGFR of 20 mL/min/1.73 m^2 or less qualifies a patient for transplant listing with the United Network for Organ Sharing (UNOS). Waiting to refer for transplantation until dialysis is initiated, when eGFR is much lower than 20 mL/min/1.73 m^2, essentially "robs" the patient of valuable waiting time (sometimes on the order of years, for those with more slowly progressive forms of nephropathy) that they could otherwise accrue on the deceased donor waiting list. Waiting to refer patients for transplantation until dialysis has been initiated will therefore produce the unintended effect of prolonging the waiting time for eventual transplantation, and potentially exposing patients to the interval development of dialysis-associated morbid events, not uncommonly rendering them subsequently unsuitable for transplantation. We recommend referral for transplantation when the eGFR is between 20–25 mL/min/1.73 m^2 so that medical and psychosocial evaluations can be completed, the patient tentatively approved, and subsequently listed as soon as the referring nephrologist documents an eGFR consistently below 20 mL/min/1.73 m^2 during serial monitoring.

Perhaps most importantly, the patient should have a functional, permanent vascular access in place when HD is initiated. This requires early referral to a vascular

surgeon, usually at least 4–6 months in advance of the anticipated time of starting HD. This provides sufficient time to allow maturation of a newly placed native arteriovenous fistula (AVF) (usually 3–6 months). Early vascular surgery referral also allows for the relatively high rate of primary failure of newly placed AV fistulae, leading to the need for repeated interventional procedures and/or revision surgeries to facilitate maturation of the fistula. If the first fistula created fails to develop in spite of optimal interventional support, the surgeon will need to place a new fistula at another site or place an arteriovenous graft (AVG) instead. Although fistulae are clearly preferable to grafts in terms of infectious risk and durability, both are vastly preferable to catheters, which are associated with the highest risks of infection, venous stenosis, and subclinical and clinically overt venous thromboembolic disease, including superior vena cava syndrome.

As the steps outlined above are being followed, the nephrologist needs to formulate an ever-refined estimate of the time when HD will need to be initiated for the patient. This requires an appropriate schedule for laboratory monitoring, with attention focused most importantly on the patient's evolving S[Cr] and eGFR, but with careful attention also being paid to serum potassium concentration, acid–base balance, serum phosphate concentration, and hemoglobin/hematocrit concentrations. From the clinical point of view, the patient should be seen at appropriate intervals by either the nephrologist or an advanced practice provider, so that a focused, renal-specific review of systems and physical examination can assess potential development of incipient signs or symptoms of uremia, which would prompt initiation of dialysis.

If the above approach is followed, the patient should be able to initiate HD on an elective, outpatient basis. If eligible, patients should already be listed for KTx. The hemoglobin concentration should be at targets set by Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, without blood transfusions. Patients should have a functional permanent vascular access, preferably an AVF. Patients should be free of severe, decompensated signs or symptoms of advanced kidney failure that would prompt emergent hospitalization for dialysis initiation—such as refractory hyperkalemia, encephalopathy, severe hypertension, congestive heart failure, or serositis (especially pericarditis).

The considerations outlined, when properly adhered to, increase the likelihood of safe and successful initiation of HD, when the nephrologist has reached the conclusion that for the individual patient, benefits of dialysis have begun to outweigh the risks associated with the procedure, and that from the patient's point of view, the lifestyle burden that maintenance dialysis will place on him or her and the family, when viewed against the perspective of worsening symptoms and/or death without provision of dialysis, now becomes acceptable.

Patient education, CV risk factor management, anemia management, vascular access placement, and timing of the initiation of HD are all critical to patient care. Some of the issues touched on above, though relevant to the management and planning stages of dialysis preparation (such as delaying the progression of disease and the details of kidney transplant planning), are outside the scope of this chapter.

PATIENT EDUCATION

A distressing and repeated observation is that the majority of patients starting HD have not been through a formal pre-ESRD teaching program designed to prepare them for transition to initiation of dialysis. Many patients report not having been made aware of modality choices other than thrice weekly in-center HD, including self-care in-center HD, home HD, nocturnal HD, PD, or KTx. The information gap regarding CKD and its treatment modalities appears more pronounced among African Americans.[13,14] The majority of patients starting HD in the US continue to begin treatment with a central venous (tunneled) catheter, as opposed to a permanent arteriovenous vascular access, whether native vein or synthetic graft.

Nevertheless, it has been repeatedly observed in multiple studies that formal pre-ESRD educational programs for patients and families result in a higher percentage of patients opting for home-based therapies; a higher percentage of patients beginning treatment with a mature, functioning vascular access, and more favorable nutritional status (assessed by S[Alb] or other parameters) at the time of dialysis start; and decreased need for emergent, hospital-based initiation of treatment, fewer hospitalizations at one year, and overall cost savings per patient during the first year of dialysis.[15–21]

Several studies have also demonstrated improved survival among patients managed before the initiation of dialysis by multidisciplinary approaches aimed at educating the patient regarding modality choice, dietary interventions, blood pressure control, and emphasis on timely vascular access placement.[20,22,23] Devins et al. reported 20-year follow-up of a cohort of patients who had been randomized in the mid-1980s to predialysis psychoeducational interventions aimed at increasing patients' knowledge of CKD and its treatment vs. usual care. These investigators found that patients who received predialysis CKD education survived a median of over 2 years longer than those assigned to usual care. Following initiation of dialysis, survival was 8 months

longer in those having received CKD education, compared to the usual care group.[24] Barriers to implementation of such predialysis educational programs are not clear, but probably include a combination of physician and institutional inertia, and the perception that implementation of such programs may prove prohibitively costly. Nevertheless, because of the evidence supporting implementation of such programs on patient outcomes and ESRD program-wide costs, the Centers for Medicare and Medicaid Services (CMS) has implemented financial incentives to foster growth of such programs. It is hoped that with ongoing, cumulative evidence demonstrating enhanced patient outcomes and cost savings, comprehensive predialysis patient education programs will become increasingly prevalent and become standard of care.

Comprehensive education regarding treatment options in ESRD should not neglect a discussion of possible conservative, nondialytic management, such as nonprovision of RRT. However, when given a choice between prolongation of life with maintenance dialysis and nonprovision or RRT (which in nearly all patients with progressive CKD would temporally hasten their demise) most patients opt for dialysis, even bearing in mind the hardships associated with the procedure. For example, for the very elderly patient with advanced CKD or persons with multiple, significant comorbidities (e.g. active, metastatic cancer), especially when functional status is impaired and life expectancy correspondingly limited, conservative, nondialytic management focused on symptom control may be more appropriate. Kurella Tamura et al. published a study in which functional capacity and mortality were examined in a national cohort ($n = 3702$) of nursing home residents initiating dialysis. Mortality one year after initiation of dialysis was a staggering 58%. Initiation of dialysis was associated with functional decline, regardless of the patient's "functional trajectory" (the ability to perform activities of daily living) during the 3 months preceding initiation of dialysis. One year after starting dialysis, only one in eight patients maintained or improved his or her functional status relative to the start of dialysis.[25]

Elderly patients with multiple comorbidities who initiate HD have a higher likelihood of dying in an acute care facility, often in a critical care setting. The choice of conservative, nondialytic management for patients with progressive CKD recognizes that some patients may prefer a shorter life expectancy, with fewer procedures, less time-consuming therapies, and equivalent or improved quality of life.[26]

The choice of conservative, nondialytic management in advanced CKD implies an understanding between patient and provider that on the one hand, lack of provision of dialysis is likely to be associated with shortened life expectancy. How much so, of course, depends on the disease trajectory of the individual patient. Moreover, pursuing conservative, nondialytic management ideally should result in a concerted effort between the patient and a dedicated nephrology-sensitive palliative care team to address the many symptoms that inevitably develop as kidney function declines. Murtagh et al. reported on a UK-based cohort of 66 elderly patients with stage 5 CKD being managed conservatively. The mean age was 82 years, and mean eGFR was 11 mL/min/1.73 m^2. The most common symptoms reported by patients were fatigue, pruritus, dyspnea, edema, generalized pain, muscle cramps, restless leg syndrome, diminished appetite, inability to concentrate, and sleep disturbance.[27] An individual office-based nephrologist, acting alone, cannot reasonably be expected to successfully address the many day-to-day issues that come up during the progressive decline of such patients.

Students and trainees commonly form the notion that death from untreated uremia is a "slow, peaceful" way to die. As practitioners, we rarely have encountered such situations where patients seem to slip painlessly and quietly into a comatose state and then expire. More commonly, the terminal event in untreated uremia—especially among those not followed closely in CKD clinic or who fail to adhere to dialysis planning—is either sudden cardiac death in the setting of electrolyte imbalance (for example hyperkalemia) or the more distressing picture of acute pulmonary edema. A carefully structured approach by a palliative care team well-versed in the specific needs of the patient with stage 5 CKD can address most of the symptoms such patients are likely to develop.

Most importantly, with judicious use of diuretics, vasodilators, and narcotic analgesics (of which low-dose oxycodone, hydromorphone, and fentanyl may be best tolerated), it should be possible to alleviate the particularly troublesome signs and symptoms of volume overload leading to pulmonary edema, which might otherwise prompt patients (and distressed, on-looking family members) to reverse a deliberately decided-upon course and request emergency care including acute dialysis.[28]

CARDIOVASCULAR RISK FACTOR MANAGEMENT

CV events account for more than 50% of premature deaths among patients receiving HD, including in particular heart failure, stroke, and sudden cardiac death. The excess burden of CVD applies to the predialysis population as well. Nephrologists caring for the patient with advanced CKD need to have a heightened awareness of the excess CV risk in this patient

population. Where possible, nephrologists must address modifiable risk factors, so that as kidney function declines and the patient approaches the need for dialysis, mortality, and morbidity associated with CV risk can be attenuated.

The last several years have seen an increased awareness of the contribution of nondialysis-requiring CKD, even at its early stages (albuminuria, or mild reductions in eGFR), to increased CV risk. Moreover, the association remains strong even in the absence of traditional risk factors such as diabetes, hypertension, dyslipidemia, and smoking.[29]

Foley et al. reported on a 5% sample of the US Medicare population (n = 1,091,201), examining the relation between CKD and diabetes mellitus with respect to CV risk, defined as atherosclerotic heart disease, congestive heart failure, and overall mortality risk. Patients were divided into four groups: those without either diabetes or CKD (79%), those with diabetes but no CKD (16%), those with CKD but no diabetes (2.2%), and those with both diabetes and CKD (1.4%). Over a 2-year follow-up period, rates per 100 patient-years for developing atherosclerotic heart disease, heart failure, and all-cause mortality were higher for patients with CKD and no diabetes (35% vs. 25%, 30% vs. 18%, and 17% vs. 8%, respectively). For patients with both diabetes and CKD, event rates were higher still at 49%, 52%, and 19%, respectively.[30] These findings were confirmed in a recent large Canadian study (n = 1,268,029), again examining the interplay between diabetes and CKD, with regard to CV risk, specifically risk of myocardial infarction (MI), with the reference group against which DM and CKD risk were compared being those with prior MI. Risk of MI was highest in patients with prior MI, regardless of DM or CKD status. Here also, CKD proved to be a stronger predictor for MI than diabetes. In patients with more advanced CKD (GFR <45 mL/min/1.73 m^2), or heavy proteinuria (>300 mg/g creatinine), the risk of MI was roughly twice that compared to the group with diabetes but without CKD (12.4 vs. 6.6 events per 1000 patient-years).[31] Thus, the presence of CKD alone appears to be a stronger predictor of CV events and all-cause mortality than diabetes mellitus. The presence of both conditions is associated with even higher risk, particularly for atherosclerotic disease and heart failure. This risk of CV-related mortality has been shown in multiple studies to increase exponentially as GFR declines, even applied to the earliest stages of CKD.[32–34]

The causes of this increased CV risk remain incompletely understood. In the CKD population, it has been estimated that traditional risk factors for CV-related morbidity and mortality account for only about 50% of risk.[35] CKD-specific physiologic derangements contributing to this increased risk of CV events are still only partially understood. Factors such as increased sympathetic hyperactivity, resistant hypertension, left ventricular hypertrophy, proteinuria and associated hypercoaguable states, oxidative stress, inflammation, malnutrition, and the effects of disordered mineral bone metabolism (hyperphosphatemia, vitamin D deficiency, and abnormal circulating levels of fibroblast growth factor-23 and soluble klotho), leading to vascular calcification and left ventricular hypertrophy, are believed to contribute to this risk.[36–46]

Preparation of the patient with advanced CKD for HD, therefore, involves early and careful attention on the nephrologist's part toward treatment and optimization of modifiable risk factors that have been shown in well-designed studies (nearly all of which were implemented in patients with normal, near normal, or only mildly impaired kidney function) to reduce CV risk.

Goals of management should be aimed at decreasing CV events during the evolution of CKD progression, preserving CV health during later stages of CKD, and to the extent that multiple CV risk factors also affect progression of CKD (such as hypertension, diabetes, and smoking), trying to delay progression of CKD where possible. As the patient approaches the time for planning RRT, the nephrologist should have a thorough knowledge of the patient's CV status, including left and right ventricular function, ischemic burden, presence or absence of left ventricular hypertrophy, history of heart failure, and the presence or absence of significant valvular heart disease, as these may influence dialysis modality choice and help the clinician envision a dialysis regimen that optimizes hypertension control and minimizes risk of heart failure, stroke, atrial and ventricular arrhythmia, endocarditis, and sudden death. Although much has been learned over the past few decades regarding the putative mechanisms of increased CV risk in CKD, the relative contributions of these various physiologic derangements, and their interactions, remain areas of intense investigation, and many questions remain unanswered. Care must be taken to interpret available and emerging data to provide an evidence-based rationale for treatment aimed at reducing CV risk.

What data from well-designed clinical trials can help guide the nephrologist during the care of the patient with progressive CKD to alleviate CV risk? The few CV clinical trials conducted specifically in patients with moderate to advanced CKD have focused on slowing progressive loss of kidney function. Few have focused on modification of CV risk. Indeed, most of the evidence on which we base our practice comes either from extrapolation of clinical trials conducted in the general population or from subgroup analyses of larger clinical trials.[47]

The Study of Heart and Renal Protection trial, addressing the treatment of hypercholesterolemia, randomized 9270 patients (6247 with nondialysis-requiring CKD and 3023 with ESRD) to simvastatin-ezetimibe vs. placebo. Active cholesterol-lowering resulted in a 17% (95% CI 6–26%) reduction in the rate of major atherosclerotic events (nonfatal MI, nonhemorrhagic stroke, any arterial revascularization, or coronary death). Results remained statistically significant in patients with stage 4 CKD (corresponding rate reduction 22%, 95% CI 2–38%).[48]

Several subgroup analyses of heart failure trials have demonstrated consistent benefits of beta-adrenergic antagonists and inhibitors of the RAAS among patients with and without CKD, although few patients in these trials had advanced CKD.[49–52]

The net benefits and risks of aspirin and other antiplatelet agents in patients with advanced CKD are unknown. In a *post hoc* subgroup analysis of the Hypertension Optimal Treatment trial, CV events were reduced by 66% (95% CI 33–83%) and mortality was reduced by 49% (95% CI 6–73%) in patients treated with aspirin. Major bleeding events were modestly increased.

A recent meta-analysis conducted by the Blood Pressure Lowering Treatment Trialists' Collaboration pooled randomized clinical trials completed between 1995 and 2012 that compared two or more active blood pressure–lowering medications, active medications with placebo, or different targets for blood pressure lowering, aiming to determine the importance of blood pressure lowering (and the specific agents used) on CV outcomes. The primary outcome of the meta-analysis was major CV events, defined as the first episode of stroke, coronary heart disease, heart failure, and CV death. Of more than 150,000 participants from 25 clinical trials, 20% had CKD, defined as an eGFR below 60 mL/min/1.73 m^2. Results showed statistically significant and substantial lowering of CV risk with blood pressure lowering, with no obvious difference by antihypertensive drug class. Unfortunately, fewer than one-half of one percent of patients included in this meta-analysis had eGFR below 30 mL/min/1.73 m^2 at baseline.[53]

Although the evidence is relatively sparse, based on the data outlined above and our clinical experience, we usually advise the use of low-dose aspirin, statins, and antihypertensive therapy for CV risk reduction in patients with advanced CKD preparing for dialysis or KTx. We generally favor the use of RAAS inhibitors in combination with diuretic agents and/or beta-adrenergic antagonists, given the potential to attenuate progression and the frequency with which we observe coincident volume overload and heart failure. We generally consider calcium channel blockers, alpha-adrenergic antagonists, and other drugs as third or fourth or fifth line agents for patients with refractory hypertension or other associated health conditions (such as benign prostatic hyperplasia with urinary retention). We recommend mindful limitation of salt intake, despite the confusion and ambiguity introduced with the recent Institute of Medicine report.[54]

ANEMIA MANAGEMENT

We address certain points regarding the use of erythropoiesis stimulating agents (ESAs) and other agents to correct anemia associated with CKD, as they pertain to the preparation of the patient-planning initiation of HD.

The story of the discovery of erythropoietin (EPO), its physiologic regulation, and mechanisms of action (not just on erythrocyte precursors but on target organs throughout the body) is an ongoing and exciting one, with original discoveries pointing to the existence of a circulating, erythropoiesis stimulating factor in the serum, dating to the end of the 19th century.[55,56] The cloning of the EPO gene,[57,58] followed soon after by the introduction of the use of recombinant human EPO to treat the anemia associated with ESRD[59,60] revolutionized the field of clinical nephrology by greatly reducing the need for frequent red blood cell transfusions in patients receiving dialysis. Recognized complications of the frequent transfusions included transmission of infectious diseases (HIV and hepatitis B and C virus infections), systemic iron overload leading to hepatic and cardiac dysfunction, and anti-HLA allosensitization.

Clinical use of ESAs eventually extended to the population of patients with nondialysis-requiring CKD, so that symptomatic anemia could be averted and allowing initiation of dialysis under conditions not requiring transfusion. The optimal target hematocrit or hemoglobin concentration has been a matter of much debate over the past several years, due to the unexpected findings of increased CV morbidity associated with higher hemoglobin concentrations, although specific adverse CV events have not been consistently observed in different trials. The reason(s) for CV morbidity related to ESA use is still a matter under intense investigation.[61–63]

We consider that optimal medical management of the patient with advanced CKD approaching HD should result, among other things, in the patient not requiring blood product administration during the course of their CKD leading up to dialysis initiation. More specifically, this recommendation applies to patients who meet criteria for future KTx. Not uncommonly, patients with limited or inadequate access to comprehensive CKD management eventually present with advanced uremia in the terminal phases of CKD, often accompanied by

severe, symptomatic anemia, prompting transfusion when hospitalized and dialysis is initiated.

Soon after the broad introduction of transplantation in the 1960s and 1970s, it was recognized that prior blood transfusion during a patient's period of dialysis requirement resulted in the development of immune sensitization against HLA antigens, and that this resulted in longer waiting times for transplantation. These effects were reversed following widespread implementation of ESAs, beginning after the approval of recombinant erythropoietin (epoetin alfa, or EPO) in the late 1980s.

Grimm et al. reported on a group of five dialysis-dependent pediatric patients who, after the introduction of EPO and the subsequent elimination of "chronic antigenic stimulation" from blood transfusions, demonstrated marked reductions in anti-HLA antibody titers and a mean reduction in percent panel reactive antibodies from 80% to 56%, while a control group matched for age, prior transfusion dependence, and sensitization status, showed no reduction in anti-HLA titer or percent PRA.[64] Subsequently, Vella et al. reported on a cohort of patients receiving dialysis before and then four years after introduction of EPO. Compared to patients receiving dialysis in the pre-EPO era, these authors noted a decrease in the number of transfusions per dialysis treatment from 0.095 to 0.06, representing a relative reduction of 36%. They also found a decrease in the number of patients being sensitized from 63% to 28%, and a resultant decrease in mean waiting time to transplant from 42 to 15 months during that era (current waiting times are considerably longer).[65]

More contemporary methodologies for assessing anti-HLA antibodies have confirmed these earlier findings and highlighted the extent, magnitude, and specificity of anti-HLA antibody formation resulting from transfusion in dialysis patients. Yabu et al. recently analyzed data on patients from our center, linking local data with the US Renal Data System (USRDS), comparing transfused and nontransfused patients awaiting primary KTx, and who had at least two HLA antibody measurements using the Luminex single-antigen bead assay (including before and after transfusion, in the transfused cohort). Twenty percent of transfused patients vs. 4% of nontransfused patients demonstrated an interval increase of at least 10 anti-HLA antibodies, meeting the cutoff of >3000 mean fluorescent intensity (MFI). Of the 50 transfused patients, 6 (12%) demonstrated an increase of 30 anti-HLA antibodies above an MFI of 3000.[66]

Such findings underscore the important adverse effect of blood product administration on HLA sensitization in patients with advanced CKD. It is during the weeks and months preceding the initiation of dialysis that these issues become paramount. Prolonged waiting time on the transplant list due to sensitized status from blood transfusion exposes the patient to increased risks of dialysis-related morbid events (primarily CV and/or infectious), which not uncommonly render the patient subsequently unsuitable for transplantation. A recent review of published studies in the postcyclosporine era has confirmed the deleterious effects of transfusion on anti-HLA sensitization, time to transplantation resulting from sensitization, and increased risk of rejection and decreased overall graft survival among patients sensitized from prior transfusion.[67] Modification of prioritization (the Kidney Allocation System) introduced in December 2014 aims to correct the disadvantages faced by sensitized patients awaiting KTx. Avoiding transfusion in the months and weeks preceding dialysis initiation, nevertheless, remains advisable.

Increased CV morbidity in clinical trial participants targeted to higher hemoglobin or hematocrit targets, along with the changes in CMS reimbursement patterns implemented in 2011, have resulted in the majority of patients being maintained at lower hemoglobin concentrations. At least among patients receiving maintenance HD, lower target hemoglobin concentrations have resulted in a higher frequency of blood transfusions since that time. Findings from the Dialysis Outcomes and Practice Patterns Study indicated a more than doubling of blood transfusions from 2.21% of patients transfused per month in September 2010 to 4.87% of patients transfused per month in September 2011. Data in the US using Medicare claims showed a similar increase in transfusions following introduction of the Prospective Payment System ("bundling") and modification of product labels for ESAs highlighting CV risks. Legitimate concern has grown that an unintended effect of these changes in practice will lead to more patients being transfused, and therefore at risk for sensitization, with consequent prolongation of time to transplantation.[68]

Extending these observations and considerations to the predialysis population, we recommend careful adherence to KDOQI guidelines regarding anemia management. Goals include avoiding the development of symptomatic anemia, preventing over-correction of anemia (which has been shown to be associated with higher CV risk and possibly accelerated decline of GFR), and readying the patient for HD without prior need for transfusion, to the extent that this may affect HLA sensitization status and adversely affect time to transplantation.

VASCULAR ACCESS MANAGEMENT

Experienced nephrologists who care for patients with ESRD will readily recognize that issues surrounding vascular access represent the "Achilles heel" for the patient requiring HD (Table 70.1). Options for vascular

TABLE 70.1 Complications of Vascular Access Catheters

All catheters
Patient discomfort, cosmetic inconvenience, adhesive dressing allergic reactions
Heightened mortality compared with patients initiated with noncatheter vascular access
Internal jugular and/or subclavian catheter (tunneled and nontunneled)
Internal jugular vein thrombosis
Subclavian vein thrombosis → interference with placement of permanent upper extremity vascular access
Superior vena cava syndrome
Distal catheter tip clot with risk of pulmonary embolus
Septic phlebitis
Catheter-associated bacteremia with or without metastatic infection
endocarditis
paraspinal abscess
vertebral osteomyelitis
septic joint
Exit site infection with or without tunnel infection (abscess)
Pneumothorax
Femoral vein temporary catheter
Retroperitoneal bleeding
Inadvertent femoral artery cannulation with pseudoaneurysm formation
Lower extremity DVT

access in maintenance HD patients include the native AVF, synthetic AVGs, and central venous catheters (CVCs). Preparing the patient with advanced CKD for initiation of maintenance HD necessarily involves a careful, patient-centered approach to timely placement of a suitable vascular access that is ready for use when initiation of dialysis is indicated.

When possible, creation of an AVF is the preferred form of vascular access because compared with AVGs and CVCs, AVFs are associated with greater long-term patency rates, decreased need for interventional procedures to maintain patency, decreased rates of infection, decreased rates of hospitalization, decreased overall cost, and, importantly, decreased patient mortality. AVGs do not technically require time to "mature" (i.e. arterialize), although it may take several weeks before local inflammation subsides and the graft can be safely cannulated with minimal discomfort. Some practitioners recommend several weeks of healing without cannulation to allow for migration of endothelial cells although the optimal timing of first graft cannulation is unknown. Relative to AVFs, AVGs are more prone to thrombosis and outflow stenosis due to neointimal hyperplasia, leading to the need sometimes for interventional procedures (often multiple) to reestablish and maintain patency.

CVCs can be placed and be ready for use on a same-day basis when the patient starts HD, yet are associated with multiple short-term and long-term complications (Table 70.1). Infection remains the most important drawback of CVCs. CVC-associated infection can be in the form of a relatively straightforward exit site infection, subcutaneous tunnel infection (which essentially is an abscess-equivalent and generally requires removal of the catheter and sometimes surgical drainage of the infected collection), and catheter-associated bacteremia. HD CVC–associated bacteremias are associated with substantial morbidity and mortality. Sepsis and septic shock may develop in the context of dialysis CVC-associated bacteremia. Metastatic infection including endocarditis, paraspinal abscess, vertebral osteomyelitis, and septic joint are relatively frequent complications of CVC-associated bacteremia. In addition to infectious complications, long-term use of CVCs is associated with development of other vascular complications, including subclavian and internal jugular vein thrombosis, leading to the need for systemic anticoagulation. Superior vena cava syndrome may also develop in patients using CVCs. These vascular complications subsequently render future placement of noncatheter forms of access far more difficult.

These observations have led to several initiatives and guideline-based recommendations to encourage efforts at timely and successful placement of AVFs. Nevertheless, in the US, the most common form of vascular access in incident HD patients remains the CVC. Foley et al. analyzed data regarding type of vascular access at the time of initiation of dialysis in patients starting dialysis for the period June 2005 through October 2007 (n = 220,157), obtained from the Centers for Medicare and Medicaid Services Medical Evidence Report (Form CMS-2728). Only 13% of patients began dialysis with a functioning AVF; 4% began with an AVG; 16% had a CVC with maturing fistula; 3.3% had a CVC with a maturing graft; and the majority, 63.2%, had a CVC alone. Compared with those patients beginning dialysis with a functioning fistula, adjusted mortality hazard ratios (HRs) were 1.39 for AVGs, 1.49 for catheter with maturing AVF, 1.74 for catheter with maturing AVG, and 2.18 for catheter alone.[69] Bray et al. reported on a prospective cohort of all patients starting dialysis in Scotland for the years 2009 through 2011 (n = 2666). Patients dialyzing through a CVC alone were found to have a higher risk of all-cause mortality, including that attributed to CV death as well as infectious causes.

The odds of dying from sepsis were 6.9-fold higher among those dialyzing through a CVC compared with those using an AVF or AVG.[70] A review of 67 cohort studies including 586,337 patients similarly demonstrated higher risks for all-cause mortality, fatal infections, and CV events in patients dialyzing with a CVC opposed to either AVG or AVF.[71]

A critique of many of the observational studies on the relation between vascular access type and mortality risk has centered on the issue of selection bias. Specifically, it is unclear whether or not underlying health status plays a role in eventual type of vascular access at the time of dialysis initiation, which in turn would account for mortality risk. Grubbs et al., looking at 117,277 patients starting dialysis from the USRDS for the period 2005–2007, examined the relation between functional status and number of hospital days in the 2 years prior to dialysis initiation, with respect to type of vascular access at dialysis initiation and subsequent mortality risk. Confirming results from other studies, these authors demonstrated increased mortality risk compared with patients starting dialysis with an AVF, among those starting with an AVG (HR 1.20), catheter plus maturing AVF (HR 1.34), catheter plus "maturing" AVG (HR 1.46), and catheter alone (HR 1.95). They also showed that functional status was strongly associated with access type at dialysis initiation, with previously "sicker" patients more likely to start dialysis with a CVC, whereas the "healthier" patients were more likely to have had a functioning AVF. Mortality risk therefore appears to be modulated not just by type of access at dialysis initiation, but by underlying health status, which in turn appears to correlate with eventual form of access placement.[72]

In addition to underlying health status predating initiation of dialysis, age at initiation of dialysis is strongly associated with type of initial vascular access and subsequent mortality risk. Although the studies cited above show heightened mortality risk associated with CVC use in all patients starting HD regardless of age, when stratified according to access type (highest risk in catheter alone > catheter with maturing AVG > catheter with maturing AVF > AVG alone > AVF alone), DeSilva et al. analyzed data on 115,425 patients above the age of 67. For patients aged 67–79 years, the HR for mortality among those with an AVG as opposed to AVF as first access placed was only marginally worse (HR 1.10), and there was no difference in patients 80 years or older.[73] These results suggest that the net benefit of AVF in older patients is attenuated, possibly related to the lower fraction of AVFs maturing to clinical use. Even among those elderly patients whose AVF does successfully mature, the prolonged use of CVCs pending AVF maturation exposes patients to the many infectious and CV-related adverse events associated with CVCs, such that the strategy in vascular access planning (at least for the elderly CKD patient) has shifted from "fistula first" to "catheter last."

The technical challenges in creating a functional native AVF appear to be more pronounced in the elderly. Several studies have shown a higher rate of primary nonfunction of native AVF placement as patients' age increases, with the result that a higher percentage of such patients will arrive at the need for dialysis requiring either AVG, catheter with maturing AVG, or catheter alone.[74,75] A growing concern is that strict adherence to KDOQI guidelines during ESRD planning in the stage 4 CKD population, when applied to the elderly, may result in an increased rate of failed attempts at AVF creation, while waiting for later placement of an AVG may be a reasonable approach. Moreover, depending on the age of the patient, underlying health status, and trajectory of the progression of CKD, there are many patients with late-stage CKD who die before requiring initiating dialysis, raising concern that many well-intended and guideline-based referrals for access placement in selected patients are futile and current practice should be reassessed. Death with a functional (but never-used) AVF or AVG is an outcome that should ideally be avoided.[76,77] Careful consideration must therefore be paid to the patient's age, life expectancy, and underlying functional status when planning vascular access. Although the "fistula first" initiative represents a sound approach to vascular access planning for younger patients and those with more robust underlying functional status, increasingly, emphasis is being placed on "catheter last," particularly in the elderly, in whom primary placement of an AVG may be an acceptable option. The reader is referred to recent elegant reviews summarizing the dilemmas, particularly surrounding the issue of vascular access placement, faced by the nephrologist caring for the elderly CKD patient.[78,79]

We recommend a patient-centered approach, bearing in mind age and functional status, particularly as we care for an ever-growing population of elderly patients with late stage CKD, in whom the anticipated probability of death prior to need for initiation of dialysis, the inherently high failure rate of primary AVF placement, and what appear to be equivalent mortality outcomes between AVF and AVG, all need to be part of the decision-making process. In younger and more robust patients, because of the overwhelming evidence implicating CVC use as a cause of increased all-cause, infectious, and CV mortality, and because of the confirmed benefit in nonelderly patients of AVF over AVG, we recommend adhering to standard guidelines emphasizing early referral to vascular surgery, at least 6 months before anticipated need for dialysis initiation, to allow maturation of the AVF. This approach also takes into account the relatively high rates of primary access

failure in AVFs, leading to the need for interventional procedures and/or revision surgery, such that ample time is allowed for maturation of a functional AVF at the time of dialysis start. Standard recommendations regarding avoidance of blood draws or IV placements above the wrist, where possible, should be adhered to, as well as avoiding placement of peripherally inserted central catheters, as these carry the risk of phlebitis and thrombosis, which can interfere with creation or placement of permanent vascular access in the affected arm.

TIMING OF THE INITIATION OF HEMODIALYSIS

Once the patient and nephrologist have agreed on eventual initiation of maintenance HD, the patient will logically ask, "when should I begin?" Without meaning to be facetious, one might reply to the patient, "not too early, but not too late"—and this of course would be an accurate response. A more refined and articulate answer might be, "When the benefits of dialysis to your health and survival begin to outweigh the risks and hardships associated with the procedure." The goal should be to preserve patient autonomy as long as possible, free of the requirement for maintenance dialysis and its many restrictions on lifestyle, as long as this does not expose the patient to either short-term or long-term morbidity (or mortality) that would result from lack of provision of dialysis. For most patients with progressive CKD, once they start dialysis, there is "no turning back" (ability to safely come off dialysis for an extended period of time). Therefore, our responsibility is to give our best recommendations to the patient based on science, where available; art, to the extent that there is no "one size fits all" answer to this question; and compassion, bearing in mind that institution of our treatment plan will have wide-ranging lifestyle consequences for the patient and his or her family. How do we come up with a more rational answer to this question? Is there high-quality evidence on which we can we rely to inform our recommendations?

Ultimately of course, the timing of dialysis initiation must be tailored to the individual patient. A common question from patients is, "At what creatinine will I need to start dialysis?" The S[Cr], or its derived eGFR for the patient in question, is only one of many considerations that come into play when deciding on the timing of dialysis initiation. For example, not all patients predictably develop dialysis-responsive uremic symptoms at the same level of eGFR. Occasionally, patients with relatively preserved eGFR (e.g. >10 mL/min/1.73 m^2) and lack of traditional uremic symptoms may have problems with volume management and recurrent hospitalizations for pulmonary edema in spite of maximal medical therapy, due to significant comorbid structural heart disease—most commonly left ventricular hypertrophy with diastolic dysfunction, systolic heart failure, or pulmonary hypertension with severe right-sided congestive symptoms including anasarca. Such patients may benefit from earlier dialysis initiation, to the extent that serial ultrafiltration may help bring the patient closer to his or her optimal volume status and thereby break the cycle of frequent rehospitalizations for heart failure exacerbation.

An important goal of managing the patient with advanced CKD is to avoid initiation of dialysis when the patient has become particularly decompensated requiring emergency hospitalization. The costs associated with "crash landing" initiations are necessarily much higher than outpatient, elective initiations, and significant morbidity may develop in the hospital setting including nosocomial infection. On the other hand, initiation of dialysis before true benefit accrues to the patient, intuitively does not make sense, only adds to cost of delivery of care and deprives the patient of whatever freedom from dialysist may reasonably persist with ongoing close medical supervision.

A common observation during the past few decades had been a trend toward earlier start of patients on dialysis (both HD and PD), often at eGFRs greater than 10 mL/min/1.73 m^2. This practice has probably been based on the supposition that earlier institution of therapy would enhance rehabilitation and prevent complications through a preemptive approach, avoiding the various manifestations uremic toxicity, before they become fully manifest. Hard evidence supporting such a practice, however, has been lacking. Key questions to be addressed include does timing of initiation of dialysis significantly affect patient morbidity and symptomatology? Does timing of initiation of dialysis affect patient mortality? What are the implications of practice guidelines regarding timing of dialysis initiation, in terms of global cost of care to society?

The landmark Initiating Dialysis Early and Late (IDEAL) study examined these questions in some detail.[80] IDEAL was a randomized, multicenter study that examined the effects on mortality from any cause among groups assigned to early-start dialysis (eGFR 10−14 mL/min/1.73 m^2) vs. those in the late-start group (5−7 mL/min/1.73 m^2). The primary outcome was death from any cause. Patients planning both HD and PD were included. Median time to start was 1.8 vs. 7.4 months in the early and late groups, respectively. The median time of follow-up was 3.5 years. The authors observed no significant difference in mortality between those assigned to early start (37.6%) vs. late start (36.6%). Moreover, there was no observed difference in the incidence of CV events, infectious

disease complications, or other dialysis-related complications. A potential limitation of this study, however, is that a substantial number of patients (75.9%) assigned to the late-start group actually needed to start dialysis above the preassigned cutoff of 7 mL/min/1.73 m^2, due to interval development of uremic symptoms. Whether or not a between-group mortality difference would have emerged had these patients actually waited to start dialysis until they reached the late-start eGFR cutoff of 5–7 mL/min/1.73 m^2, is uncertain. In other words, one could criticize IDEAL in that it compared very early start with relatively early start, rather than late start, and the modest separation in kidney function between groups resulted in an underpowered study. Nevertheless, based on the IDEAL results, there is no clinical trials–based evidence to support a very early preemptive initiation of dialysis strategy. It is noteworthy that left ventricular hypertrophy was present in a large fraction of IDEAL participants at the time of study enrollment. A substudy found no difference in left ventricular hypertrophy regression or progression at 12 months.[81] There was no significant difference in mortality, CV events, infections, or access related complications, restricting analysis to those patients in IDEAL who eventually underwent HD as a modality choice. Fluid and electrolyte complications were more common, however, among patients randomized to the "late" start group.[82]

Whether or not these findings apply to a generally healthier population of prospective HD patients—those without diabetes and for whom the only significant comorbid condition in addition to CKD was hypertension—was examined in a large cohort of 81,176 patients starting in-center HD by Rosansky et al.[83] The reference group included those patients assigned to dialysis initiation at an eGFR <5 mL/min/1.73 m^2, who were compared across various strata of ever-increasing eGFRs at time of dialysis initiation, with the highest group being those with eGFR >15 mL/min/1.73 m^2. Among these patients with limited comorbidity, unadjusted 1-year mortality for the reference group was 6.8%, while in the patients with eGFR >15 mL/min/1.73 m^2 was 20.1%. Adjusted mortality hazards were progressively higher among patients starting dialysis at higher eGFR. These findings contradict those reported in the IDEAL study and suggest either that earlier start of dialysis may be harmful—at least in this select group of nondiabetic patients—or, most likely, that there is confounding by indication. In other words, patients sicker in ways that were not measured and/or adjusted for received dialysis earlier. Although confounding is likely to explain the findings reported by Rosansky et al., one should consider the possibility that early initiation of dialysis may in fact be harmful. In addition to risks associated with creation or placement of vascular access, initiation of HD may accelerate loss of residual kidney function or lead to other untoward effects.

Taken together, these observations suggest that in the majority of patients, initiation of HD can be delayed until eGFR is somewhere between 5–10 mL/min/1.73 m^2, but that the ultimate decision should be patient-specific. Initiation of dialysis at eGFRs closer to 10 mL/min/1.73 m^2 is reasonable if unequivocal symptoms of uremia have begun to develop. Special populations, such as those with heart failure, may also benefit from earlier initiation, for volume control. For the majority of patients, initiation of dialysis at eGFR greater than 10 mL/min/1.73 m^2 appears to confer no survival benefit, is associated with increased cost, and in the nondiabetic subgroups, may actually be associated with higher 1-year mortality risk.

CONCLUSION

Decisions regarding the initiation of RRT are critical in the relationships among nephrologists, patients, family members, and other health personnel. The transition from CKD to ESRD requires the nephrologist to have a clear understanding of the disease trajectory in the individual patient, and to function as a teacher for the patient and the important members of his or her family, and professional and social networks. Recent advances in clinical research allow the nephrologist to advise patients regarding timing of initiation of HD, and factors related to successful creation of vascular access, which will promote the best health outcomes. The nephrologist, while managing a complex set of medical problems in patients with late stages of CKD, can play a key role in determining the characteristics of the start of RRT with HD. Patient education, CV risk factor management, anemia management, vascular access placement, and timing the initiation of HD are all critical to patient care. When these issues are properly addressed, the safe and successful initiation of HD may be more likely.

References

1. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. *U.S. renal data system, USRDS 2013 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2013.
2. Raghavan D, Holley JL. Conservative care of the elderly CKD patient: a practical guide. *Adv Chron Kidney Dis* 2016;**23**(1):51–6.
3. Winkelmayer WC, et al. Predialysis nephrology care of older patients approaching end-stage renal disease. *Arch Intern Med* 2011;**171**(15):1371–8.
4. Ghaffari A, et al. PD First: peritoneal dialysis as the default transition to dialysis therapy. *Semin Dial* 2013;**26**(6):706–13.

5. Chiu YW, et al. An update on the comparisons of mortality outcomes of hemodialysis and peritoneal dialysis patients. *Semin Nephrol* 2011;**31**(2):152–8.
6. Vilar E, Farrington K. Emerging importance of residual renal function in end-stage renal failure. *Semin Dial* 2011;**24**(5):487–94.
7. Brener ZZ, et al. Clinical benefit of preserving residual renal function in dialysis patients: an update for clinicians. *Am J Med Sci* 2010; **339**(5):453–6.
8. Perl J, Bargman JM. The importance of residual kidney function for patients on dialysis: a critical review. *Am J Kidney Dis* 2009;**53**(6): 1068–81.
9. Bushinsky DA, et al. Patiromer induces rapid and sustained potassium lowering in patients with chronic kidney disease and hyperkalemia. *Kidney Int* 2015;**88**(6):1427–33.
10. Packham DK, et al. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med* 2015;**372**(3):222–31.
11. Weir MR, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 2015; **372**(3):211–21.
12. Georgianos PI, Agarwal R. Revisiting RAAS blockade in CKD with newer potassium-binding drugs. *Kidney Int* 2018;**93**(2):325–34.
13. Mehrotra R, et al. Patient education and access of ESRD patients to renal replacement therapies beyond in-center hemodialysis. *Kidney Int* 2005;**68**(1):378–90.
14. Finkelstein FO, et al. Perceived knowledge among patients cared for by nephrologists about chronic kidney disease and end-stage renal disease therapies. *Kidney Int* 2008;**74**(9):1178–84.
15. Golper TA, Mehrotra R, Schreiber MS. Is Dorothy correct? The role of patient education in promoting home dialysis. *Semin Dial* 2013; **26**(2):138–42.
16. Davis JS, Zuber K. Implementing patient education in the CKD clinic. *Adv Chron Kidney Dis* 2013;**20**(4):320–5.
17. Ribitsch W, et al. Effects of a pre-dialysis patient education program on the relative frequencies of dialysis modalities. *Perit Dial Int* 2013;**33**(4):367–71.
18. Levin A, et al. Multidisciplinary predialysis programs: quantification and limitations of their impact on patient outcomes in two Canadian settings. *Am J Kidney Dis* 1997;**29**(4):533–40.
19. Goldstein M, et al. Multidisciplinary predialysis care and morbidity and mortality of patients on dialysis. *Am J Kidney Dis* 2004;**44**(4):706–14.
20. Kurella Tamura M, et al. Educational programs improve the preparation for dialysis and survival of patients with chronic kidney disease. *Kidney Int* 2014;**85**(3):686–92.
21. Johns TS, et al. Interdisciplinary care clinics in chronic kidney disease. *BMC Nephrol* 2015;**16**:161.
22. Jungers P, et al. Longer duration of predialysis nephrological care is associated with improved long-term survival of dialysis patients. *Nephrol Dial Transplant* 2001;**16**(12):2357–64.
23. Curtis BM, et al. The short- and long-term impact of multidisciplinary clinics in addition to standard nephrology care on patient outcomes. *Nephrol Dial Transplant* 2005;**20**(1):147–54.
24. Devins GM, et al. Predialysis psychoeducational intervention extends survival in CKD: a 20-year follow-up. *Am J Kidney Dis* 2005;**46**(6):1088–98.
25. Kurella Tamura M, et al. Functional status of elderly adults before and after initiation of dialysis. *N Engl J Med* 2009;**361**(16):1539–47.
26. Murtagh FE, et al. Supportive care: comprehensive conservative care in end-stage kidney disease. *Clin J Am Soc Nephrol* 2016; **11**(10):1909–14.
27. Murtagh FE, et al. Symptoms in advanced renal disease: a cross-sectional survey of symptom prevalence in stage 5 chronic kidney disease managed without dialysis. *J Palliat Med* 2007;**10**(6): 1266–76.
28. Davison SN. The ethics of end-of-life care for patients with ESRD. *Clin J Am Soc Nephrol* 2012;**7**(12):2049–57.
29. He J, et al. Risk factors for heart failure in patients with chronic kidney disease: the CRIC (chronic renal insufficiency cohort) study. *J Am Heart Assoc* 2017;**6**(5).
30. Foley RN, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 2005;**16**(2): 489–95.
31. Tonelli M, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet* 2012;**380**(9844):807–14.
32. Tonelli M, et al. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006;**17**(7):2034–47.
33. Di Angelantonio E, et al. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. *Br Med J* 2010;**341**:c4986.
34. Briasoulis A, Bakris GL. Chronic kidney disease as a coronary artery disease risk equivalent. *Curr Cardiol Rep* 2013;**15**(3):340.
35. Kaisar M, Isbel N, Johnson DW. Cardiovascular disease in patients with chronic kidney disease. A clinical review. *Minerva Urol Nefrol* 2007;**59**(3):281–97.
36. Palmer SC, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. *JAMA* 2011;**305**(11):1119–27.
37. Faul C, et al. FGF23 induces left ventricular hypertrophy. *J Clin Investig* 2011;**121**(11):4393–408.
38. Kahn MR, et al. Management of cardiovascular disease in patients with kidney disease. *Nat Rev Cardiol* 2013;**10**(5):261–73.
39. Garimella PS, Sarnak MJ. Cardiovascular disease in CKD in 2012: moving forward, slowly but surely. *Nat Rev Nephrol* 2013;**9**(2): 69–70.
40. Gansevoort RT, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013; **382**(9889):339–52.
41. Menon MC, Ix JH. Dietary phosphorus, serum phosphorus, and cardiovascular disease. *Ann N Y Acad Sci* 2013;**1301**(1):21–6.
42. Quarles LD. Reducing cardiovascular mortality in chronic kidney disease: something borrowed, something new. *J Clin Investig* 2013;**123**(2):542–3.
43. Zoccali C, Yilmaz MI, Mallamaci F. FGF23: a mature renal and cardiovascular risk factor? *Blood Purif* 2013;**36**(1):52–7.
44. Major RW, et al. Cardiovascular disease risk factors in chronic kidney disease: a systematic review and meta-analysis. *PLoS One* 2018; **13**(3):e0192895.
45. Rutherford E, Mark PB. What happens to the heart in chronic kidney disease? *J R Coll Phys Edinb* 2017;**47**(1):76–82.
46. Grabner A, Faul C. The role of fibroblast growth factor 23 and Klotho in uremic cardiomyopathy. *Curr Opin Nephrol Hypertens* 2016; **25**(4):314–24.
47. Bansal N. Evolution of cardiovascular disease during the transition to end-stage renal disease. *Semin Nephrol* 2017;**37**(2): 120–31.
48. Baigent C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**(9784):2181–92.
49. Badve SV, et al. Effects of beta-adrenergic antagonists in patients with chronic kidney disease: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011;**58**(11):1152–61.
50. Desai AS, et al. Incidence and predictors of hyperkalemia in patients with heart failure: an analysis of the CHARM Program. *J Am Coll Cardiol* 2007;**50**(20):1959–66.
51. Anand IS, et al. Proteinuria, chronic kidney disease, and the effect of an angiotensin receptor blocker in addition to an angiotensin-converting enzyme inhibitor in patients with moderate to severe heart failure. *Circulation* 2009;**120**(16):1577–84.

52. Tokmakova MP, et al. Chronic kidney disease, cardiovascular risk, and response to angiotensin-converting enzyme inhibition after myocardial infarction: the Survival and Ventricular Enlargement (SAVE) study. *Circulation* 2004;**110**(24):3667–73.
53. Blood Pressure Lowering Treatment Trialists C, et al. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials. *Br Med J* 2013;**347**:f5680.
54. Brian LS, Ann LY, Maria O, editors. *Sodium intake in populations: assessment of evidence*. The National Academies Press; 2013.
55. Jelkmann W. Erythropoietin after a century of research: younger than ever. *Eur J Haematol* 2007;**78**(3):183–205.
56. Bunn HF. Erythropoietin. *Cold Spring Harb Perspect Med* 2013;**3**(3): a011619.
57. Jacobs K, et al. Isolation and characterization of genomic and cDNA clones of human erythropoietin. *Nature* 1985;**313**(6005): 806–10.
58. Lin FK, et al. Cloning and expression of the human erythropoietin gene. *Proc Natl Acad Sci U S A* 1985;**82**(22):7580–4.
59. Winearls CG, et al. Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. *Lancet* 1986;**2**(8517):1175–8.
60. Eschbach JW, et al. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med* 1987;**316**(2):73–8.
61. Inrig JK, et al. Effect of hemoglobin target on progression of kidney disease: a secondary analysis of the CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) trial. *Am J Kidney Dis* 2012;**60**(3):390–401.
62. Patel TV, Singh AK. Anemia in chronic kidney disease: new advances. *Heart Fail Clin* 2010;**6**(3):347–57.
63. Singh AK. What is causing the mortality in treating the anemia of chronic kidney disease: erythropoietin dose or hemoglobin level? *Curr Opin Nephrol Hypertens* 2010;**19**(5):420–4.
64. Grimm PC, et al. Effects of recombinant human erythropoietin on HLA sensitization and cell mediated immunity. *Kidney Int* 1990; **38**(1):12–8.
65. Vella JP, et al. Sensitization to human leukocyte antigen before and after the introduction of erythropoietin. *Nephrol Dial Transplant* 1998;**13**(8):2027–32.
66. Yabu JM, et al. Sensitization from transfusion in patients awaiting primary kidney transplant. *Nephrol Dial Transplant* 2013;**28**(11): 2908–18.
67. Scornik JC, et al. An update on the impact of pre-transplant transfusions and allosensitization on time to renal transplant and on allograft survival. *BMC Nephrol* 2013;**14**:217.
68. Macdougall IC, Obrador GT. How important is transfusion avoidance in 2013? *Nephrol Dial Transplant* 2013;**28**(5):1092–9.
69. Foley RN, Chen SC, Collins AJ. Hemodialysis access at initiation in the United States, 2005 to 2007: still "catheter first". *Hemodial Int* 2009;**13**(4):533–42.
70. Bray BD, et al. Vascular access type and risk of mortality in a national prospective cohort of haemodialysis patients. *QJM* 2012; **105**(11):1097–103.
71. Ravani P, et al. Associations between hemodialysis access type and clinical outcomes: a systematic review. *J Am Soc Nephrol* 2013;**24**(3): 465–73.
72. Grubbs V, et al. Health status as a potential mediator of the association between hemodialysis vascular access and mortality. *Nephrol Dial Transplant* 2014;**29**(4):892–8.
73. DeSilva RN, et al. Fistula first is not always the best strategy for the elderly. *J Am Soc Nephrol* 2013;**24**(8):1297–304.
74. Lazarides MK, et al. A meta-analysis of dialysis access outcome in elderly patients. *J Vasc Surg* 2007;**45**(2):420–6.
75. Lok CE, Foley R. Vascular access morbidity and mortality: trends of the last decade. *Clin J Am Soc Nephrol* 2013;**8**(7):1213–9.
76. O'Hare AM, et al. When to refer patients with chronic kidney disease for vascular access surgery: should age be a consideration? *Kidney Int* 2007;**71**(6):555–61.
77. Demoulin N, et al. Preparing renal replacement therapy in stage 4 CKD patients referred to nephrologists: a difficult balance between futility and insufficiency. A cohort study of 386 patients followed in Brussels. *Nephrol Dial Transplant* 2011;**26**(1):220–6.
78. Vachharajani TJ, et al. Elderly patients with CKD-dilemmas in dialysis therapy and vascular access. *Nat Rev Nephrol* 2014;**10**(2): 116–22.
79. Quinn RR, Ravani P. Fistula-first and catheter-last: fading certainties and growing doubts. *Nephrol Dial Transplant* 2014;**29**(4): 727–30.
80. Cooper BA, et al. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med* 2010;**363**(7):609–19.
81. Whalley GA, et al. Effect of early initiation of dialysis on cardiac structure and function: results from the echo substudy of the IDEAL trial. *Am J Kidney Dis* 2013;**61**(2):262–70.
82. Collins J, et al. Outcomes of patients with planned initiation of hemodialysis in the IDEAL trial. *Contrib Nephrol* 2011;**171**:1–9.
83. Rosansky SJ, et al. Early start of hemodialysis may be harmful. *Arch Intern Med* 2011;**171**(5):396–403.

QUESTIONS AND ANSWERS

Question 1

You are following a 62-year-old man with progressive CKD secondary to diabetic nephropathy. His current eGFR is 22 mL/min/1.73 m^2. He comes to clinic to discuss renal replacement options.

Which **one** of the following is true regarding his options for dialysis?

A. PD is associated with enhanced survival compared to HD
B. HD is a less costly form of RRT
C. PD is associated with preservation of residual kidney function
D. HD is associated with superior quality of life and patient independence

Answer: C

PD is associated with preservation of residual kidney function. This is important because persistence of residual kidney function is associated with improved fluid and blood pressure control, phosphate and middle molecule clearance, nutritional status, and attenuation of left ventricular hypertrophy and CV risk, decreased inflammatory markers, and prolonged survival.[6–8] Answer A is incorrect as long-term survival among patients receiving HD and PD are generally similar. PD is typically associated with improved perception of quality of life and patient independence and is less costly on an annual basis than HD making Answers B and D incorrect.[4,5]

Question 2

In preparing for RRT, discussions should take place with the patient and family regarding which of the following:

A. Symptomatic consequences of progressive kidney failure
B. The different modalities of RRT including HD, PD, and KTx
C. The expected scheduling and logistic requirements
D. Dietary restrictions with which the patient will need to adhere
E. All of the above

Answer: E

From the educational point of view, the patient and family should have a reasonable understanding of the functional and symptomatic consequences of progressive kidney failure. Patients and families should have a good understanding of the various modalities of RRT, with the eventual modality choice being tailored to the individual circumstances, taking into account medical and surgical comorbidities, age and projected life expectancy, lifestyle and occupation, social support system, and of course, personal choice. Patients should have a reasonable set of expectations regarding what HD can and cannot replace for the failing kidneys. Patients should have a clear understanding of the scheduling and logistic requirements that will be expected and how new dietary restrictions will be necessary. For selected patients, because of either advanced age or other significant co-morbid conditions, there should be an understanding that a conservative, symptom-based and comfort-driven approach may be preferred.

Question 3

Which one of the following is true regarding referring patients for KTx?

A. Patients should be treated with HD for at least one year before they are referred for consideration of KTx
B. Patients can be on the deceased donor waiting list when their eGFR is $\leq$20 mL/min/1.73 m^2
C. Patients must be started on dialysis before they qualify for listing on the deceased donor waiting list
D. Patients can be first placed on the deceased donor waiting list when their eGFR is $\leq$10 mL/min/1.73 m^2

Answer: B

For those patients deemed to be medically and otherwise suitable for transplantation, they should, ideally, be seen and evaluated by a local transplant center and listed for deceased donor transplantation. This should occur well before the actual time of dialysis initiation because an eGFR of 20 mL/min/1.73 m^2 or less qualifies a patient for transplant listing with the UNOS making Answer B true and Answers A, C, and D incorrect. Waiting to refer for transplantation until dialysis is initiated, when eGFR is much lower than 20 mL/min/1.73 m^2, essentially deprives the patient of valuable time (sometimes on the order of years, for those with more slowly progressive CKD) that could otherwise accrue on the deceased donor waiting list. This has the effect of prolonging the waiting time for eventual transplantation and exposing patients to potential interval development of dialysis-related morbid events, not uncommonly rendering them unsuitable for transplantation. Referral for transplantation is appropriate when eGFR is between 20–25 mL/min/1.73 m^2, so that medical and psychosocial evaluations can be completed, the patient tentatively approved, and subsequently listed as soon as the referring nephrologist documents an eGFR consistently below 20 mL/min/1.73 m^2 during serial monitoring.

Question 4

A 54-year-old woman is followed for progressive kidney disease secondary to IgA nephropathy. She is scheduled to see you in a few hours. Which of the following are the goals in planning for HD?

A. The hemoglobin concentration should be at targets defined by clinical practice guidelines without the need for transfusion
B. Patients should have a functional permanent vascular access, preferably an AVF
C. The patient should be followed at close intervals to avoid the need for an emergent inpatient start of HD treatment ("crash landing")
D. If eligible, patients should be listed for KTx when eGFR is $\leq$20 mL/min/1.73 m^2
E. All of the above

Answer: E

The above-listed goals should all be part of the management of the patient being prepared for HD. When these are properly adhered to, the likelihood of safe and successful initiation of HD is increased. Patient education, CV risk factor management, anemia management, vascular access placement, and timing the initiation of HD are all critical to patient care.

Question 5

Which ONE of the following is true regarding formal pre-ESRD educational programs for patients and families?

A. Families should not be included since it violates confidential patient information rules
B. Education has no effect on type of dialysis selected by the patient
C. Patients are started on dialysis earlier than necessary
D. A higher percentage of patients begin dialysis with a mature functioning vascular access

Answer: D

Multiple studies have demonstrated that formal pre-ESRD educational programs for patients and families result in a higher percentage of patients opting for home-based therapies (Answer B is not true), a greater percentage of incident HD patients beginning treatment with a mature, functioning vascular access (Answer D is true and the correct answer), prolongation of time to need for initiation of dialysis (Answer C is incorrect), improved S[Alb] at the time of dialysis start, decreased need for emergent, hospital-based initiation of treatment, fewer hospitalizations at one year, and overall cost savings per patient during the first year of dialysis.[15–19] Involvement of families, with the permission of the patient, is critical to the success of any treatment plan for RRT, making Answer A not true.

Question 6

Which ONE of the following is true regarding the timing of the initiation of HD?

A. Early-start dialysis (eGFR 10–14 mL/min/1.73 m^2) results in lower mortality compared to late-start dialysis (eGFR 5–7 mL/min/1.73 m^2)
B. No significant difference in mortality is seen with late-start dialysis (eGFR 5–7 mL/min/1.73 m^2) compared to early-start dialysis (eGFR 10–14 mL/min/1.73 m^2)
C. Early-start dialysis (eGFR 10–14 mL/min/1.73 m^2) results in a lower incidence of CV and infectious disease complications
D. Early-start dialysis (eGFR 10–14 mL/min/1.73 m^2) results in a lower incidence of dialysis-related complications

Answer: B

The landmark Initiating Dialysis Early and Late (IDEAL) trial was a randomized, multicenter randomized trial that evaluated effects on mortality from any cause among groups assigned to earlier initiation of dialysis (eGFR 10–14 mL/min) vs. those assigned to later initiation of dialysis (eGFR 5–7 mL/min).[80] Patients planning both HD and PD were included. Median time to start was 1.8 vs. 7.4 months in the earlier and later initiation groups, respectively. The median time of follow-up was 3.5 years. There were no significant differences in mortality between those assigned to earlier initiation (37.6%) and later initiation (36.6%), making Answer B correct and Answer A incorrect. Moreover, there was no observed difference in the incidence of CV events, infectious disease complications, or other dialysis-related complications, making Answers C and D incorrect. A potential limitation of this study, however, is that a substantial number of patients (75.9%) assigned to the later initiation group were started on dialysis above the preassigned cutoff of 7 mL/min, due to interval development of uremic symptoms. Whether or not a between-group mortality difference would have emerged had these patients waited to start dialysis until they reached the late-start eGFR cutoff of 5–7 mL/min, is uncertain. In other words, one could criticize IDEAL in that it compared very early initiation with relatively early initiation, rather than late initiation, and the modest separation in kidney function between groups resulted in an underpowered study. Nevertheless, based on the IDEAL results, there is no clinical trials-based evidence to support a very early preemptive initiation of dialysis strategy.

Question 7

A 45-year-old woman presents to clinic for management of progressive CKD secondary to focal and segmental glomerulosclerosis. Her current eGFR is 20 mL/min/1.73 m^2.

Which ONE of the following statements is true regarding vascular access management in this patient?

A. Native AVF is the preferred form of vascular access
B. CVCs are not associated with any long-term complications
C. In the US, the most common form of vascular access in incident HD patients is the AVF
D. The patient should be referred for vascular access placement one month before anticipated start of dialysis

Answer: A

Answer A is correct because compared with synthetic AVGs and CVCs, AVFs are associated with greater long-term patency rates, decreased need for interventional procedures to maintain patency, decreased rates of infection, decreased rates of patient hospitalization, decreased overall cost, and importantly, decreased patient mortality. Answer B is incorrect as long-term use of CVCs is associated with development of vascular complications, including subclavian and internal jugular vein thrombosis. Superior vena cava syndrome may also develop in patients using CVCs. These vascular complications subsequently render future placement of noncatheter forms of access more difficult. In the US, the most common form of vascular access in incident HD patients remains the CVC, making Answer C incorrect.[55] Answer D is incorrect as at least 6 months before anticipated need for dialysis initiation is needed to allow maturation of the AVF. This also takes into account the relatively high rates of primary access failure in AVFs, leading to the need for interventional procedures and/or revision surgery, such that ample time is allowed for maturation of a functional AVF at the time of dialysis start.

CHAPTER

71

Preparing for Peritoneal Dialysis

Rajnish Mehrotra[a], *Beth Piraino*[b]

[a]University of Washington, Seattle, WA, United States; [b]University of Pittsburgh, Pittsburgh, PA, United States

Abstract

Preparation for home dialysis begins with a robust modality education program because patients cannot make a decision regarding the type of dialysis if they are not provided adequate information. This requires infrastructure that some programs do not have, as well as nephrologists who are welcoming and receptive to their patients' choice of home dialysis. Unfortunately, many dialysis patients in the US do not recall receiving much information about peritoneal dialysis (PD), indicating that the process is often inadequate. This is one barrier to PD. Another is the nephrologist. The nephrologist is the most important influence regarding the decision for PD, so it is critically important that the nephrologist be trained in PD sufficiently to eliminate biases.

The program must have the infrastructure to provide robust and comprehensive modality education to patients and their support persons. This includes a one-on-one session with an educator (often a nurse), videos, visits to a home program, peer-to-peer discussion with a PD patient, and follow-up with the nephrologist. Because many patients with advanced chronic kidney disease present urgently with signs and symptoms that require rapid dialysis implementation, an in-house education program is desirable but requires an investment in a nurse educator on site.

Once the decision is made to start PD, arrangements are made for PD catheter placement. In most centers, scheduling this procedure can be delayed, so careful planning is necessary. Some innovative programs incorporate interventional nephrologists or radiologists in the program who can place PD catheters and thus ensure that rapid start PD is available. These approaches have been shown to greatly increase PD program size and allow a higher proportion of patients to choose PD at the outset. Use of the buried catheter technique is another approach that may facilitate timely PD start.

The home dialysis program must be supported by the dialysis provider or hospital or institution, as appropriate. Adequate staffing is critical to the success of the program, allowing time for training (which is usually one on one), and for meeting the regulations in place for home programs. Space for the home program is also essential, with room for private training and for clinic visits.

INTRODUCTION

The choice of dialysis modality to manage advanced kidney disease is intensely personal. The initiation of dialysis has a tremendous impact on the person's life.[1] If done badly, a person who may have been functioning at a high level may abruptly become a "patient," with disruption of work and other activities. Depression often ensues and is common in patients undergoing maintenance dialysis.[2] Therefore, the process of dialysis preparation is essential for good outcomes.

Unfortunately, many patients do not receive adequate modality education.[3–5] Study after study of patients recently started on dialysis have shown that many treated with in-center hemodialysis (HD) do not recall receiving education about a choice of home dialysis.[3–5] Even allowing for impaired recall, it is clear that modality education in many programs is woefully inadequate. There are many reasons for this, but leading are nephrologist bias against peritoneal dialysis (PD) due to lack of training in PD, as well as a failure of adequate infrastructure for the process.[6–8] The need for urgent start dialysis is another reason given for inadequate or no modality education.

Data suggest that survival is similar on in-center HD and PD.[9–17] Early studies that showed an HD survival advantage were flawed by excluding many who were survivors, such as patients who were transplanted early in the course of dialysis.[18,19] Patients treated with PD are more likely to be transplanted quickly than those on HD.[10] This is one source of bias in such comparative studies. Another is selection bias. In The Choice study, done at Dialysis Clinic Inc units plus one unit in Connecticut, almost all the PD patients in the centers participating were included, whereas HD patients were a convenience sample, because the social workers recruited those that were available (that is those who

https://doi.org/10.1016/B978-0-12-815876-0.00071-1

were not in the hospital on the recruitments days, and who had arrived for dialysis).[20] Such an approach can impact the survival outcomes because some of the sicker patients on HD (as opposed to PD) were not included in the sample. More recent studies using large databases and controlling for all important variables show similar 5-year survival.[9–17] Therefore, choice should be made by the patient after being fully informed of the options based on the patients' preferences and the impact on lifestyle.

Access plays an important role in subsequent survival on dialysis. Those with a HD catheter are more likely to die than those with a PD catheter or with an arteriovenous fistula (AVF) or graft.[21] Therefore, proper and timely education of modality choice is very important to ensure that the right access is placed at the right time for each patient.

INDICATIONS AND CONTRAINDICATIONS FOR PD

There are only a few contraindications for PD (Table 71.1). These include inability to do PD, or lack of a helper to perform the procedure for the patient. Most people can perform PD or may have a family member who is willing to assist. An attempt at a randomized controlled trial done in the Netherlands found that ~65% of people had no contraindication to doing either PD or in-center HD.[22] Once these patients were fully informed regarding PD and HD, to permit consent for randomization, almost everyone refused to be randomized after learning of the difference. Patients had a distinct preference for one dialysis method vs. another.[22] 45% chose PD. This study, although unsuccessful in its recruitment efforts, provides an important lesson, in that it clearly showed that given full information, patients want a choice of modality.

TABLE 71.1 Contraindications to Peritoneal Dialysis (PD)

ABSOLUTE CONTRAINDICATIONS
Nonfunctioning peritoneum (for example, history of abdominal radiation)
Inability to perform PD combined with lack of a partner to perform PD
Homeless state
RELATIVE CONTRAINDICATIONS
Ostomy (presternal catheter allows PD)
Right-sided heart failure with ascites
Ligation of thoracic duct and chylous ascites
Active colitis

Dementia, if severe, may lead to problems with both in-center HD and PD. More attention is being given to conservative care approaches in older patients, those with considerable comorbidity and demented patients who will gain little benefit from starting dialysis.[23] Patients who require nursing home care are often provided HD, and this is sometimes done on site. Nursing home PD programs are not common, but have been successful, and may lead to lower costs.[24] One issue is ensuring that those doing the PD are adequately trained on the technique to prevent high peritonitis rates.[24]

Those patients with mental illness are problematic when treated with in-center HD. Paranoid patients have anxieties and fear increased by being attached to a machine and may lash out at healthcare providers and even prove dangerous. Such patients if able to perform PD and have a safe home environment may be offered PD and may do well.

Nonadherence and anger expressed by those starting in-center HD may reflect in part lack of control and lack of autonomy. Having control over the dialysis such as is the case with self-care HD or PD may improve adherence and sense of control. Therefore, nonadherence should not be a reason to deny a patient full modality education.

A nonfunctioning peritoneum is likely to be the case in someone with a prior ruptured viscus, or someone with prior history of radiation to the abdomen. Prior surgery is not a contraindication, as it is impossible to determine before the peritoneal catheter placement is attempted whether there will be too extensive adhesion formation to obtain a well-functioning catheter.[25] In some cases, the adhesions may be lysed and PD successfully achieved.[25] Experience of the operator placing the catheter is particularly important in such cases.[25]

Patients who have right-sided heart failure with extensive ascites, as seen with severe pulmonary hypertension or severe tricuspid regurgitation, do not do well on PD as fluid losses tend to be so great that there is profound hypovolemia. Similarly, ligation or damage to the thoracic lymphatic duct leads to chylous ascites; these patients tend to become malnourished and volume depleted on PD. Those with severe ascites from liver failure also are prone to development of hypotension and hypovolemia from excessive fluid removal. Such patients are not likely to do well on HD either. The prognosis is dictated by the underlying liver disease and not by the choice of dialysis modality.

Some consider an ostomy to be a contraindication to PD. This issue can sometimes be managed with a sternal exit site for the PD catheter. Again the experience and comfort of the operator placing the PD catheter is key in these situations. There are few data on outcomes of PD patients with ostomies.

Some patients do particularly well on PD, such as those that are younger with less comorbidity.[26] However, PD is underutilized in the elderly, who sometimes prefer to stay at home for dialysis, and is underutilized in certain racial and ethnic groups.[27] Asian Americans are somewhat more likely to do PD and African Americans are least likely.[27–29] This is not based on outcome data, but is likely a consequence of inadequate preparation for dialysis based on bias, either implicit or overt, of the healthcare provider team. Implicit bias training of all healthcare providers might be an approach to ensure equity of care for our patients.

EDUCATION OF THE CKD PATIENT ABOUT DIALYSIS MODALITIES

PD is a good choice to manage end-stage renal disease for many.[30] Studies have shown that approximately three-fourths to two-thirds of patients may be suitable for modality education.[17,31] With full education, a substantial proportion chose PD.[32–34] The most important reason for the low uptake of home dialysis in many developed countries, and particularly in the US, is inadequate dialysis modality education, not contraindications to PD. Surveys of nephrologists from different parts of the world suggest that ideally approximately half of patients starting dialysis would start with in-center HD, either due to contraindications to home dialysis or patient choice, with about 11% on home HD and 38% on PD.[35,36] In countries with a PD first approach, such as Hong Kong and Thailand, as many as 80% start dialysis with continuous ambulatory PD (CAPD)[37–41] mostly due to economics. In such situations, patient choice is confined by the government's wish to save money with a high proportion of PD patients.

PD is easy to learn and does not require a partner. Nighttime PD allows the patient to continue daytime activities including attendance at jobs and school. Perhaps, for this reason, children are often started on PD. CAPD, on the other hand, is a good choice for those who prefer not to be attached to a machine and for those who are restless sleepers and get up frequently at night. Cycler PD and CAPD, from the patient's perspective, are quite different. Therefore, modality education needs to cover both options, outlining the differences and the advantages and disadvantages of each. CAPD is easier to learn than the cycler. Therefore, some older patients who wish to remain independent may chose CAPD, but not find cycler PD attractive. Although PD is usually performed by the patient independently, in some situations, there is a helper, who may be a spouse or an adult child, who performs the dialysis.

TABLE 71.2 Approach to Education of the Patient on Modality Choice

Introduction of the topic by the nephrologist as CKD advances.
Referral for education and decision support
By physician or advanced care practitioner
By nurse educator
By social worker
Videos
Online information
Visit to the home program
Peer-to-peer education
Follow-up visits with the nephrologist for decision support

Because incremental dialysis is possible in many who start dialysis with residual kidney function, CAPD does not have to be prescribed initially as four exchanges per day. For some patients, two or three exchanges per day may initially suffice.[42] Similarly, cycler PD may only need to be done at nighttime with no day dwell or exchanges.[42] This information can impact the decision made by the patient regarding modality.

It has been shown time and time again that most patients treated with in-center HD have received inadequate education about the modality choice. There may be multiple reasons for this. The physician has been shown to be the person who most influences patient choice of modality, but most nephrologists and almost no internists have training or experience in supporting informed modality choice (decision support). Discussion of modality takes time and an adequate knowledge of the details of PD, including management of supplies, access, infection risk, different types of PD, training time, follow-up procedures, and support. Most nephrologists are familiar with in-center HD, but many have little training and are uncomfortable with home dialysis including PD.[6,8] Many trainees make inappropriate assumptions about who might be "suitable" for PD or home HD. This is likely due to insufficient knowledge of the modalities by both the trainee and the faculty mentors.

A comprehensive approach to modality education is shown in Table 71.2. Modality education is best done in a stepwise fashion.[43] Patients when hearing about the upcoming need for dialysis are often frightened and in denial. Thus, many do not hear much of the initial information on this topic. The introduction of the topic of dialysis choice can begin with the patient once estimated glomerular filtration rate (eGFR) approaches around 20 mL/min/1.73 m^2, although this must be tailored to rapidity of progression. This initial

introduction should be followed by a referral to an educator. The patient should be encouraged to visit the home program, as well as meeting with the home training nurse, viewing the equipment, and understanding the storage space needed, and, as appropriate, meeting other patients doing home dialysis. Subsequent follow-up with the nephrologist then can begin to pin down the choice with which the patient is most comfortable. This needs to be an iterative process, as many have such a fear of dialysis that the initial discussions are not fully absorbed.[43] The partner or any significant support person should be present at some of these education sessions. Group sessions can be used to supplement the information, but alone are not adequate for education. One-on-one sessions allow the teacher to explore the level of understanding of the modalities. Because the physician is the most influential person in the patient's final decision, the information process should not be entirely assigned to educators. The nephrologist should be the leader in the education process and ensure that sufficient steps are taken to guarantee understanding. Having the patient reflect back on information received is a helpful technique to ensure that misconceptions and biases have not crept into the process. Many patients have misconceptions about home dialysis that can be explored in conversations. Sometimes this misinformation comes from support persons who have not been part of the process. In other cases, misinformation can come from the primary care physician who may not be acquainted with PD.

Fully informed patients have many reasons for their choices.[1] One patient may elect to choose PD simply because of a fear of needles, another because it allows the patient to continue with a job or school or both. Yet another patient may like the independence and flexibility home dialysis brings vs. in-center HD.[1] Patient autonomy is an important reason that patients choose home dialysis.[1]

It is important to understand that patients will not pick home dialysis without substantial and detailed education about this choice. Patients do not choose a modality they know little or nothing about. Many patients find the entire concept of dialysis frightening and intimidating. Therefore, a full understanding of the choices, and the impact this choice will have on lifestyle, requires considerable investment by the program. Most patients are capable of doing PD but have little confidence in their ability. Some develop depression on learning dialysis will be needed. This depression may paralyze decision making. Reassurance that patients can learn the technique if they chose to and a supportive approach are key parts of the process.

Too often, the default is inadequate, cursory modality education and a default to in-center HD. This is one reason why the majority of patients in most western countries are treated with in-center HD. A survey of nephrologists showed that a minority would pick in-center HD for themselves.[44] Therefore, it is ironic that most patients in Canada and the US are maintained on in-center HD.

In the US, with the implementation of the expanded prospective payment bundle for dialysis, PD became more economically advantageous for dialysis units.[45,46] This is in part because PD patients require less erythropoietin and intravenous iron (drugs which are now included in the bundled rate) than HD patients. This incentive encouraged dialysis programs to enhance their modality education programs. One such program developed by Fresenius Medical Care, Treatment Options Program, was quite successful in increasing the uptake of patients on PD.[47] However, many patients were not referred for the educational program. More recently, dialysis providers are employing nephrologists and thus have more control over the chronic kidney disease (CKD) clinics and the education process. Many patients once started on one modality are reluctant to make a switch.[48] Therefore, education is best done before starting dialysis. This allows avoidance of placement of a HD catheter as a way of starting dialysis. However, late-referred patients should not be denied a choice, and all patients should receive iterative modality education with decision support.

PLANNED VERSUS NONPLANNED (URGENT) START PD

Patient education on modality choice may take months to achieve. However, a large number of patients present with very advanced CKD, requiring urgent start dialysis due to uremia, hyperkalemia, volume overload, or other indications. The default approach is to place a HD catheter and start HD in the hospital. Discussion of modalities does not happen in most of these cases. However, several publications have shown that by implementing an in-house modality education program, the uptake of home dialysis, particularly PD, can be greatly increased.[49,50] This requires that the program makes an educator available for late-referred patients and may involve visits to the home program and contact with a current PD patient for peer-to-peer education.[51] The nephrologists in the program need to be supportive of this approach for it to be successful. Such an approach can be cost-effective.[52,53] Numerous reports from around the world have shown that such an approach results in a significant proportion of late-referred patients starting with PD with good results.[51,54–62] Infrastructure needed for a successful PD program, including one with an urgent start capability, is shown in Table 71.3.

TABLE 71.3 Infrastructure Needed for Peritoneal Dialysis (PD) Including Urgent Start

Ability to provide modality education and decision support on short notice
Resources for rapid placement of PD catheter
Ability to provide supine PD until patient can be trained
Available nurse trainers, protected from in-center HD demands
Adequate space for PD training and follow-up visits

ASSISTED HOME DIALYSIS

There was a period of time in the US when assisted home HD was supported by the payors for dialysis, such that a nurse or dialysis technician would go to the home to do the HD. Because of costs, this quickly fell out of favor and is now rarely if ever an option. However, innovative programs in different parts of the world have implemented assisted PD.[63–68] In such a situation, mostly involving elderly patients who prefer to do PD at home at night on a cycler, but do not feel capable of being completely independent, a visiting nurse travels to the home and sets up the cycler each day, sometimes also attaching the patient. Often the patient is able to disconnect from the cycler (which is an easy maneuver) in the morning. A proportion of these patients will eventually be able to perform dialysis at home independently.[65] In France, there is a substantial home PD assisted program for elderly patients.[64] This approach has not been implemented in the US, but given the economic advantage of PD over in-center HD for the dialysis provider, should be tested in the US on a trial basis. For now, patients in the US can benefit from assistance from their family members. In some states, publicly funded compensation is available for the provision of in-home support services.

TIMING AND PREPARATION FOR CATHETER PLACEMENT

Once the patient has decided on PD, there is no need to put the access in until close to the timing of PD start. However, once the patient arrives at stage 5 CKD, follow-up should be performed with frequent laboratory checks to ensure that the timing of PD catheter placement is optimal. It is often prudent to send the patient to the person placing the PD catheter ahead of time to ensure there are no barriers.

The PD catheter is most often placed by a surgeon. Although this is not a difficult surgery, it is important that each program finds surgeons who are interested in working as a team, will appreciate feedback, and who are good communicators. Some programs have had good success by having a nephrologist or radiologist train in PD catheter placement, which allows quick access to PD and PD training. This approach has led to dramatic increases in the size of already large PD programs.[69] Because interventional nephrology as a subspecialty is gaining attention, PD catheter placement should be part of this training.

Actual placement of the catheter should be timed so that there remain 10 days to two weeks for healing before training begins. There is no need to place the PD catheter earlier than this, although there are programs who prefer to use the buried catheter approach. With this approach, the tunneled portion of the catheter is completely within the subcutaneous tissue, with no external portion.[70,71] The advantage of this approach is that when the patient is ready to start dialysis, the PD catheter can be brought to the exterior with the creation of an exit site, and because the cuffs are fully embedded, the catheter can be used immediately. Furthermore, during the waiting period to start dialysis, no care is needed for the catheter. Limited research indicates that catheter outcomes are no different with this approach, and there is no reduction in early PD-related infections as was posited. While offering the advantage of elective start of PD, in some patients the placement may be futile, as they may die before needing dialysis or start with HD, either because they may change their mind or may have had a change in health or social condition that may preclude home dialysis. In 10–15% of the cases, the catheter may have problems with drainage, which are generally readily resolved with vigorous flushing. Some programs routinely use this approach with good results.[71–73]

There is no preferred type of PD catheter. At one time, the literature suggested that a downward directed exit site would decrease the risk of exit site infection. However, there is little research to support this hypothesis and a laterally directed exit site may provide the same results.[70] A skilled operator is the key to successful outcomes with a PD catheter.

Generally, the catheter is placed when the eGFR is around 10 mL/min/1.73 m^2. Placing a HD catheter in a patient who wants PD should be avoided as much as possible, as this leads to increased risk of infection and exposes the patient to HD which may decrease residual kidney function, lead to cardiac arrhythmias, and cause emotional distress to the patient and interfere with daily activities. PD catheter placement should be elective and done as an outpatient as much as possible, as a planned event.

Once PD catheter placement is scheduled, the patient should be carefully instructed in the preparations for the placement. The skin should be clean and without

infections. The patient should take a cathartic before the procedure to ensure that the colon is relatively empty. The patient should void before the procedure and if there is any suggestion of a neurogenic bladder, a bladder scan should be done to ensure that the bladder is empty. A single dose of preoperative intravenous antibiotics reduces the risk for early infection and should be the standard of care.[74]

After the catheter is placed, the patient will be generally discharged home, but should be instructed to keep the dressing dry and clean and to not change the dressing. Approximately one week later, the patient should visit the training center, where the nurse will do a dressing change, inspect the exit site, and, in some programs, flush the catheter to ensure proper function.[70] Training can generally start 10 days to 2 weeks after catheter placement. Only when the exit site is well healed is the patient to resume showers and start performing daily exit site care.

BARRIERS TO PATIENT-DRIVEN MODALITY CHOICE

Unfortunately, one of the major barriers to patient choice is the lack of training about home dialysis in many countries, including the US. Early in the growth of PD, in the 1980s, most PD patients were dialyzed at centers with a particular interest in PD, and at least one nephrologist who was a champion of PD. As HD centers became more and more common, there was pressure to fill HD seats, and less emphasis on providing modality education to patients. The proportion of patients starting dialysis with PD fell from a peak of about 15% to 6%.[75] Training programs had small numbers of patients on PD, and some programs had no patients.[6] This led to a cycle of newly graduated nephrologists being quite comfortable with in-center HD (although even training in this area sometimes was lacking) and with very little knowledge about home dialysis (either home HD or PD).[8] Because the nephrologist is the main influencer on the patient's decision about dialysis, this led to even fewer patients starting PD.

Modality education takes time. If the program does not have a robust predialysis education program for patients, the burden falls almost entirely on the nephrologist. Modality education is best done with repetitive information sessions and multiple modalities, and nephrologists may not be able to schedule the necessary sessions.

Economic barriers are greater with frequent home HD than with PD. With the implementation of the expanded prospective payment system in the US, PD became quite profitable for the dialysis providers who increased efforts to educate patients about home modalities.[45] This has led to about 10% of new patients starting dialysis with PD.[75,76] However, with increased demands for training patients, which in US is done one on one with the PD nurse trainer and the patient with or without family member, staffing needs to be adequate to still run the clinics, answer phone calls, complete paper work, and do home visits. In addition, there needs to be adequate support by the social worker and the dietician. Data particularly hospitalization and infection rates, especially peritonitis and exit site infections, and outcomes of catheter placement must be tracked. In some programs, the home dialysis nurses are also part of the modality education program. Such personnel are ideal for assessing a patient's ability to learn PD and are often better at this than the nephrologist (especially an inexperienced nephrologist).

Support for the home program by the dialysis provider, hospital, or institution is critical for the success of the home program. This includes provision of adequate space for the home program and deployment of adequate personnel.

SUMMARY

Preparation for PD involves a comprehensive education process for the patient and the patient's support person(s). This takes infrastructure from the program, but the nephrologist needs to take the lead. Unfortunately, in the US, in particular, nephrologists are often inadequately trained in PD and many have significant biases against PD and biases about who can perform PD. Until these barriers can be overcome, despite the economic advantages of PD over in-center HD in the US, PD growth will be limited.

References

1. Morton RL, Tong A, Howard K, Snelling P, Webster AC. The views of patients and carers in treatment decision making for chronic kidney disease: systematic review and thematic synthesis of qualitative studies. *BMJ* 2010;**340**:c112.
2. Palmer S, Vecchio M, Craig JC, et al. Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. *Kidney Int* 2013;**84**(1):179–91.
3. Mehrotra R, Marsh D, Vonesh E, Peters V, Nissenson A. Patient education and access of ESRD patients to renal replacement therapies beyond in-center hemodialysis. *Kidney Int* 2005;**68**(1):378–90.
4. Finkelstein FO, Story K, Firanek C, et al. Perceived knowledge among patients cared for by nephrologists about chronic kidney disease and end-stage renal disease therapies. *Kidney Int* 2008; **74**(9):1178–84.
5. Kutner NG, Zhang R, Huang Y, Wasse H. Patient awareness and initiation of peritoneal dialysis. *Arch Intern Med* 2011;**171**(2):119–24.
6. Mehrotra R, Blake P, Berman N, Nolph KD. An analysis of dialysis training in the United States and Canada. *Am J Kidney Dis* 2002; **40**(1):152–60.

7. Golper TA, Saxena AB, Piraino B, et al. Systematic barriers to the effective delivery of home dialysis in the United States: a report from the public policy/advocacy committee of the North American chapter of the International Society for Peritoneal Dialysis. *Am J Kidney Dis* 2011;**58**(6):879–85.
8. Berns JS. A survey-based evaluation of self-perceived competency after nephrology fellowship training. *Clin J Am Soc Nephrol* 2010; **5**(3):490–6.
9. Weinhandl ED, Foley RN, Gilbertson DT, Arneson TJ, Snyder JJ, Collins AJ. Propensity-matched mortality comparison of incident hemodialysis and peritoneal dialysis patients. *J Am Soc Nephrol* 2010;**21**(3):499–506.
10. Mehrotra R, Chiu YW, Kalantar-Zadeh K, Bargman J, Vonesh E. Similar outcomes with hemodialysis and peritoneal dialysis in patients with end-stage renal disease. *Arch Intern Med* 2011;**171**(2): 110–8.
11. Chang YK, Hsu CC, Hwang SJ, et al. A comparative assessment of survival between propensity score-matched patients with peritoneal dialysis and hemodialysis in Taiwan. *Medicine (Baltim)* 2012; **91**(3):144–51.
12. Yeates K, Zhu N, Vonesh E, Trpeski L, Blake P, Fenton S. Hemodialysis and peritoneal dialysis are associated with similar outcomes for end-stage renal disease treatment in Canada. *Nephrol Dial Transplant* 2012;**27**(9):3568–75.
13. Heaf JG, Wehberg S. Relative survival of peritoneal dialysis and haemodialysis patients: effect of cohort and mode of dialysis initiation. *PLoS One* 2014;**9**(3):e90119.
14. Marshall MR, Polkinghorne KR, Kerr PG, Agar JW, Hawley CM, McDonald SP. Temporal changes in mortality risk by dialysis modality in the Australian and New Zealand dialysis population. *Am J Kidney Dis* 2015;**66**(3):489–98.
15. Ryu JH, Kim H, Kim KH, et al. Improving survival rate of Korean patients initiating dialysis. *Yonsei Med J* 2015;**56**(3):666–75.
16. van de Luijtgaarden MW, Jager KJ, Segelmark M, et al. Trends in dialysis modality choice and related patient survival in the ERA-EDTA Registry over a 20-year period. *Nephrol Dial Transplant* 2016;**31**(1):120–8.
17. Wong B, Ravani P, Oliver MJ, et al. Comparison of patient survival between hemodialysis and peritoneal dialysis among patients eligible for both modalities. *Am J Kidney Dis* 2018;**71**(3):344–51.
18. Bloembergen WE, Port FK, Mauger EA, Wolfe RA. A comparison of mortality between patients treated with hemodialysis and peritoneal dialysis. *J Am Soc Nephrol* 1995;**6**(2):177–83.
19. Vonesh EF, Moran J. Mortality in end-stage renal disease: a reassessment of differences between patients treated with hemodialysis and peritoneal dialysis. *J Am Soc Nephrol* 1999;**10**(2):354–65.
20. Jaar BG, Coresh J, Plantinga LC, et al. Comparing the risk for death with peritoneal dialysis and hemodialysis in a national cohort of patients with chronic kidney disease. *Ann Intern Med* 2005;**143**(3): 174–83.
21. Perl J, Wald R, McFarlane P, et al. Hemodialysis vascular access modifies the association between dialysis modality and survival. *J Am Soc Nephrol* 2011;**22**(6):1113–21.
22. Korevaar JC, Feith GW, Dekker FW, et al. Effect of starting with hemodialysis compared with peritoneal dialysis in patients new on dialysis treatment: a randomized controlled trial. *Kidney Int* 2003; **64**(6):2222–8.
23. Davis JL, Davison SN. Hard choices, better outcomes: a review of shared decision-making and patient decision aids around dialysis initiation and conservative kidney management. *Curr Opin Nephrol Hypertens* 2017;**26**(3):205–13.
24. Carey HB, Chorney W, Pherson K, Finkelstein FO, Kliger AS. Continuous peritoneal dialysis and the extended care facility. *Am J Kidney Dis* 2001;**37**(3):580–7.
25. Crabtree JH, Fishman A. A laparoscopic method for optimal peritoneal dialysis access. *Am Surg* 2005;**71**(2):135–43.
26. Vonesh EF, Snyder JJ, Foley RN, Collins AJ. The differential impact of risk factors on mortality in hemodialysis and peritoneal dialysis. *Kidney Int* 2004;**66**(6):2389–401.
27. Mehrotra R, Soohoo M, Rivara MB, et al. Racial and ethnic disparities in use of and outcomes with home dialysis in the United States. *J Am Soc Nephrol* 2016;**27**(7):2123–34.
28. Wallace EL, Lea J, Chaudhary NS, et al. Home dialysis utilization among racial and ethnic minorities in the United States at the national, regional, and state level. *Perit Dial Int* 2017;**37**(1):21–9.
29. Turenne M, Baker R, Pearson J, Cogan C, Mukhopadhyay P, Cope E. Payment reform and health disparities: changes in dialysis modality under the new medicare dialysis payment system. *Health Serv Res* 2018;**53**(3):1430–57.
30. Mehrotra R, Devuyst O, Davies SJ, Johnson DW. The current state of peritoneal dialysis. *J Am Soc Nephrol* 2016;**27**(11):3238–52.
31. Mendelssohn DC, Mujais SK, Soroka SD, et al. A prospective evaluation of renal replacement therapy modality eligibility. *Nephrol Dial Transplant* 2009;**24**(2):555–61.
32. Devoe DJ, Wong B, James MT, et al. Patient education and peritoneal dialysis modality selection: a systematic review and meta-analysis. *Am J Kidney Dis* 2016;**68**(3):422–33.
33. Manns BJ, Taub K, Vanderstraeten C, et al. The impact of education on chronic kidney disease patients' plans to initiate dialysis with self-care dialysis: a randomized trial. *Kidney Int* 2005;**68**(4): 1777–83.
34. Devins GM, Mendelssohn DC, Barre PE, Taub K, Binik YM. Predialysis psychoeducational intervention extends survival in CKD: a 20-year follow-up. *Am J Kidney Dis* 2005;**46**(6):1088–98.
35. Mendelssohn DC, Mullaney SR, Jung B, Blake PG, Mehta RL. What do American nephologists think about dialysis modality selection? *Am J Kidney Dis* 2001;**37**(1):22–9.
36. Jassal SV, Krishna G, Mallick NP, Mendelssohn DC. Attitudes of British Isles nephrologists towards dialysis modality selection: a questionnaire study. *Nephrol Dial Transplant* 2002;**17**(3): 474–7.
37. Liu FX, Gao X, Inglese G, Chuengsaman P, Pecoits-Filho R, Yu A. A global overview of the impact of peritoneal dialysis first or favored policies: an opinion. *Perit Dial Int* 2015;**35**(4):406–20.
38. Li PK, Chow KM. Peritoneal dialysis-first policy made successful: perspectives and actions. *Am J Kidney Dis* 2013;**62**(5):993–1005.
39. Chuengsaman P, Kasemsup V. PD first policy: Thailand's response to the challenge of meeting the needs of patients with end-stage renal disease. *Semin Nephrol* 2017;**37**(3):287–95.
40. Li PK, Szeto CC. Success of the peritoneal dialysis programme in Hong Kong. *Nephrol Dial Transplant* 2008;**23**(5):1475–8.
41. Tantivess S, Werayingyong P, Chuengsaman P, Teerawattananon Y. Universal coverage of renal dialysis in Thailand: promise, progress, and prospects. *BMJ* 2013;**346**:f462.
42. Ankawi GA, Woodcock NI, Jain AK, Garg AX, Blake PG. The use of incremental peritoneal dialysis in a large contemporary peritoneal dialysis program. *Can J Kidney Health Dis* 2016;**3**. 2054358116679131.
43. Saggi SJ, Allon M, Bernardini J, et al. Considerations in the optimal preparation of patients for dialysis. *Nat Rev Nephrol* 2012;**8**(7): 381–9.
44. Merighi JR, Schatell DR, Bragg-Gresham JL, Witten B, Mehrotra R. Insights into nephrologist training, clinical practice, and dialysis choice. *Hemodial Int* 2012;**16**(2):242–51.
45. Hirth RA, Turenne MN, Wheeler JR, et al. The initial impact of Medicare's new prospective payment system for kidney dialysis. *Am J Kidney Dis* 2013;**62**(4):662–9.
46. Golper TA. A view of the bundle from a home dialysis perspective: present at the creation. *Clin J Am Soc Nephrol* 2018;**13**(3):471–3.
47. Lacson Jr E, Wang W, DeVries C, et al. Effects of a nationwide predialysis educational program on modality choice, vascular access, and patient outcomes. *Am J Kidney Dis* 2011;**58**(2):235–42.

48. Bass EB, Wills S, Fink NE, et al. How strong are patients' preferences in choices between dialysis modalities and doses? *Am J Kidney Dis* 2004;**44**(4):695–705.
49. Rioux JP, Cheema H, Bargman JM, Watson D, Chan CT. Effect of an in-hospital chronic kidney disease education program among patients with unplanned urgent-start dialysis. *Clin J Am Soc Nephrol* 2011;**6**(4):799–804.
50. Hanko J, Jastrzebski J, Nieva C, White L, Li G, Zalunardo N. Dedication of a nurse to educating suboptimal haemodialysis starts improved transition to independent modalities of renal replacement therapy. *Nephrol Dial Transplant* 2011;**26**(7):2302–8.
51. Ghaffari A. Urgent-start peritoneal dialysis: a quality improvement report. *Am J Kidney Dis* 2012;**59**(3):400–8.
52. Liu FX, Ghaffari A, Dhatt H, et al. Economic evaluation of urgent-start peritoneal dialysis versus urgent-start hemodialysis in the United States. *Medicine (Baltim)* 2014;**93**(28):e293.
53. Piwko C, Vicente C, Marra L, et al. The STARRT trial: a cost comparison of optimal vs sub-optimal initiation of dialysis in Canada. *J Med Econ* 2012;**15**(1):96–104.
54. Song JH, Kim GA, Lee SW, Kim MJ. Clinical outcomes of immediate full-volume exchange one year after peritoneal catheter implantation for CAPD. *Perit Dial Int* 2000;**20**(2):194–9.
55. Banli O, Altun H, Oztemel A. Early start of CAPD with the Seldinger technique. *Perit Dial Int* 2005;**25**(6):556–9.
56. Povlsen JV, Ivarsen P. How to start the late referred ESRD patient urgently on chronic APD. *Nephrol Dial Transplant* 2006;**21**(Suppl. 2):ii56–59.
57. Jo YI, Shin SK, Lee JH, Song JO, Park JH. Immediate initiation of CAPD following percutaneous catheter placement without break-in procedure. *Perit Dial Int* 2007;**27**(2):179–83.
58. Lobbedez T, Lecouf A, Ficheux M, Henri P, Hurault de Ligny B, Ryckelynck JP. Is rapid initiation of peritoneal dialysis feasible in unplanned dialysis patients? A single-centre experience. *Nephrol Dial Transplant* 2008;**23**(10):3290–4.
59. Casaretto A, Rosario R, Kotzker WR, Pagan-Rosario Y, Groenhoff C, Guest S. Urgent-start peritoneal dialysis: report from a U.S. private nephrology practice. *Adv Perit Dial Conf* 2012; **28**:102–5.
60. Koch M, Kohnle M, Trapp R, Haastert B, Rump LC, Aker S. Comparable outcome of acute unplanned peritoneal dialysis and haemodialysis. *Nephrol Dial Transplant* 2012;**27**(1):375–80.
61. Alkatheeri AM, Blake PG, Gray D, Jain AK. Success of urgent-start peritoneal dialysis in a large Canadian renal program. *Perit Dial Int* 2016;**36**(2):171–6.
62. Jin H, Ni Z, Mou S, et al. Feasibility of urgent-start peritoneal dialysis in older patients with end-stage renal disease: a single-center experience. *Perit Dial Int* 2018;**38**(2):125–30.
63. Povlsen JV, Ivarsen P. Assisted automated peritoneal dialysis (AAPD) for the functionally dependent and elderly patient. *Perit Dial Int* 2005;**25**(Suppl. 3):S60–63.
64. Verger C, Duman M, Durand PY, Veniez G, Fabre E, Ryckelynck JP. Influence of autonomy and type of home assistance on the prevention of peritonitis in assisted automated peritoneal dialysis patients. An analysis of data from the French Language Peritoneal Dialysis Registry. *Nephrol Dial Transplant* 2007;**22**(4):1218–23.
65. Oliver MJ, Quinn RR, Richardson EP, Kiss AJ, Lamping DL, Manns BJ. Home care assistance and the utilization of peritoneal dialysis. *Kidney Int* 2007;**71**(7):673–8.
66. Lobbedez T, Verger C, Ryckelynck JP, Fabre E, Evans D. Is assisted peritoneal dialysis associated with technique survival when competing events are considered? *Clin J Am Soc Nephrol* 2012; **7**(4):612–8.
67. Franco MR, Fernandes N, Ribeiro CA, Qureshi AR, Divino-Filho JC, da Gloria Lima M. A Brazilian experience in assisted automated peritoneal dialysis: a reliable and effective home care approach. *Perit Dial Int* 2013;**33**(3):252–8.
68. Brown EA, Wilkie M. Assisted peritoneal dialysis as an alternative to in-center hemodialysis. *Clin J Am Soc Nephrol* 2016;**11**(9):1522–4.
69. Asif A, Pflederer TA, Vieira CF, Diego J, Roth D, Agarwal A. Does catheter insertion by nephrologists improve peritoneal dialysis utilization? A multicenter analysis. *Semin Dial* 2005;**18**(2):157–60.
70. Crabtree JH. Selected best demonstrated practices in peritoneal dialysis access. *Kidney Int Suppl* 2006;(103):S27–37.
71. McCormick BB, Brown PA, Knoll G, et al. Use of the embedded peritoneal dialysis catheter: experience and results from a North American Center. *Kidney Int Suppl* 2006;(103):S38–43.
72. Prischl FC, Wallner M, Kalchmair H, Povacz F, Kramar R. Initial subcutaneous embedding of the peritoneal dialysis catheter–a critical appraisal of this new implantation technique. *Nephrol Dial Transplant* 1997;**12**(8):1661–7.
73. Crabtree JH, Burchette RJ, Siddiqi RA. Embedded catheters: minimizing excessive embedment time and futile placement while maintaining procedure benefits. *Perit Dial Int* 2015;**35**(5):545–51.
74. Gadallah MF, Ramdeen G, Mignone J, Patel D, Mitchell L, Tatro S. Role of preoperative antibiotic prophylaxis in preventing postoperative peritonitis in newly placed peritoneal dialysis catheters. *Am J Kidney Dis* 2000;**36**(5):1014–9.
75. Rivara MB, Mehrotra R. The changing landscape of home dialysis in the United States. *Curr Opin Nephrol Hypertens* 2014;**23**(6): 586–91.
76. Lin E, Cheng XS, Chin KK, et al. Home dialysis in the prospective payment system era. *J Am Soc Nephrol* 2017;**28**(10):2993–3004.

QUESTIONS AND ANSWERS

Question 1

You are seeing a 65-year-old woman with diabetes mellitus who has advancing CKD, now with eGFR of 11 mL/min/1.73 m^2. She is asymptomatic at this time and has trace edema and clear lungs on examination. Her BMI is 32 kg/m^2. She lives alone and is fiercely independent. Her diabetes is reasonably well controlled. You explain to her that her kidney disease is quite advanced and she needs to consider her options. What options do you discuss with her?

A. In-center HD is the best choice given she lives alone and is a diabetic
B. Kidney transplantation should be the focus as perhaps she can receive a kidney without going on dialysis
C. In-center HD and PD are both reasonable choices and referral for education about these is appropriate
D. Refer her for placement of a central venous catheter to start dialysis as soon as possible as her kidney disease is so advanced
E. PD is the best choice given that she is fiercely independent

Answer: C

Both in-center HD and home PD are choices for this woman. She may well prefer one over the other. Until the choice is made based on full information, no access should be placed. Although renal transplantation is certainly an option, the referral, workup, and wait time make the timing not very feasible for preemptive kidney transplantation unless she has a living donor. While her kidney disease is advanced, she is asymptomatic and there is no need to initiate dialysis urgently.

Question 2

A 24-year-old single woman who still lives with her parents is followed for chronic glomerulonephritis, which despite immunosuppression is progressing. She has a full-time desk job working from 8 a.m. to 5 p.m. She has been reluctant to receive much information about dialysis. The family's plan is to have the father donate a kidney to her. Once the evaluation is done, the father is found to have unrecognized coronary artery disease, and the transplant team refuses to consider him further as a donor. The mother is not a suitable donor. The sister is 21 years old, and the parents ask you about her as a candidate. Now the patient's creatinine is 13 mg/dL, and even though she is still asymptomatic and the rest of the laboratory not worrisome, you are concerned about the very advanced state of her renal function (eGFR 4 mL/min/1.73 m^2).

A. You call her once you receive this laboratory result and tell her to go to the emergency department to get admitted to start HD *via* a HD catheter
B. You tell her that the nurse is going to schedule outpatient placement of a tunneled HD catheter, following which she will start in-center HD
C. You again explain the choice of in-center HD vs. PD to her and encourage her to consider nighttime PD so she can continue with her job
D. You tell her that home HD is the best choice given that her parents can do this with her
E. You encourage her to ask her sister to be a living donor to avoid dialysis

Answer: C

Because she is asymptomatic, there is no need to admit her to the hospital. However, dialysis needs to be implemented very soon, within a few weeks. If she agrees with PD, a PD catheter would need to be placed promptly and then urgent start PD can be implemented, with training starting simultaneously. There is insufficient time to get a transplant from the sister even if the sister is willing. If she does not want PD, then a tunneled HD catheter can be placed as an outpatient and she can be started on in-center HD at a center convenient, but this should be a choice, not mandated by the nephrology team.

Question 3

All of the following are absolute or relative contraindications to PD except?

A. A 68-year-old woman who has received radiation to her abdomen for metastatic ovarian cancer
B. A 50-year-old man with pulmonary hypertension and severe right heart failure with large ascites
C. A 72-year-old woman with mild dementia who lives with her devoted husband and adult son
D. A 48-year-old woman with diabetes mellitus who has a BMI of 42 who wants to undergo bariatric surgery to become eligible for a kidney transplant
E. A 70-year-old man who lives alone, who has marked impaired vision due to macular degeneration

Answer: C

Radiation to the abdomen makes PD not very feasible as the peritoneum is likely somewhat damaged. Those with severe right-sided heart failure and large ascites, tend to lose too much fluid with PD, leading to profound hypotension, difficult to manage. PD in a person with a BMI of 42 and wants to undergo bariatric surgery is challenging. The patient with impaired vision who lives alone and is therefore unlikely to have a helper is at high risk for peritonitis, unless an assisted PD program is available. The woman with dementia who lives with

supportive family may well decide with her family that home dialysis is best, because the son and/or the husband could do the PD for her. Therefore, Answer C is the correct answer.

Question 4

You follow a 55-year-old man who works as an electrician, BMI 35, who is approaching the need to start dialysis. He is interested in kidney transplantation and has been accepted on the transplant list but has no donors. After appropriate education about modalities, he has chosen cycler nocturnal PD, because he wants to keep his job and hates needles. His eGFR is now 10 mL/min/1.73 m^2. He has mild symptoms of fatigue and has lost 5 pounds in the last month. S[K] is 5 mEq/L and Hb is 10 g/dL. Which of the following is your course of action at this time?

A. Refer to the surgeon for placement of PD catheter, then start PD training 1−2 weeks later
B. Admit him to the hospital, place HD catheter, and place on HD, with a plan to start PD later
C. Tell him that as he has few symptoms that it is fine to wait longer before starting dialysis
D. Have the PD catheter placed and then have the nurse train him on CAPD before allowing him to train on the cycler. He can miss work while on CAPD because he says it is not feasible to do an exchange while working
E. Explain to him that both a PD catheter and an AVF will be placed by the surgeon because HD backup access is necessary

Answer: A

Because the eGFR is now 10 mL/min/1.73 m^2, it is better to plan on PD catheter placement and starting because sometimes it takes a bit of time to arrange the PD catheter placement. In addition, the patient needs to be alert to train on PD. There is no need to place him on HD first, and this places the patient at risk of infection from the HD catheter, and possibly some harm to residual kidney function. Backup AVF is not needed at this time, as he may get a kidney transplant and never need HD. Choice D is somewhat controversial and depends on the program—some train directly on the cycler and others place the patient on CAPD first. Nevertheless, even such programs will likely make an exception for the patient to accommodate the limitations on his schedule imposed by work.

Question 5

You are the medical director of a dialysis program that has 70 patients treated with in-center HD and 5 patients in the PD program and no home HD patients. The nurse assigned to PD is also expected to work on the in-center HD side if there are shortfalls in staffing. The space for the home program consists of one room that is a combined storage space and home nurse office and one clinic room. Five physicians send their patients to the clinic and all seem eager to expand the home program. The modality education program is done at a separate location by a nurse educator who is eager to do a good job but is not being referred many patients. Which of the following might be the most effective approach by the director to increase the home program census?

A. Focus on the current HD patients and ask the home nurse to talk to them about home dialysis
B. Meet with the five physicians and the nurse educator and develop an approach to referring all patients anticipated to transition to dialysis for iterative modality education
C. Arrange a group modality education program to which you invite the current in-center HD patients and all CKD stage 4 patients
D. Talk to the HD staff about promoting PD to the in-center HD patients
E. Put posters about the advantages of home dialysis in the in-center waiting room

Answer: B

The physicians need to be behind the effort to educate the patents on modality choice as the physician has the most influence in this process, not only by the referral but by speaking positively about home dialysis. Although A, C, D, and E can be easily implemented, these approaches will be much less effective than B.

Question 6

You provide care to a 35-year-old man with IgA nephropathy with progressive decline in kidney function and now with advanced CKD. His last eGFR was 12 mL/min/1.73 m^2. He has undergone iterative modality education and has decided to be treated with PD when he needs dialysis. He has no potential living donor. He has recently been placed on a deceased donor transplant list (wait time, 5−7 years). You recommend the placement of an embedded PD catheter and he wants to understand the potential risks with such an approach.

Which of the following are the risks associated with placement of embedded PD catheters?

A. Problems with catheter drainage on exteriorization from fibrin thrombi
B. Higher risk of peritonitis in the 3-month period following exteriorization

C. A higher likelihood of internal leaks on initiation of PD
D. More frequent occurrence of hernias
E. Greater need to replace the PD catheter because of primary nonfunction

Answer: A

Placement of an embedded PD catheter allows for an elective start of PD while precluding the need for caring for an externalized PD catheter for long before patients need dialysis. The catheter can be exteriorized in the office setting and can be used for full-dose PD from day 1. Up to 15% of patients have problems with drainage on exteriorization, but these are often readily resolved with vigorous flushing. The rate of primary nonfunction is <5% and it is rare to need to replace the PD catheter. There is no difference in rates of peritonitis or herniae, and there is a lower likelihood of leak.

CHAPTER

72

Emerging Therapies

Bijin Thajudeen[a,b], *Sangeetha Murugapandian*[a,b], *Prabir Roy-Chaudhury*[c]

[a]Division of Nephrology, University of Arizona College of Medicine, Tucson, AZ, United States; [b]Banner University Medical Center Tucson and South, Tucson, AZ, United States; [c]The University of North Carolina Kidney Center, Chapel Hill, NC, United States

Abstract

Chronic kidney disease (CKD) is likely to be the public health epidemic of the 21st century. Despite the magnitude of the clinical problem, there are currently no truly effective therapies for this condition. Novel therapies could influence the way we manage CKD patients in the future. Combining biology, technology, and processes of care to develop therapies that are not only clinically effective but which are also patient friendly and cost-effective and which lend themselves to being used within existing or improved process of care paradigms may affect outcomes.

SCOPE OF THE PROBLEM

Chronic kidney disease (CKD) is currently a global health epidemic. In the US, it is estimated there are approximately 30 million people with CKD. Recent USRDS data describe the Medicare CKD population as comprising 11.1% of the total Medicare population, but consuming 21.2% of overall Medicare costs, likely due to the high incidence of cardiovascular complications.[1] The greatest impact of CKD, both with regard to morbidity/mortality and cost, however, is likely to be in the developing world (particularly in the large emerging economies of Brazil, China, and India), due to expected huge increases in the incidence of both diabetes and hypertension over the next 20 or more years in these locations.[2,3] It is projected that there will be 366 million people with diabetes worldwide by 2030, of which 298 million (81%) will be in the developing world with limited resource utilization.[3] Thus, it is critical for the renal community and for overall healthcare delivery systems that we develop innovative and cost-effective therapies for both the prevention and treatment of CKD, to prevent a future increase in end-stage renal disease (ESRD), for which most developing and indeed developed economies may simply not have the healthcare resources.

While recognizing the significant depth and breadth of emerging therapies for CKD, this chapter will focus on the following therapy domains (recognizing that these address most but not all aspects of innovation and entrepreneurship in CKD):

- Prevention of CKD progression
- Novel therapies for CKD-associated anemia
- Therapies for vascular calcification
- Renal denervation therapies
- Novel therapies for vascular access dysfunction
- Innovative renal replacement therapy (RRT)

Our hope for the future is that the availability of a wide spectrum of safe, effective, and financially viable therapies for the prevention and treatment of both CKD and its complications will allow individualization of care for every CKD patient worldwide (regardless of whether they live in the developed world or in emerging economies).

PREVENTION OF CKD PROGRESSION

There exist data on agents that may have a future role in the prevention of the final common pathway of interstitial fibrosis and tubular atrophy, albeit through the modulation of a variety of different pathways. Renal inflammation plays a key role in the progression of kidney disease. There are a number of drugs in clinical trials that decrease albuminuria, but whether this effect always translates to decreasing progression of kidney disease is yet to be studied. Only agents that have been used in clinical studies in humans are described.[4]

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00072-3

Pentoxifylline

Pentoxifylline is a nonselective phosphodiesterase inhibitor with antiinflammatory and immunomodulatory activities. Clinical studies in patients with primary glomerular diseases, diabetic nephropathy, and CKD suggest the drug decreases proteinuria, possibly through the MCP-1 pathway, albeit without changing the rate of decline of glomerular filtration rate (GFR).[5–7] The benefits of proteinuria reduction were more evident in patients with type 1 diabetes mellitus, earlier stages of CKD, and higher baseline proteinuria.[8] In a *post hoc* analysis of the PREDIAN trial (Effect of pentoxifylline on renal function and urinary albumin excretion in patients with diabetic kidney disease), pentoxifylline decreased serum and urinary TNF-α levels, but increased urinary and serum klotho levels in CKD stage 3–4 diabetic kidney disease, likely due to its antiinflammatory and antiproteinuric effects.[9] More studies with longer follow-up and meaningful renal endpoints are needed to support use of this agent to prevent progression of CKD.

Statins

In addition to their cholesterol-lowering effects, the statins as a group have important antiproliferative, antimacrophage, and endothelium stabilization effects, all of which could be beneficial in preventing the progression of CKD.[10,11] In an observational prospective study of HIV-infected patients with CKD and hyperlipidemia, the rosuvastatin and atorvastatin groups had a lower decline in estimated GFR (eGFR) compared with the omega-3 fatty acid group.[12] However, in the effects of atorvastatin on renal function in patients with dyslipidemia and chronic kidney disease: Assessment of clinical usefulness in CKD patients with atorvastatin (ASUCA) trial no renal protection was observed in the atorvastatin group.[13] In patients with hypertensive nephropathy, statins were found to be renoprotective by downregulating the angiotensin II-AT1 pathway in hypertensive nephropathy.[14] Although there may be a reduction in proteinuria, this has not translated into reduction in decline of eGFR.[15]

Mammalian Target of Rapamycin Inhibitors

Based on *in vitro* and experimental data which suggested a central role for mammalian target of rapamycin (mTOR) in the pathogenesis of autosomal-dominant polycystic kidney disease (ADPKD), two clinical trials have examined the role of these agents in early and late ADPKD patients.[16] Unfortunately, the results from these studies did not document a role for mTOR inhibitors in ADPKD. Serra et al.[17] demonstrated no decrement in kidney size in ADPKD patients treated with sirolimus. In contrast, Walz et al.[18] demonstrated a decrease in kidney size in patients with more advanced ADPKD treated with everolimus, but no benefit in GFR. There was no difference in the decline in GFR in patients in the everolimus group compared with the controls. Whether there is a role for mTOR inhibitors, perhaps in a subset of patients with ADPKD, is presently unclear.

V2 Receptor Antagonists

V2 receptor antagonists, such as tolvaptan, decrease renal cAMP levels, thereby inhibiting cytogenesis and preventing renal enlargement in patients with polycystic kidney disease.[19] In the tolvaptan in ADPKD (TEMPO 3:4 Trial), tolvaptan slowed the increase in total kidney volume and decline in kidney function over a period of 3 years. However, there was a higher discontinuation rate owing to aquaresis and hepatic events in the tolvaptan group.[20] In the REPRISE trial (Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease), patients with later-stage ADPKD treated with tolvaptan had a slower decline in kidney function, if they could tolerate the drug.[21] Tolvaptan is therefore now FDA approved to slow progression of kidney disease in patients with ADPKD. An important reason for this somewhat rare "success" in the CKD arena likely includes the availability of a surrogate endpoint (total kidney volume), which facilitated the product development pathway for ADPKD therapies.

Anti-Uric Acid Agents

In addition to precipitating acute attacks of gouty arthritis, high levels of uric acid have significant proinflammatory and profibrotic effects, which could contribute to the progression of CKD. Current data suggest an association between high uric acid levels and CKD progression. However, there have only been a handful of interventional studies that have attempted to address the question of whether lowering uric acid levels results in slowing CKD progression. While studies suggest that there may be a role for uric acid-lowering therapy in patients with CKD, more data are needed before this approach can be routinely recommended.[22,23] A large randomized trial (PERL) is underway to study the efficacy of allopurinol vs. placebo on change in measured GFR in patients with type 1 diabetes.[24]

SGLT-2 Inhibitors and Other Newer Glucose-Lowering Drugs

Sodium-glucose cotransporter type 2 (SGLT-2) inhibitors are a new class of antidiabetic drugs which have demonstrated promising results on cardiovascular and renal endpoints, that are distinct from their glucose lowering effects. Animal studies have shown that they inhibit glomerulosclerosis, with alteration of tubular cell metabolism to a more ketone-prone pathway.[25] In the EMPA-REG OUTCOME trial, empagliflozin, a member of the SGLT-2 inhibitor family, reduced progression to ESRD in patients with type 2 diabetes mellitus and established cardiovascular disease.[26] Similarly in the CREDENCE study, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group in patients with type 2 diabetes mellitus and kidney disease[27] (Figure 72.1). The exact mechanisms that result in empagliflozin's and canagliflozin's renal protective effects are not fully understood, but it seems likely that the increase in sodium delivery to the macula densa results in a tubuloglomerular feedback loop that decreases afferent arterial blood flow.[28,29] This results in an initial well-documented decrease in GFR, following which the decrease in intraglomerular pressures could potentially result in longer-term improvements in microalbuminuria and GFR slope (Figure 72.2).

The SGLT-2 inhibitor agents are not the only glucose-lowering drugs that appear to have beneficial cardiovascular and renal endpoints. In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, the glucagon-like peptide-1 analogue (GLP-1 analogue) liraglutide was shown to decrease proteinuria with an albumin: creatinine ratio approximately 20% lower in the treatment compared with the control arm, regardless of the baseline level of eGFR.[30]

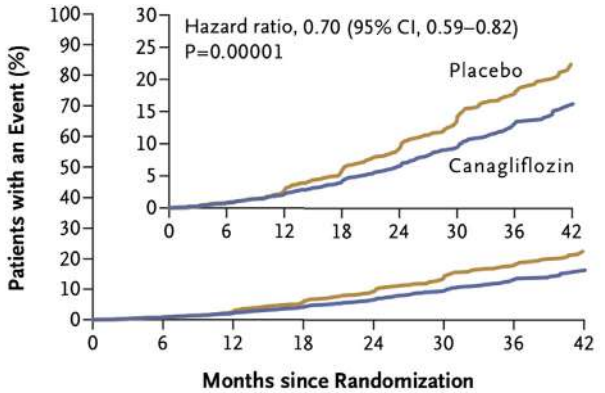


FIGURE 72.1 30% relative risk reduction in the primary composite endpoint of ESRD, doubling of serum creatinine and renal or cardiovascular death, with line segments diverging as early as 12 months after randomization. *Adapted from reference 27.*

There is excitement at present regarding the potential impact of the SGLT-2 inhibitors on the progression of CKD. Their effects on the reduction of cardiovascular endpoints can only augur well for patients with diabetes, who in addition to the risks of diabetic kidney disease also have very high cardiovascular morbidity and mortality. Thus, the SGLT-2 inhibitors and drugs such as finerenone (see below) could potentially have opened a whole new therapeutic area of cardiorenal intervention which focuses on the cotargeting of cardiovascular and renal pathogenesis, pathology, morbidity, and mortality.

The beneficial cardiovascular and renal effects of drugs such as the SGLT-2 inhibitors and GLP-1 analogues were initially discovered as a result of an FDA requirement for the conduct of cardiovascular outcome studies (CVOT) for glucose-lowering agents to identify adverse cardiovascular outcomes. These same agents are now being described by cardiologists and nephrologists as primarily cardiorenal agents that also have a glucose-lowering effect!

There are three key issues that need to be addressed for these agents to have their true kidney and cardiovascular impact. First and foremost, we need more data from clinical studies with renal endpoints such as CREDENCE in both diabetic and nondiabetic patients. Secondly, we need to analyze these data to develop and inform clinical algorithms for the use of these agents in different clinical settings. Finally, we need to develop a comprehensive safety profile for these agents and identify whether different agents in the same class have differing adverse event rates and profiles.

Finerenone

Finerenone is a nonsteroidal chemical entity that functions as a mineralocorticoid receptor antagonist in a fashion similar to spironolactone, but without steroid-induced side effects such as gynecomastia. Initial Phase II studies demonstrated a decrease in proteinuria compared with controls. There are currently two large ongoing Phase III clinical trials to elucidate both the cardiac and renal benefits of this agent, in the setting of diabetic kidney disease. The FIDELIO study has a primary cardiac endpoint with a secondary kidney endpoint, whereas the FIGARO study has a primary renal endpoint with a secondary cardiac endpoint. Similarly to the SGLT-2 inhibitors and GLP-1 analogue agents, the data from these two large studies should help to inform an algorithm for the most appropriate

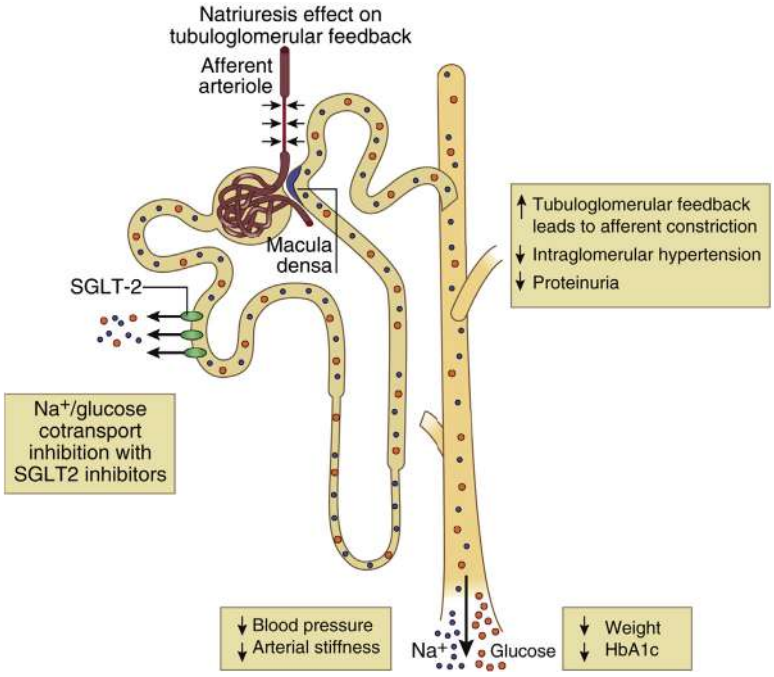


FIGURE 72.2 Mechanism of action of the sodium-glucose cotransporter type 2 (SGLT-2) inhibitors. The key mechanism appears to be a tubuloglomerular feedback loop due to increased sodium delivery to the macula densa, resulting in afferent arteriolar constriction (*arrows*) and a decrease in intraglomerular pressures, which could then result in decreased albuminuria. *Adapted from reference 28.*

clinical use of both finerenone and the SGLT-2 inhibitors and GLP-1 analogue agents in patients with chronic kidney disease (diabetic or non-diabetic).[31]

Endothelin Receptor Antagonists

Endothelin (ET) has vasoconstrictive and profibrotic properties which could contribute to the progression of renal disease. The specific ETa receptor antagonists atrasentan and sitaxsentan have been shown to result in significant reductions in albuminuria.[32,33] The major side effect of this class of drugs is fluid overload. More trials with harder clinical outcomes are needed to clearly study the effect of this class of drugs on renal disease progression. The results from the SONAR (NCT01858532) study which compared the incidence of a composite renal endpoint in patients treated with atrasentan as compared to placebo were recently published and showed a significant reduction in renal events even though the the study was terminated early as a result of a business decision.[34]

Cellular Therapies

Taking their lead from other branches of medicine, investigators are looking at the role of stem cells and bioengineering, in exploring the potential of human renal tissue to form patient-matched identical kidney tissues. With the help of cellular reprogramming technology, one can develop nephron progenitor cells which can be converted into structurally complex and functionally rudimentary kidney tissues. This technology has the potential to replace renal transplantation and thus avoid expensive immunosuppressive medications. Based on *in vitro*[35,36] studies, a prospective study is currently underway looking at the role of injecting neo-kidney augment, which is made from expanded autologous renal cells obtained from each individual participant's kidney biopsy, back into the kidney.[37]

Other Potential Agents

There is increasing interest in fibrotic pathway modulators such as bone morphogenetic protein (BMP)-7 and connective tissue growth factor which have a protective role against TNF-β1 in kidney fibrosis.[38] However, further clinical trials aimed at specific renal endpoints are needed to recommend changes in clinical practice.

Activation of the sirtuin-1 enzyme, a nicotinamide adenine dinucleotide-dependent deacetylase, which plays a role in preventing the diseases of aging, might be an important evolving therapy pertinent to the deterrence of age-related chronic diseases such as CKD. Resveratrol found in red wine and similar activators of sirtuin-1 are also in the development phase.[39]

Knowledge regarding the role of oxidative stress in the progression of vascular disease as well as CKD has led to the development of nuclear factor E2-

related factor 2 activators, such as bardoxolone methyl.[40] Bardoxolone, which attenuates inflammation, was studied in patients with type 2 diabetes with nephropathy. Unfortunately, the study had to be terminated due to an excess of serious adverse events and mortality in the bardoxolone methyl-treated group, likely related to fluid retention.[41] Such agents may still have role in the treatment of CKD, if selection of patients is done more carefully.

B7-1 receptors are present in podocytes and are involved in the pathogenesis of proteinuria through beta 1 integrin activation and cell motility. Abatacept, which is an antibody against B7-1 used in the treatment of rheumatoid arthritis, might help in reducing proteinuria and the ensuing reduction in GFR. This agent has also been used in the treatment of focal segmental glomerulosclerosis resistant to current therapies in patients who had high expression of B7-1.[42]

NOVEL THERAPIES FOR CKD-ASSOCIATED ANEMIA

The introduction of erythropoietin (EPO) into clinical practice in the late 1980s completely changed the care of CKD and ESRD patients.[43] More recently, conventional wisdom about the benefits of normalizing hemoglobin levels with EPO has not turned out to be accurate. Several nephrology and oncology studies have documented a higher incidence of cardiovascular events in patients treated to target higher hemoglobin levels.[44–47] While the exact reasons for this remain unclear, much attention has focused on the potential proliferative effects of exogenous EPO as a possible mechanism. Prolyl hydroxylase domain (PHD) inhibitors have therefore been developed as oral erythropoiesis-stimulating agents. Studies suggest an intriguing linkage between this class of drugs and oxygen biology, hypoxia, inflammation, and renal fibrosis.[48–50]

Mechanism of Action of PHD Inhibitors

EPO gene transcription is under the control of the transcription factor hypoxia-inducible factor 2 alpha (HIF-2α). The stability and transcriptional activity of HIFα molecules is regulated by molecular oxygen–dependent hydroxylation of two prolyl residues. These hydroxylation reactions are mediated through a family of PHD enzymes (Figure 72.3). Inhibition of these enzymes, which require oxoglutarate as substrates, theoretically should increase HIF and subsequently EPO levels.[51–55] Oxoglutarate mimics could therefore serve as competitive inhibitors, which could potentially result in the development of a new class of PHD inhibitors, without the cardiovascular side effects of conventional ESAs.

Clinical Experience with PHD Inhibitors for the Treatment of Anemia

There are currently a number of oral PHD inhibitors at different stages of clinical development. Initial published data on FG-2216 (FibroGen) demonstrated that the drug increases EPO levels not only in HD patients

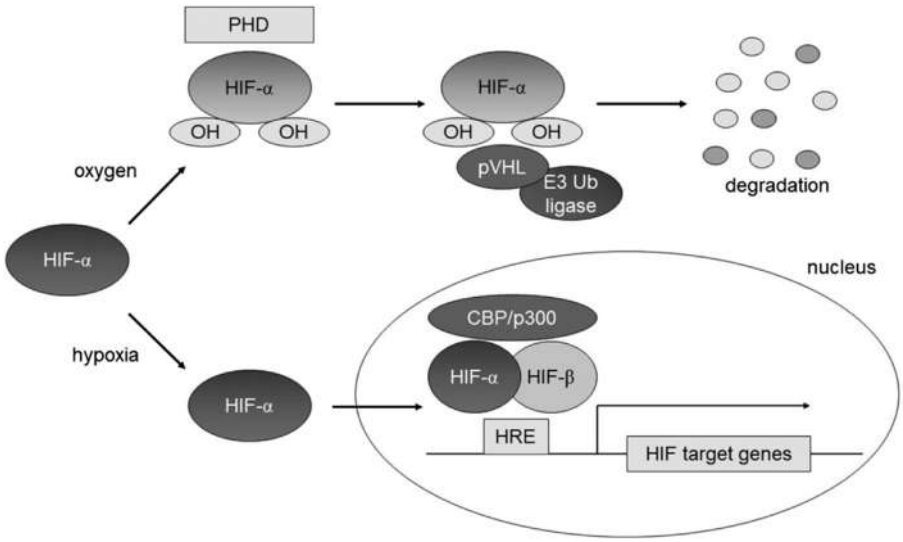


FIGURE 72.3 Erythropoietin (EPO) regulation through hypoxia-inducible factor (HIF). Under normoxic conditions, the transcription factor HIF alpha is hydroxylated by prolyl hydroxylase domain (PHD) enzymes, which results in its ultimate degradation and an inability to increase EPO (an HIF target gene) levels. The obverse occurs under hypoxic conditions because of a decrease in PHD activity resulting in an increase in EPO levels. The presence of PHD inhibitors stabilizes HIF and results in an appropriate (hopefully not excessive) increase in EPO levels. *Adapted from reference 64.*

who still had native kidneys but also in anephric HD patients.[48] The increase in EPO in HD patients who still had native kidneys was more than in the anephric patients, who had increases in EPO levels similar to that of normal healthy volunteers. These results shed light on some important potential mechanisms linked to EPO gene regulation, and the source of EPO in patients with renal failure. The greater increase in EPO levels in patients who still had native kidneys, compared not only with anephric patients but also healthy volunteers, suggests that there could be an element of dysregulated EPO gene expression in uremia, because the nonfunctional kidneys still retained the ability to significantly increase EPO levels. Important proof to support this hypothesis comes from experimental data which suggest that indoxyl sulfate, which is increased in the circulation of uremic patients, could have independent effects on HIF transcription.[56] In addition, the increase in EPO levels in response to PHD inhibitors in anephric patients suggests the presence of EPO-producing cells in organs other than the kidney, even in adults.[57]

Modulating physiological mechanisms related to EPO gene transcription and activation of downstream pathways may therefore be critical in ameliorating factors associated with the pathogenesis of cardiovascular disease linked with exogenous EPO administration that results in high hemoglobin levels.

Links Between Oxygen Biology, Inflammation, and Fibrosis

Oxygen biology pathways affected by therapeutic strategies for renal anemia could have unexpected ancillary benefits on mechanisms associated with renal fibrosis. Tissue hypoxia occurs in the setting of experimental models of CKD.[58,59] Hypoxia can activate downstream inflammatory, oxidative stress and fibrotic pathways.[60] The resolution of tissue hypoxia could be potentiated through the use of PDH inhibitors. Unfortunately, all the currently available inhibitors are nonspecific. Thus, in addition to potentially beneficial effects on tissue hypoxia, they would also likely increase erythrocytosis and angiogenesis. Alteration of angiogenic pathways might then promote fibrosis[50] or predispose to tumorigenesis.

However, more specific PHD-1 inhibitors that could protect hypoxic tissues through a reduction in oxidative stress without affecting angiogenesis and erythropoiesis might have beneficial effects on mechanisms associated with fibrosis.[61] Phase II clinical trials demonstrating safety and efficacy signals have been conducted using at least 5 PHD-1 inhibitors. Three large pivotal trials with roxadustat, vadadustat, and daprodustat are currently in progress, and the results are eagerly awaited. If successful, these data could allow targeting of normal hemoglobin values in CKD and ESRD patients, without the fear of cardiovascular events and the potential for other beneficial effects on fibrogenesis.[62–64]

THERAPIES FOR VASCULAR CALCIFICATION

Premature cardiovascular disease (including sudden cardiac death, coronary heart disease, acute myocardial infarction, and congestive heart failure) in CKD patients is perhaps the single most important problem currently faced by the renal community. To place the magnitude of this risk in perspective, the chances of a cardiovascular event in a 20- to 40-year-old treated with HD is equivalent to that of an 80-year-old without renal disease.[65–68] Traditional cardiovascular interventions such as lifestyle changes and treatment of blood pressure and dyslipidemia do not appear to have the same beneficial impact on cardiovascular mortality as in patients without renal disease. This paradox has resulted in increased attention paid to interventions that target novel pathways such as bone mineral disorder, inflammation,[69] oxidative stress,[70] endothelial dysfunction,[71,72] retention of uremic toxins,[73] and vascular calcification.[74,75] Perhaps the most exciting area in the context of emerging therapies for vascular disease in CKD patients is vascular calcification.[74–76] Vascular calcification in the general population occurs mainly within the neointima and in atherosclerotic plaques, resulting in vascular stenosis and dysfunction, especially in the setting of a thrombotic event. In CKD and ESRD patients, however, vascular calcification could be due to either neointimal calcification in the context of accelerated atherosclerosis or medial vascular calcification, which results in increased arterial stiffness, left ventricular hypertrophy, heart failure, and sudden cardiac death.[74,77]

Mechanisms of Vascular Calcification

The major mechanisms and mediators of vascular calcification have been well described.[74] They include failed anti-calcific processes involving a decrease in Fetuin A and an increased serum osteoprotegerin (OPG)/RANKL ratio, promotion of vascular smooth muscle cells by Prelamin A, the induction of osteochondrogenesis involving diabetic/inflammatory pathways and specific microRNAs such as miR-125b, cell death, and apoptosis, dysregulated calcium-phospate homeostasis which is particularly relevant to CKD, calciprotein particles, and various effects on matrix degradation/modification. Additional proteins that have associations with vascular calcification include matrix Gla protein and osteopontin, which inhibits calcium crystal growth,

ectonucleotide pyrophosphatase phosphodiesterase which regulates extracellular phosphate, and inhibition of VSMC apoptosis. Novel therapies may inhibit vascular calcification through modulation of some of these pathways.

RANK/RANKL/OPG Pathways

RANK is a type I membrane protein expressed on osteoclasts. When RANK binds to its ligand RANKL,[78] osteoclasts are activated. The resulting release of calcium from bone can then cause increased vascular calcification. In contrast, OPG is produced by osteoblasts and is a potent inhibitor of osteoclast differentiation and survival by functioning as a decoy receptor for RANKL.[78] OPG appears to protect against vascular calcification because $OPG^{-/-}$ mice develop spontaneous arterial calcifications.[79] RANKL on the other hand increases vascular smooth muscle cell calcification by increasing BMP-4 production.[80] Interest in the RANK/RANKL/OPG pathway as a mechanism to inhibit vascular calcification is particularly topical because of the availability of a monoclonal antibody (denosumab; indicated for patients with osteoporosis), which binds to RANKL, thus preventing RANK–RANKL interactions and subsequent osteoclast activation. Studies with denosumab have demonstrated reduced vascular calcification in a mouse model of glucocorticoid-induced calcification.[81] An important caveat, however, is that treatment with denosumab has been associated with significant and prolonged hypocalcemia in some patients with CKD.[82,83]

Vitamin D Receptor Agonists

Vitamin D receptor antagonists are thought to work by increasing levels of osteopontin and klotho. Vitamin D receptor antagonism reduces aortic calcification in uremic mice fed high phosphate diets.[84] There are no available human data on the ability of this therapy to reduce vascular calcification in CKD patients, although lower levels of vitamin D may be associated with increased mortality in incident hemodialysis patients.[85]

Vitamin K

CKD patients are often deficient in vitamin K, an important cofactor for a number of metabolic pathways, especially one involving matrix GLA protein.[74] A specific mechanism by which vitamin K repletion may reduce vascular calcification is by more efficient utilization of menaquinone-4, which could then inhibit arterial calcification.[86]

Calcimimetics

Cinacalcet is a calcimimetic agent which acts *via* allosteric activation of the calcium-sensing receptor on parathyroid tissue.[87] A large multicenter study (EVOLVE) evaluated the impact of cinacalcet on a composite endpoint of time to death or first nonfatal cardiovascular event and demonstrated a nonsignificant, 7% reduction in treated HD patients vs. placebo. A parallel analysis with lag censoring of data at 6 months after study drug discontinuation, however, demonstrated a nominally significant 15% relative reduction in the primary endpoint and a 17% relative reduction in mortality (absolute reduction of 2–3%).[87] In another large randomized clinical trial, the ADVANCE trial, cinacalcet plus vitamin D vs. vitamin D alone did not show a significant difference in the percentage change of coronary artery calcification scores.[88]

Role of Glucocorticoid-Inducible Kinase 1 Receptors

Both glucocorticoids and aldosterone act on the kidney though serum and glucocorticoid-inducible kinase 1 receptors. These receptors are responsible for the deleterious effects of these hormones on the cardiovascular system such as cardiac hypertrophy, cardiac fibrosis, and promotion of arrythmias. An inhibitor to this receptor has been developed called EMD638683.[89]

In summary, emerging therapies for vascular calcification must still be developed. Although the field is rapidly moving forward with regard to understanding the mechanisms involved in vascular calcification, there are still no truly effective clinical therapies shown to reduce vascular calcification in CKD.

RENAL DENERVATION THERAPIES FOR HYPERTENSION AND CKD

Despite the fact that a large array of effective therapeutic agents for the treatment of hypertension are available, treatment on a population and perhaps on an individual basis is still suboptimal. Indeed, if the target is set at 140/90 mm Hg, the success rate in the US is only 29%.[90] An important reason for this remains the side effect profile of antihypertensive agents in the context of an asymptomatic disease. Another important issue is poor compliance with both follow-up and medication adherence.[91]

An alternate approach to the therapy of hypertension is the use of renal denervation. Renal denervation could potentially address the previously described problems with conventional treatment approaches to hypertension.[92,93]

Biologic Rationale for Renal Denervation Therapy

The sympathetic nerve supply to the kidney is responsible for multiple renal effects, including increased production of renin, increased tubular reabsorption of salt and water, and renal vasoconstriction.[94] The potential benefit of completely blocking the sympathetic nerve supply of the kidney could therefore be particularly effective in patients with renal disease because of increased sympathetic activity.[95]

Interventional Technique

An important technological step forward that has allowed this concept to become a therapeutic reality was the development of an interventional technique that allowed selective renal sympathetic denervation. This was possible primarily because the sympathetic nerve supply to the kidney runs along the renal artery. As a result, the placement of a special catheter within the renal artery could allow low intensity radiofrequency ablation of the entire renal sympathetic nerve supply. There are currently a number of such catheters available for clinical use. The radiofrequency ablation (RFA) catheter is positioned in the distal portion of the renal artery and then gradually withdrawn in a spiral fashion while administering RFA charges.

Early Human Studies of Current Renal Denervation Approaches

A landmark study documented significant reduction in renal sympathetic spillover, 30 days after bilateral renal denervation.[96] This was followed by a nonrandomized 50-patient study of bilateral renal denervation, which documented blood pressure decreases of 14/10 mm Hg (systolic/diastolic) at 1 month and 27/17 mm Hg at 1 year.[91]

Randomized Clinical Trials

These initial nonrandomized studies were followed by the Symplicity HTN-2 clinical trial, a randomized study of over 100 subjects with refractory hypertension (blood pressure greater than 160/90 mm Hg in a patient taking three antihypertensive medications).[97,98] The results documented significant decreases in systolic blood pressure, from a 20-point reduction at 1 month to a 32-point reduction at 6 months. There was no change in blood pressure in patients in the control arm. There were, however, a number of drawbacks to this study, including the lack of a sham procedure and also the use of office blood pressures only, which could be more dependent on sympathetic nerve activity compared with 24-hour ambulatory blood pressures. These weaknesses were addressed in the Symplicity HTN-3 study, a prospective, single-blind, randomized, sham-controlled trial of renal denervation in participants with resistant hypertension. The primary safety endpoint was a composite of death, ESRD, embolic events resulting in end organ damage, renovascular complications, and new renal artery stenosis. The primary efficacy endpoint was a change in office systolic blood pressure of greater than 5 mm Hg compared with the control group, with a secondary efficacy endpoint of a 2-mm reduction in ambulatory systolic blood pressure. In marked contrast to the results from the Symplicity HTN-1 and Symplicity HTN-2 studies, Symplicity HTN-3 study did not demonstrate a statistically significant improvement in either the primary or secondary endpoints. There were no differences between the control and treatment groups with regard to the safety endpoint.

Why were the results from Symplicity HTN-3 so different from the earlier Symplicity studies, and what do the results of this study mean for the future of renal denervation therapy? Above all, the Symplicity HTN-3 study once again emphasizes the importance of having a true control group. The control group in Symplicity HTN-3 (as opposed to Symplicity HTN-2) underwent a sham procedure and therefore believed that they had received therapy. This together with participation in the trial (Hawthorne effect) could have had a beneficial impact on blood pressure. A *post hoc* analysis of the data appears to demonstrate a statistically significant benefit in non-African Americans in the study.[99] In addition, some concerns have been raised about the lack of experience of the Symplicity HTN-3 investigators[100] as opposed to the greater experience currently available in Europe (over 15,000 cases have gone into the European Registry). In summary, while the results of the Symplicity HTN-3 study do not support use of renal denervation therapy, there is ongoing speculation about whether there are in fact certain subgroups such as non-African Americans who might still benefit from this therapy. It is also unclear regarding whether there could be some benefit from its use in CKD patients. While an eGFR of less than 45 mL/min/1.73 m^2 was an exclusion for the Symplicity HTN-3 study, there are some data which suggest that renal denervation therapy does not have a negative impact on GFR[101] and may in fact have a beneficial effect on microalbuminuria.[102] A recent study in a mouse model of renal fibrosis due to unilateral ureteral obstruction documented a significant reduction in renal fibrosis in animals subjected to sympathectomy.[103] Future research is likely to be directed

toward the identification of such niche populations. More than anything else, however, the Symplicity HTN-3 study emphasizes once again the absolute necessity of using an appropriate control group.

One of the technical factors that might have been responsible for the failure of the Symplicity trial is incomplete denervation of the renal nerves due to inadequate cauterization. The Paradise Ultrasound Renal Denervation System (PRDS)-001 which uses ultrasound might be a solution to this issue. This system allows sufficient periarterial nerve damage using ultrasound. At the same time, it uses a cooling balloon which reduces the risk of overheating the arterial wall and prevents tissue damage.[104] The safety and effectiveness of this technique has been demonstrated in porcine models and in humans. A clinical trial (REQUIRE), in which an ultrasound renal denervation system is being used to treat resistant hypertension, is ongoing in Japan and Korea.[105]

There are also two other ongoing clinical trials, the REDUCE HTN REINFORCE study which uses the Vessix system (Vessix Reduce™ Catheter and Vessix™ Generator) and the SPYRAL HTN OFF-MED trial using the Symplicity Spyral catheter. Both will use advanced catheters which can more precisely induce nerve damage without injuring surrounding arterial tissue.[106]

A Holistic View of Renal Denervation

The currently available data on renal denervation therapy is exciting, while also deserving of a note of caution. There is no question that the ability to have a significant impact on blood pressure levels using a one time interventional procedure that targets renal sympathetic nerves, does not require long-term therapy with medications, and which may have a role in the prevention of renal fibrosis is a step forward. On the other hand, we should be cognizant of the fact that (a) long-term efficacy data using a sham intervention and 24-hour ambulatory blood pressure monitoring are still pending and (b) we are perhaps evaluating a potentially expensive and invasive therapy because lack of adequate processes of care addressing issues such as compliance and physician/patient fatigue pose challenges to current therapeutic approaches. It is possible that the advantages of a one-stop shop approach may be particularly valuable in the context of CKD patients in many parts of the world (both developed and developing), where poor compliance and a lack of adequate early referral and follow-up continue to be important deficiencies within CKD programs. The downstream result of poorly controlled blood pressure in CKD patients is of course ESRD, with its associated morbidity, mortality, and economic costs.

NOVEL THERAPIES FOR VASCULAR ACCESS DYSFUNCTION

Dialysis vascular access is currently considered to be both the "lifeline" and the "Achilles heel" for patients on hemodialysis.[107–111] Perhaps the most disturbing statistic regarding vascular access is that approximately 80% of incident patients start HD with a tunneled dialysis catheter (TDC),[112] with as much as a fivefold increase in mortality in the first 90 days of treatment, compared with patients who start with an arteriovenous fistula (AVF) or arteriovenous graft (AVG).[113] The battle for vascular access will therefore likely be won or lost during the CKD phase. The way to achieve vascular access success during the CKD phase is likely through a combinatorial approach that includes both process of care interventions and the development of novel and innovative therapies. Process of care interventions would include early referral to kidney disease specialists, prevention of delays in referrals by nephrologists to radiology and surgery for vessel mapping and surgery, availability of committed and dedicated vascular access surgeons, close patient and vascular access follow-up post surgery, and the use of master cannulators for the initial cannulations of an AVF (Figure 72.4). Investing in a dedicated vascular access coordinator would address many of the above issues.

Biology of AVF Maturation Failure

Early AVF maturation failure is probably due to a combination of aggressive neointimal hyperplasia in combination with a lack of outward remodeling.[108–111,114] At a more pathogenic level, it is likely that the interaction between hemodynamic shear stress and the vascular response of the uremic vein to these stressors determines ultimate AVF success or failure. Our group and others have documented a

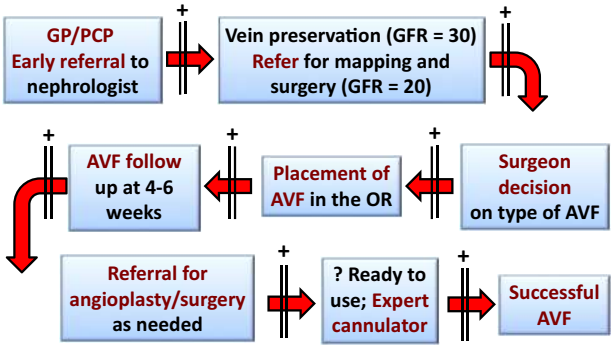


FIGURE 72.4 Process of care barriers for arteriovenous fistula (AVF) maturation. Note that each of these barriers (parallel lines) is also an opportunity (+) for local and meaningful process of care innovation. GFR units mL/min/1.73 m^2.

significant amount of neointimal hyperplasia within venous segment tissue collected from the site of AVF surgery, suggesting that uremia, oxidative stress, and endothelial dysfunction can result in preexisting neointimal hyperplasia even before AVF creation.[115,116] This preexisting neointimal hyperplasia does not seem to be linked to future AVF stenosis and failure.[117]

Novel Therapies for AVF Maturation

The goal of the therapies described in this section is primarily to enhance AVF maturation during the CKD phase, so that patients are able to start dialysis with a mature ready-to-use AVF.

PRT 201 Elastase

The rationale for this intervention is that the application of a recombinant elastase will destroy elastin fibers in both the artery and the vein and allow rapid AVF dilation and maturation. This concept is particularly important, because it goes to the heart not only of "fistula first" but also incorporates the "catheter last or catheter out" concept, because rapid AVF maturation would allow for the rapid removal of TDCs. Initial Phase II studies suggest that the mechanism may be somewhat more complex, in that the best results were seen in the low dose group,[118] suggesting that fragmentation of elastin fibers into protein fragments with potential biological activity could be the mechanism of action. An initial large Phase III randomized clinical trial in the setting of radiocephalic fistulae using unassisted primary patency as the primary endpoint did not show a statistically significant difference between the control and treated arms. There was, however, a difference in the secondary endpoint of cumulative patency. The results from a larger Phase II study with cumulative patency as the primary endpoint have just been described and there was once again disappointingly, no difference between the treatment and control arms.

Sirolimus COL-R Wraps

Sirolimus is an antiproliferative agent that blocks neointimal hyperplasia in the setting of coronary restenosis. The COL-R wrap comprises a biodegradable sirolimus-eluting wrap (antiproliferative agent) which is placed around the arteriovenous anastomosis of an AVF, or around the graft-vein anastomosis of a PTFE (polytetrafluoroethylene) graft (Figure 72.5). An initial Phase II study demonstrated primary unassisted AV graft patencies of 75% and 38% at 1 and 2 years, in patients treated with the COL-R wrap, albeit in the absence of a control arm.[119] Similar pilot studies in AVFs have documented excellent AVF maturation rates. A Phase III randomized controlled trial to assess the safety, efficacy, and maturation outcomes of a perivascular sirolimus-eluting implant placed at the AVF anastomosis in hemodialysis patients is currently ongoing. Results are expected by 2022.

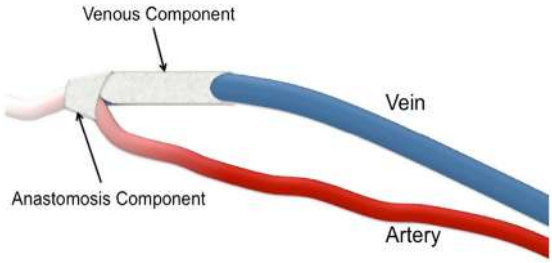


FIGURE 72.5 Sirolimus COL-R wraps for arteriovenous fistula maturation. Elution of sirolimus from these biodegradable wraps is expected to enhance arteriovenous fistula maturation. *Courtesy Dr. Iyer.*

Vascugel Endothelial Cell–Loaded Wraps

This comprises a gel-foam wrap, embedded with endothelial cells. The biological rationale behind "Vascugel" is that endothelial cells are bioreactors for "good" mediators. Thus, the delivery of "good" endothelial cells to the local vicinity of the AVF should allow a local milieu that inhibits neointimal hyperplasia and enhances outward remodeling. Initial experimental studies documented a beneficial effect of endothelial cell–loaded gel-foam wraps in porcine models of AV fistula and graft stenosis.[120,121] More recently, human studies have described the technical feasibility of improvement in primary patency when Vascugel wraps were used in diabetic patients with PTFE grafts.[122,123] Patients on an active transplant list or who are likely to get a transplant in the future should not be treated with this therapy because of some risk of sensitization to HLA antigens. Shire Regenerative Medicine recently initiated two large studies using these wraps in the setting of AVFs and AVGs, respectively. Both studies were unfortunately stopped due to business considerations. It is therefore unclear as to whether this therapy will enter into clinical practice.

Nitroglycerine Ointment

Glyceryl trinitrate (GTN) is a nitrate-based vasodilator that can increase blood flow and prevent platelet aggregation. Use of GTN at the time of creation of an AVF may help in the maturation process. Although there were some positive results in early trials, a randomized controlled trial evaluating the role of locally administered nitroglycerin ointment to enhance local nitric oxide bioavailability in improving AVF maturation did not show significant effect on maturation.[124]

Percutaneous AVF Creation

An important cause of AVF maturation failure is thought to be the surgical handling and potential vascular torsion that occurs at the time of its surgical creation, which then predisposes to perianastomotic stenosis. Recently, there have been some exciting technological advances that have resulted in FDA approval of two techniques for the creation of percutaneous AVFs. One of the techniques uses ultrasound to place a percutaneous device across a vein and artery in the upper forearm that is close together and then delivers a burst of energy to create an AVF (Figure 72.6). The other technique uses catheters with magnets to bring the appropriate artery and vein close together and then creates a connection through a burst of energy (Figure 72.7). The important advantages of this technique include the avoidance of a surgical procedure, no need for preoperative evaluation, and the lack of a surgical scar. In addition, the initial nonrandomized data describe outstanding patency for these techniques. It is important, however, for additional real-world data to be collected and evaluated. Perhaps the greatest impact of the percutaneous techniques could be on the process of care for AVF creation, because these technologies now allow the creation of AVFs by endovascular and ultrasound specialists (interventional radiologists and interventional nephrologists in particular). This more egalitarian approach to AVF creation may result in better access to care for AVF creation, and potentially for the ultrasound-based technology, in parts of the world where there is limited access to endovascular suites.[125,126]

Bioengineered Vessels

The creation of a bioengineered vessel that could be used as a vascular conduit has for long been the holy grail for vascular surgery and applied vascular biology. In the context of dialysis vascular access, the availability of a vascular conduit that could be used in patients who are not suitable candidates for an AVF, without the

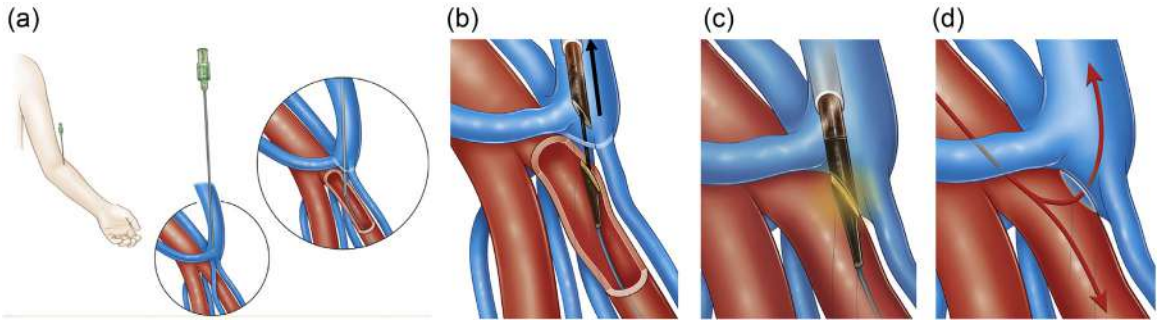


FIGURE 72.6 Percutaneous arteriovenous fistula (AVF) creation with the Ellipsys device. The proximal radial artery is initially punctured through the deep communicating vein and a guide wire is placed through the vein into the artery (a). The Ellipsys catheter is then advanced over the wire and traction (*arrow*) is applied to make sure that the device has captured the arterial wall (b). The device is then closed and activated with thermal energy, resulting in a communication between the DCM and the radial artery (c), to create an AVF (d). *Adapted from reference 126.*

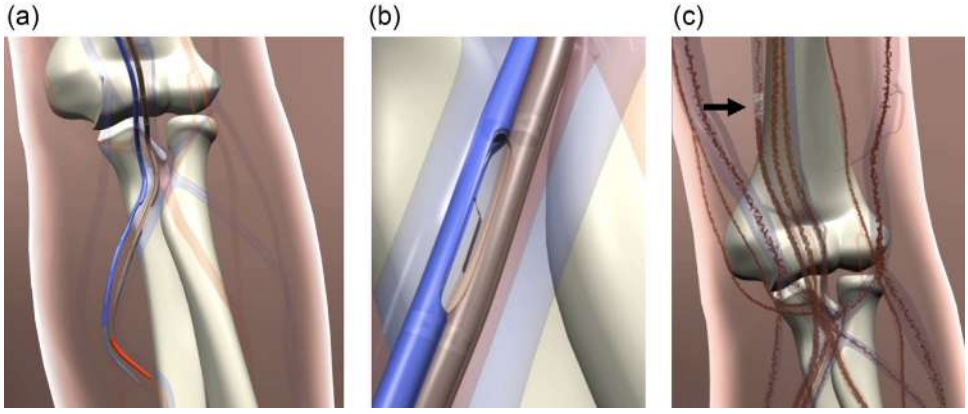


FIGURE 72.7 Percutaneous arteriovenous fistula (AVF) creation with the WavelinQ device. Guidewires and special catheters are placed into an adjoining artery and vein (a). Catheter magnets are then activated resulting in the vessels coming close together, following which an electrode delivers a burst of radiofrequency energy to create an AVF (b). In a final step, a deep vein is coiled (*horizontal arrow*) in an attempt to preferentially drive blood through the superficial venous system (both basilic and cephalic; c).

stenosis and thrombosis that characterizes PTFE graft use, would be an important advance. Humacyte recently described a bioengineered vessel in which a biodegradable scaffold in the form of a dialysis access graft is seeded with mesenchymal cells which then produce matrix proteins, resulting in a collagenous tube. This device is then treated to remove all living cells to minimize allorecognition and potential sensitization to HLA antigens. The final device, which looks like a vessel, has been placed in a number of patients on hemodialysis in the form of an AVG. Initial results demonstrate a primary patency similar to PTFE grafts, but perhaps with less infection and with the need for fewer interventions to maintain patency. Humacyte is currently conducting two large randomized studies where these grafts are compared with standard ePTFE. The results will be available shortly.[127]

INNOVATIVE RENAL REPLACEMENT THERAPIES

Since the advent of chronic hemodialysis at Northwest Kidney Centers, in Seattle in the early 1960s, this technology has saved millions of lives. Dialysis still remains the only form of organ replacement therapy that is effective over prolonged periods of time. The huge success of this technology, however, has perhaps lulled the kidney community into a false sense of complacency, in that the basic construct of hemodialysis has not changed significantly over the last 40 years. The current survival on hemodialysis for all patients in the US is a dismal 41% at 5 years, which is lower than the five-year survival of most cancers (Figure 72.8). More importantly, patients treated with maintenance hemodialysis have poor quality of life, with an extremely limited ability to do the things that are important to them (such as being able to travel and not feeling washed out after dialysis). To address this issue, there has been a great deal of interest recently in home hemodialysis, portable and wearable hemodialysis, and in sensors that could create a real-time feedback loop (Figure 72.9).[128–130] There has also been some exciting experimental work on an implantable kidney by a group led by Drs. Shuvo Roy and William Fissell (Figure 72.10).[131] In addition, the Kidney Health Initiative, a public–private partnership between the American Society of Nephrology and the FDA[132,133] has recently described a road map for innovative RRT which we hope will serve as a catalyst to focus interest, investment, and innovation in this area.[134] In parallel with the description of the innovative RRT road map, the Kidney Innovation Accelerator or KidneyX, a public–private partnership between the Department of Health and Human Services and the American Society of Nephrology recently announced a prize competition which focuses on "Redesigning Dialysis."[135] We feel that these two policy and funding initiatives will nicely complement each other to truly jump start advances in this area. Thus, while the road map

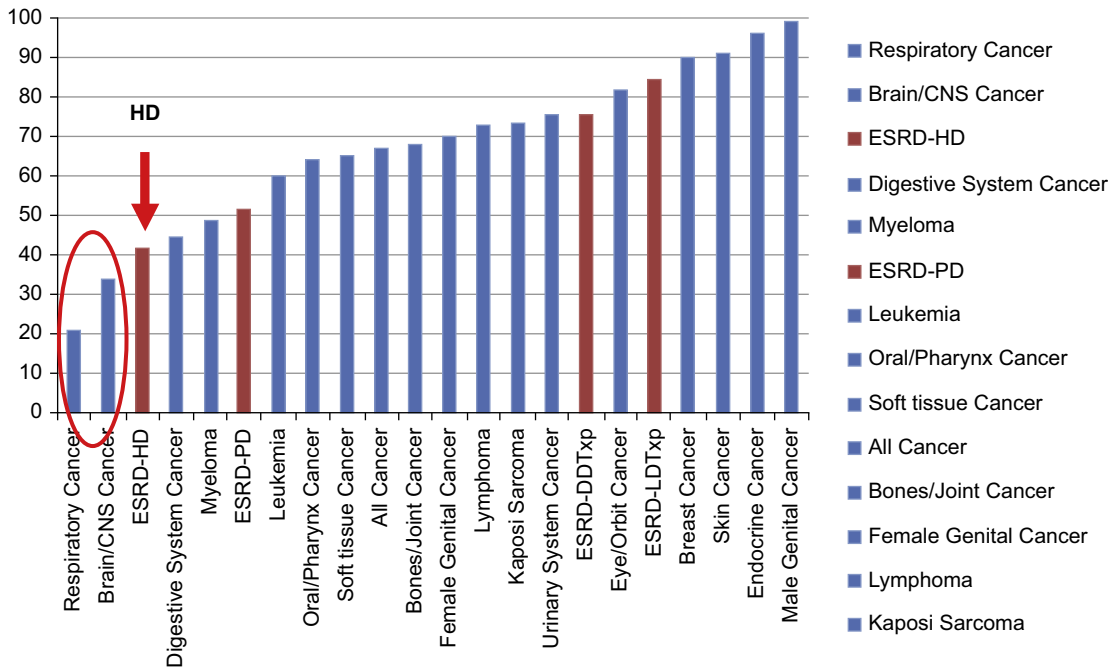


FIGURE 72.8 Poor survival of hemodialysis patients. The 5-year survival of end-stage renal disease (ESRD) patients treated with hemodialysis is worse than many forms of cancer. *Adapted from an original figure; courtesy Frank Hurst.*

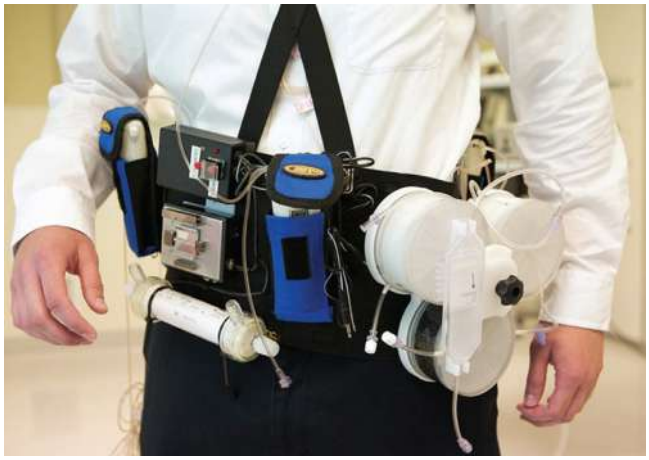


FIGURE 72.9 Prototype of a wearable artificial kidney. This would allow better quality of life using slow continuous dialysis. *Adapted from reference 129.*

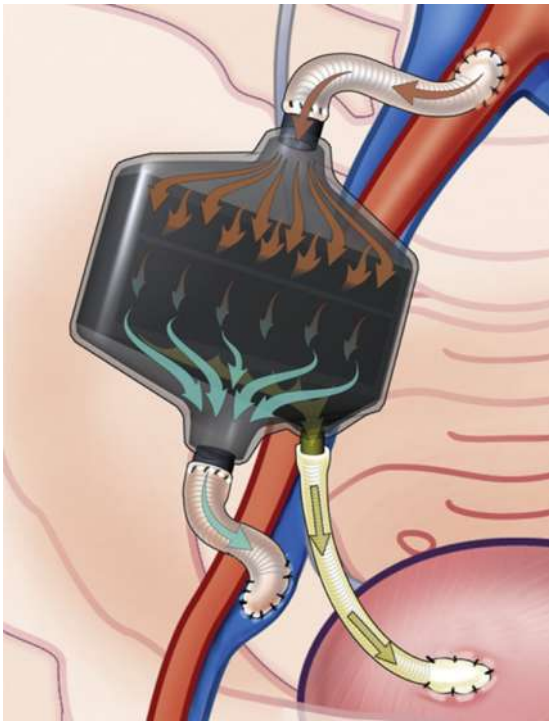


FIGURE 72.10 Implantable artificial kidney. Representation of an implantable artificial kidney with blood being initially filtered through a hemocartridge comprising silicon nanomembranes, followed by passage through a biocartridge comprising living tubular cells, thus mimicking the natural glomerulus-tubule construct. *Adapted from reference 131.*

could serve as the technical construct for the Redesign Dialysis initiative, the funds available for the Redesign Dialysis competition could function as the implementer arm for the milestones described in the innovative RRT road map.

CONCLUSION

In summary, we have presented data on a number of novel therapeutic concepts that could completely change the way we care for CKD patients in the coming years. The true way to move any field forward, however, is to synergize biological and technological advances with the clinical setting/process of care pathways and with regulatory/reimbursement pathways. The presence of public–private partnerships such as the Kidney Health Initiative, which aims to create an innovation substrate for kidney diseases, is an important step forward to achieving this goal. Our hope for the future is that the availability of a number of novel therapies to individualize the management of CKD and its complications will allow us to get the right therapy to the right patient at the right time.

Disclosures

Dr. Prabir Roy-Chaudhury is a consultant/advisory board member for Bard BD, WL Gore, Medtronic, Cormedix, Humacyte, Vifor, Akebia, Reata, and Bayer. He is also the Founder and Chief Scientific Officer of Inovasc LLC.

References

1. United States Renal Data System. *2017 USRDS annual data report: epidemiology of kidney disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2017.
2. Jha V, Wang AY, Wang H. The impact of CKD identification in large countries: the burden of illness. *Nephrol Dial Transplant* 2012;**27**(Suppl. 3):32–8.
3. Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world – a growing challenge. *N Engl J Med* 2007; **356**:213–5.
4. Vilayur E, Harris DC. Emerging therapies for chronic kidney disease: what is their role? *Nat Rev Nephrol* 2009;**5**:375–83.
5. Navarro JF, Mora C, Muros M, Garcia J. Additive antiproteinuric effect of pentoxifylline in patients with type 2 diabetes under angiotensin II receptor blockade: a short-term, randomized, controlled trial. *J Am Soc Nephrol* 2005;**16**:2119–26.
6. Chen YM, Lin SL, Chiang WC, Wu KD, Tsai TJ. Pentoxifylline ameliorates proteinuria through suppression of renal monocyte chemoattractant protein-1 in patients with proteinuric primary glomerular diseases. *Kidney Int* 2006;**69**:1410–5.
7. Lin SL, Chen YM, Chiang WC, Wu KD, Tsai TJ. Effect of pentoxifylline in addition to losartan on proteinuria and GFR in CKD: a 12-month randomized trial. *Am J Kidney Dis* 2008;**52**:464–74.
8. Leporini C, Pisano A, Russo E, DA G, de Sarro G, Coppolino G, et al. Effect of pentoxifylline on renal outcomes in chronic kidney disease patients: a systematic review and meta-analysis. *Pharmacol Res* 2016;**107**:315–32.
9. Navarro-Gonzalez JF, Sanchez-Nino MD, Donate-Correa J, Martin-Nunez E, Ferri C, Perez-Delgado N, et al. Effects of pentoxifylline on soluble klotho concentrations and renal tubular cell expression in diabetic kidney disease. *Diabetes Care* 2018; **41**(8):1817–20.
10. Athyros VG, Mikhailidis DP, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, et al. The effect of statins versus

untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. *J Clin Pathol* 2004;**57**:728–34.
11. Campese VM, Nadim MK, Epstein M. Are 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors renoprotective? *J Am Soc Nephrol* 2005;**16**(Suppl. 1):S11–17.
12. Calza L, Colangeli V, Borderi M, Manfredi R, Marconi L, Bon I, et al. Rosuvastatin and atorvastatin preserve renal function in HIV-1-infected patients with chronic kidney disease and hyperlipidaemia. *HIV Clin Trials* 2018;**19**(3):120–8.
13. Kimura G, Kasahara M, Ueshima K, Tanaka S, Yasuno S, Fujimoto A, et al. Effects of atorvastatin on renal function in patients with dyslipidemia and chronic kidney disease: assessment of clinical usefulness in CKD patients with atorvastatin (ASUCA) trial. *Clin Exp Nephrol* 2017;**21**(3):417–24.
14. Zhang Z, Li Z, Cao K, Fang D, Wang F, Bi G, et al. Adjunctive therapy with statins reduces residual albuminuria/proteinuria and provides further renoprotection by downregulating the angiotensin II-AT1 pathway in hypertensive nephropathy. *J Hypertens* 2017;**35**(7):1442–56.
15. Zhang Z, Wu P, Zhang J, Wang S, Zhang G. The effect of statins on microalbuminuria, proteinuria, progression of kidney function, and all-cause mortality in patients with non-end stage chronic kidney disease: a meta-analysis. *Pharmacol Res* 2016;**105**:74–83.
16. Watnick T, Germino GG. mTOR inhibitors in polycystic kidney disease. *N Engl J Med* 2010;**363**:879–81.
17. Serra AL, Poster D, Kistler AD, et al. Sirolimus and kidney growth in autosomal dominant polycystic kidney disease. *N Engl J Med* 2010;**363**:820–9.
18. Walz G, Budde K, Mannaa M, Nurnberger J, Wanner C, Sommerer C, et al. Everolimus in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2010;**363**:830–40.
19. Torres VE, Wang X, Qian Q, Somlo S, Harris PC, Gattone 2nd VH. Effective treatment of an orthologous model of autosomal dominant polycystic kidney disease. *Nat Med* 2004;**10**(4):363–4.
20. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012;**367**(25):2407–18.
21. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Koch G, et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. *N Engl J Med* 2017;**377**(20):1930–42.
22. Tsuji T, Ohishi K, Takeda A, Goto D, Sato T, Ohashi N, et al. The impact of serum uric acid reduction on renal function and blood pressure in chronic kidney disease patients with hyperuricemia. *Clin Exp Nephrol* 2018;**22**(6):1300–8.
23. Srivastava A, Kaze AD, McMullan CJ, Isakova T, Waikar SS. Uric acid and the risks of kidney failure and death in individuals with CKD. *Am J Kidney Dis* 2018;**71**(3):362–70.
24. Maahs DM, Caramori L, Cherney DZ, Galecki AT, Gao C, Jalal D, et al. Uric acid lowering to prevent kidney function loss in diabetes: the preventing early renal function loss (PERL) allopurinol study. *Curr Diabetes Rep* 2013;**13**(4):550–9.
25. MacIsaac RJ, Jerums G, Ekinci EI. Cardio-renal protection with empagliflozin. *Ann Transl Med* 2016;**4**(20):409.
26. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**(22):2117–28.
27. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 2019;**380**(24):2295–306.
28. Mima A. Renal protection by sodium-glucose cotransporter 2 inhibitors and its underlying mechanisms in diabetic kidney disease. *J Diabet Complicat* 2018;**32**(7):720–5.
29. Heerspink HJL, Kosiborod M, Inzucchi SE, Cherney DZI. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors. *Kidney Int* 2018;**94**(1):26–39.
30. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;**375**:311–22.
31. Lytvyn Y, Godoy LC, Scholtes RA, van Raalte DH, Cherney DZ. Mineralocorticoid antagonism and diabetic kidney disease. *Curr Diabetes Rep* 2019;**19**(1):4.
32. Dhaun N, Melville V, Blackwell S, Talwar DK, Johnston NR, Goddard J, et al. Endothelin-A receptor antagonism modifies cardiovascular risk factors in CKD. *J Am Soc Nephrol* 2013;**24**(1):31–6.
33. Kohan DE, Pritchett Y, Molitch M, Wen S, Garimella T, Audhya P, et al. Addition of atrasentan to renin-angiotensin system blockade reduces albuminuria in diabetic nephropathy. *J Am Soc Nephrol* 2011;**22**(4):763–72.
34. Heerspink HJL, Parving HH, Andress DL, et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. *Lancet* 2019;**393**(8):1937–47.
35. Bantounas I, Ranjzad P, Tengku F, et al. Generation of functioning nephrons by implanting human pluripotent stem cell-derived kidney progenitors. *Stem Cell Reports* 2018;**10**:766–79.
36. Weber EJ, Chapron A, Chapron BD, et al. Development of a microphysiological model of human kidney proximal tubule function. *Kidney Int* 2016;**90**:627–37.
37. Basu J, Genheimer CW, Rivera EA, Payne R, Mihalko K, Guthrie K, et al. Functional evaluation of primary renal cell/biomaterial neo-kidney augment prototypes for renal tissue engineering. *Cell Transplant* 2011;**20**(11–12):1771–90.
38. Lee SY, Kim SI, Choi ME. Therapeutic targets for treating fibrotic kidney diseases. *Transl Res* 2015;**165**(4):512–30.
39. Hou X, Rooklin D, Fang H, Zhang Y. Resveratrol serves as a protein-substrate interaction stabilizer in human SIRT1 activation. *Sci Rep* 2016;**6**:38186.
40. Fernandez-Fernandez B, Ortiz A, Gomez-Guerrero C, Egido J. Therapeutic approaches to diabetic nephropathy–beyond the RAS. *Nat Rev Nephrol* 2014;**10**:325–46.
41. de Zeeuw D, Akizawa T, Audhya P, et al. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med* 2013;**369**:2492–503.
42. Salant DJ. Podocyte expression of B7-1/CD80: is it a reliable biomarker for the treatment of proteinuric kidney diseases with abatacept? *J Am Soc Nephrol* 2016;**27**:963–5.
43. Eschbach JW, Kelly MR, Haley NR, Abels RI, Adamson JW. Treatment of the anemia of progressive renal failure with recombinant human erythropoietin. *N Engl J Med* 1989;**321**:158–63.
44. Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006;**355**:2071–84.
45. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009;**361**:2019–32.
46. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;**355**:2085–98.
47. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;**339**:584–90.
48. Bernhardt WM, Wiesener MS, Scigalla P, Chou J, Schmieder RE, Gunzler V, et al. Inhibition of prolyl hydroxylases increases erythropoietin production in ESRD. *J Am Soc Nephrol* 2010;**21**:2151–6.
49. Beuck S, Schanzer W, Thevis M. Hypoxia-inducible factor stabilizers and other small-molecule erythropoiesis-stimulating agents in current and preventive doping analysis. *Drug Test Anal* 2012;**4**:830–45.

50. Miyata T, Suzuki N, van Ypersele de Strihou C. Diabetic nephropathy: are there new and potentially promising therapies targeting oxygen biology? *Kidney Int* 2013;**84**:693–702.
51. Franke K, Gassmann M, Wielockx B. Erythrocytosis: the HIF pathway in control. *Blood* 2013;**122**:1122–8.
52. Zhao S, Wu J. Hypoxia inducible factor stabilization as a novel strategy to treat anemia. *Curr Med Chem* 2013;**20**:2697–711.
53. Denny WA. Giving anemia a boost with inhibitors of prolyl hydroxylase. *J Med Chem* 2012;**55**:2943–4.
54. Muchnik E, Kaplan J. HIF prolyl hydroxylase inhibitors for anemia. *Expert Opin Investig Drugs* 2011;**20**:645–56.
55. Smith TG, Talbot NP. Prolyl hydroxylases and therapeutics. *Antioxidants Redox Signal* 2010;**12**:431–3.
56. Chiang CK, Tanaka T, Inagi R, Fujita T, Nangaku M. Indoxyl sulfate, a representative uremic toxin, suppresses erythropoietin production in a HIF-dependent manner. *Lab Invest* 2011;**91**:1564–71.
57. Minamishima YA, Kaelin Jr WG. Reactivation of hepatic EPO synthesis in mice after PHD loss. *Science* 2010;**329**:407.
58. Tanaka T, Miyata T, Inagi R, Fujita T, Nangaku M. Hypoxia in renal disease with proteinuria and/or glomerular hypertension. *Am J Pathol* 2004;**165**:1979–92.
59. Manotham K, Tanaka T, Matsumoto M, et al. Evidence of tubular hypoxia in the early phase in the remnant kidney model. *J Am Soc Nephrol* 2004;**15**:1277–88.
60. Prabhakar S, Starnes J, Shi S, Lonis B, Tran R. Diabetic nephropathy is associated with oxidative stress and decreased renal nitric oxide production. *J Am Soc Nephrol* 2007;**18**:2945–52.
61. Aragones J, Schneider M, Van Geyte K, Fraisl P, Dresselaers T, Mazzone M, et al. Deficiency or inhibition of oxygen sensor Phd1 induces hypoxia tolerance by reprogramming basal metabolism. *Nat Genet* 2008;**40**:170–80.
62. Del Vecchio L, Locatelli F. Roxadustat in the treatment of anaemia in chronic kidney disease. *Expert Opin Investig Drugs* 2018;**27**(1): 125–33.
63. Joharapurkar AA, Pandya VB, Patel VJ, Desai RC, Jain MR. Prolyl hydroxylase inhibitors: a breakthrough in the therapy of anemia associated with chronic diseases. *J Med Chem* 2018;**61**(16):6964–82.
64. Hasegawa S, Tanaka T, Nangaku M. Hypoxia-inducible factor stabilizers for treating anemia of chronic kidney disease. *Curr Opin Nephrol Hypertens* 2018;**27**(5):331–8.
65. Stenvinkel P. Chronic kidney disease: a public health priority and harbinger of premature cardiovascular disease. *J Intern Med* 2010; **268**:456–67.
66. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998;**32**: S112–9.
67. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**:1296–305.
68. Foley RN, Murray AM, Li S, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 2005;**16**:489–95.
69. Mallamaci F, Tripepi G, Cutrupi S, Malatino LS, Zoccali C. Prognostic value of combined use of biomarkers of inflammation, endothelial dysfunction, and myocardiopathy in patients with ESRD. *Kidney Int* 2005;**67**:2330–7.
70. Himmelfarb J. Uremic toxicity, oxidative stress, and hemodialysis as renal replacement therapy. *Semin Dial* 2009;**22**:636–43.
71. Brunet P, Gondouin B, Duval-Sabatier A, Dou L, Cerini C, Dignat-George F, et al. Does uremia cause vascular dysfunction? *Kidney Blood Press Res* 2011;**34**:284–90.
72. Jourde-Chiche N, Dou L, Cerini C, Dignat-George F, Brunet P. Vascular incompetence in dialysis patients – protein-bound uremic toxins and endothelial dysfunction. *Semin Dial* 2011;**24**:327–37.
73. Calaf R, Cerini C, Genovesio C, Verhaeghe P, Jourde-Chiche N, Bergé-Lefranc D, et al. Determination of uremic solutes in biological fluids of chronic kidney disease patients by HPLC assay. *J Chromatogr B Analyt Technol Biomed Life Sci* 2011;**879**:2281–6.
74. Wu M, Rementer C, Giachelli CM. Vascular calcification: an update on mechanisms and challenges in treatment. *Calcif Tissue Int* 2013;**93**:365–73.
75. Leonard O, Spaak J, Goldsmith D. Regression of vascular calcification in chronic kidney disease – feasible or fantasy? A review of the clinical evidence. *Br J Clin Pharmacol* 2013;**76**:560–72.
76. Rezg R, Barreto FC, Barreto DV, Liabeuf S, Drueke TB, Massy ZA. Inhibitors of vascular calcification as potential therapeutic targets. *J Nephrol* 2011;**24**:416–27.
77. Giachelli CM. Mechanisms of vascular calcification in uremia. *Semin Nephrol* 2004;**24**:401–2.
78. Liu C, Walter TS, Huang P, Zhang S, Zhu X, Wu Y, et al. Structural and functional insights of RANKL-RANK interaction and signaling. *J Immunol* 2010;**184**:6910–9.
79. Bucay N, Sarosi I, Dunstan CR, Morony S, Tarpley J, Capparelli C, et al. osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. *Genes Dev* 1998;**12**:1260–8.
80. Panizo S, Cardus A, Encinas M, Parisi E, Valcheva P, López-Ongil S, et al. RANKL increases vascular smooth muscle cell calcification through a RANK-BMP4-dependent pathway. *Circ Res* 2009;**104**:1041–8.
81. Helas S, Goettsch C, Schoppet M, Zeitz U, Hempel U, Morawietz H, et al. Inhibition of receptor activator of NF-kappaB ligand by denosumab attenuates vascular calcium deposition in mice. *Am J Pathol* 2009;**175**:473–8.
82. Ungprasert P, Cheungpasitporn W, Srivali N, Kittanamongkolchai W, Bischof EF. Life-threatening hypocalcemia associated with denosumab in a patient with moderate renal insufficiency. *Am J Emerg Med* 2013;**31**(756):e1–2.
83. McCormick BB, Davis J, Burns KD. Severe hypocalcemia following denosumab injection in a hemodialysis patient. *Am J Kidney Dis* 2012;**60**:626–8.
84. Lau WL, Leaf EM, Hu MC, Takeno MM, Kuro-o M, Moe OW, et al. Vitamin D receptor agonists increase klotho and osteopontin while decreasing aortic calcification in mice with chronic kidney disease fed a high phosphate diet. *Kidney Int* 2012;**82**:1261–70.
85. Wolf M, Thadhani R. Vitamin D in patients with renal failure: a summary of observational mortality studies and steps moving forward. *J Steroid Biochem Mol Biol* 2007;**103**:487–90.
86. Spronk HM, Soute BA, Schurgers LJ, Thijssen HH, De Mey JG, Vermeer C. Tissue-specific utilization of menaquinone-4 results in the prevention of arterial calcification in warfarin-treated rats. *J Vasc Res* 2003;**40**:531–7.
87. EVOLVE Trial Investigators, Chertow GM, Block GA, Correa-Rotter R, Drüeke TB, Floege J, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012;**367**:2482–94.
88. Raggi P, Chertow GM, Torres PU, et al. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrol Dial Transplant* 2011;**26**:1327–39.
89. Gan W, Ren J, Li T, et al. The SGK1 inhibitor EMD638683, prevents Angiotensin II-induced cardiac inflammation and fibrosis by blocking NLRP3 inflammasome activation. *Biochim Biophys Acta* 2018;**1864**:1–10.
90. Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR, et al. Hypertension treatment and control in five European countries, Canada, and the United States. *Hypertension* 2004; **43**:10–7.
91. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, et al. Catheter-based renal sympathetic denervation

for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009;**373**:1275–81.
92. Esler M. The 2009 Carl Ludwig Lecture: pathophysiology of the human sympathetic nervous system in cardiovascular diseases: the transition from mechanisms to medical management. *J Appl Physiol* 2010;**108**:227–37.
93. Esler M. The sympathetic nervous system through the ages: from Thomas Willis to resistant hypertension. *Exp Physiol* 2011;**96**: 611–22.
94. DiBona GF, Esler M. Translational medicine: the antihypertensive effect of renal denervation. *Am J Physiol Regul Integr Comp Physiol* 2010;**298**:R245–53.
95. Converse Jr RL, Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F, et al. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992;**327**:1912–8.
96. Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD. Renal sympathetic-nerve ablation for uncontrolled hypertension. *N Engl J Med* 2009;**361**:932–4.
97. Symplicity HTN-2 Investigators Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, et al. Renal sympathetic denervation in patients with treatment-resistent hypertension (The Symplicity HTN-2 Trial): a randomized controlled trial. *Lancet* 2010; **376**(9756):1903–9.
98. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014;**370**:1393–401.
99. Schmieder RE. Hypertension: how should data from SYMPLICITY HTN-3 be interpreted? *Nat Rev Cardiol* 2014;**11**:375–6.
100. Luscher TF, Mahfoud F. Renal nerve ablation after SYMPLICITY HTN-3: confused at the higher level? *Eur Heart J* 2014;**35**: 1706–11.
101. Hering D, Mahfoud F, Walton AS, Krum H, Lambert GW, Lambert EA, et al. Renal denervation in moderate to severe CKD. *J Am Soc Nephrol* 2012;**23**:1250–7.
102. Ott C, Mahfoud F, Schmid A, Ditting T, Veelken R, Ewen S, et al. Improvement of albuminuria after renal denervation. *Int J Cardiol* 2014;**173**:311–5.
103. Kim J, Padanilam BJ. Renal nerves drive interstitial fibrogenesis in obstructive nephropathy. *J Am Soc Nephrol* 2013;**24**:229–42.
104. Sakakura K, Roth A, Ladich E, et al. Controlled circumferential renal sympathetic denervation with preservation of the renal arterial wall using intraluminal ultrasound: a next-generation approach for treating sympathetic overactivity. *EuroIntervention* 2015;**10**:1230–8.
105. Mauri L, Kario K, Basile J, et al. A multinational clinical approach to assessing the effectiveness of catheter-based ultrasound renal denervation: the RADIANCE-HTN and REQUIRE clinical study designs. *Am Heart J* 2018;**195**:115–29.
106. Sanghvi K, McGrew A, Hegde K. Rationale and design for studies of renal denervation in the absence (SPYRAL HTN OFF-MED) and presence (SPYRAL HTN ON-MED) of antihypertensive medications. *Am Heart J* 2016;**180**:e1–2.
107. Riella MC, Roy-Chaudhury P. Vascular access in haemodialysis: strengthening the Achilles' heel. *Nat Rev Nephrol* 2013;**9**:348–57.
108. Roy-Chaudhury P, Sukhatme VP, Cheung AK. Hemodialysis vascular access dysfunction: a cellular and molecular viewpoint. *J Am Soc Nephrol* 2006;**17**:1112–27.
109. Roy-Chaudhury P, Lee TC. Vascular stenosis: biology and interventions. *Curr Opin Nephrol Hypertens* 2007;**16**:516–22.
110. Roy-Chaudhury P, Spergel LM, Besarab A, Asif A, Ravani P. Biology of arteriovenous fistula failure. *J Nephrol* 2007;**20**:150–63.
111. Lee T, Roy-Chaudhury P. Advances and new frontiers in the pathophysiology of venous neointimal hyperplasia and dialysis access stenosis. *Adv Chron Kidney Dis* 2009;**16**:329–38.
112. USRDS. *USRDS 2010 Annual data report: atlas of end-stage renal disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2011.
113. Perl J, Wald R, McFarlane P, Bargman JM, Vonesh E, Na Y, et al. Hemodialysis vascular access modifies the association between dialysis modality and survival. *J Am Soc Nephrol* 2011;**22**:1113–21.
114. Roy-Chaudhury P, Arend L, Zhang J, Krishnamoorthy M, Wang Y, Banerjee R, et al. Neointimal hyperplasia in early arteriovenous fistula failure. *Am J Kidney Dis* 2007;**50**:782–90.
115. Lee T, Chauhan V, Krishnamoorthy M, Wang Y, Arend L, Mistry MJ, et al. Severe venous neointimal hyperplasia prior to dialysis access surgery. *Nephrol Dial Transplant* 2011;**26**: 2264–70.
116. Wasse H, Huang R, Naqvi N, Smith E, Wang D, Husain A. Inflammation, oxidation and venous neointimal hyperplasia precede vascular injury from AVF creation in CKD patients. *J Vasc Access* 2012;**13**(2):168–74.
117. Cheung AK, Imrey PB, Alpers CE, Robbin ML, Radeva M, Larive B, et al. Intimal hyperplasia, stenosis, and arteriovenous fistula maturation failure in the hemodialysis fistula maturation study. *J Am Soc Nephrol* 2017;**28**(10):3005–13.
118. Peden EK, Leeser DB, Dixon BS, El-Khatib MT, Roy-Chaudhury P, Lawson JH, et al. A multi-center, dose-escalation study of human type I pancreatic elastase (PRT-201) administered after arteriovenous fistula creation. *J Vasc Access* 2013;**14**:143–51.
119. Paulson WD, Kipshidze N, Kipiani K, Beridze N, DeVita MV, Shenoy S, et al. Safety and efficacy of locally eluted sirolimus for prolonging AV graft patency (PTFE Graft Plus Coll-R) first in man experience. *Am Soc Nephrol Phila* 2008;**27**(3):1219–24.
120. Nugent HM, Groothuis A, Seifert P, Guerraro JL, Nedelman M, Mohanakumar T, et al. Perivascular endothelial implants inhibit intimal hyperplasia in a model of arteriovenous fistulae: a safety and efficacy study in the pig. *J Vasc Res* 2002;**39**:524–33.
121. Nugent HM, Sjin RT, White D, Milton LG, Manson RJ, Lawson JH, et al. Adventitial endothelial implants reduce matrix metalloproteinase-2 expression and increase luminal diameter in porcine arteriovenous grafts. *J Vasc Surg* 2007;**46**:548–56.
122. Conte MS, Nugent HM, Gaccione P, Guleria I, Roy-Chaudhury P, Lawson JH. Multicenter phase I/II trial of the safety of allogeneic endothelial cell implants after the creation of arteriovenous access for hemodialysis use: the V-HEALTH study. *J Vasc Surg* 2009;**50**: 1359–68. e1.
123. Conte MS, Nugent HM, Gaccione P, Roy-Chaudhury P, Lawson JH. Influence of diabetes and perivascular allogeneic endothelial cell implants on arteriovenous fistula remodeling. *J Vasc Surg* 2011;**54**:1383–9.
124. Field M, McGrogan D, Marie Y, et al. Randomized clinical trial of the use of glyceryl trinitrate patches to aid arteriovenous fistula maturation. *Br J Surg* 2016;**103**:1269–75.
125. Rajan DK, Ebner A, Desai SB, Rios JM, Cohn WE. Percutaneous creation of an arteriovenous fistula for hemodialysis access. *J Vasc Interv Radiol* 2015;**26**:484–90.
126. Mallios A, Jennings WC, Boura B, Costanzo A, Bourquelot P, Combes M. Early results of percutaneous arteriovenous fistula creation with the Ellipsys Vascular Access System. *J Vasc Surg* 2018;**68**(4):1150–6.
127. Lawson JH, Glickman MH, Ilzecki M, et al. Bioengineered human acellular vessels for dialysis access in patients with end-stage renal disease: two phase 2 single-arm trials. *Lancet* 2016;**387**: 2026–34.
128. Takahashi S. Future home hemodialysis - advantages of the NxStage system one. *Contrib Nephrol* 2012;**177**:117–26.
129. Gura V, Rivara MB, Bieber S, et al. A wearable artificial kidney for patients with end-stage renal disease. *JCI Insight* 2016;**1**.
130. Wieringa FP, Broers NJH, Kooman JP, Van Der Sande FM, Van Hoof C. Wearable sensors: can they benefit patients with chronic kidney disease? *Expert Rev Med Devices* 2017;**14**:505–19.

131. Salani M, Roy S, Fissell WH. Innovations in wearable and implantable Artificial kidneys. *Am J Kidney Dis* 2018;**72**(5):745–51.
132. Archdeacon P, Shaffer RN, Winkelmayer WC, Falk RJ, Roy-Chaudhury P. Fostering innovation, advancing patient safety: the kidney health initiative. *Clin J Am Soc Nephrol* 2013;**8**(9): 1609–17.
133. Linde PG, Archdeacon P, Breyer MD, Ibrahim T, Inrig JK, Kewalramani R, et al. Overcoming barriers in kidney health-forging a platform for innovation. *J Am Soc Nephrol* 2016;**27**(7): 1902–10.
134. Kidney health initiative roadmap for innovative renal replacement therapy and press release at https://khi.asn-online.org/pages/?ID=8.
135. Kidney innovation accelerator (KidneyX) prize competition to redesign dialysis at http://www.kidneyx.org.

CHAPTER

73

The Renal Biopsy in Chronic Kidney Disease

Casey N. Gashti, Pravir V. Baxi, William L. Whittier, Stephen M. Korbet

Division of Nephrology, Rush University Medical Center, Chicago, IL, United States

Abstract

The renal biopsy remains the gold standard for diagnosis, therapeutic management, and outcome prediction in patients with renal parenchymal disease. The indications for a renal biopsy in evaluation of proteinuria, microscopic hematuria, renal manifestations of systemic disease, and unexplained acute kidney injury are discussed. The utility of renal biopsy in patients with chronic kidney disease (CKD) is less defined. Given higher risk of complications and a lower chance of diagnostic or therapeutic success in CKD, the risk–benefit analysis in the context of clinical setting is of utmost importance. Percutaneous renal biopsy is the most widely accepted approach to obtaining renal tissue. Absolute and relative contraindications to the percutaneous approach are discussed. Alternative methods such as transvenous or an open renal biopsy can be used as substitute in high risk patients. Finally, the spectrum of minor and major complications and associated risk factors are explored.

INTRODUCTION

Prior to the introduction of the percutaneous kidney biopsy (PRB) in the 1950s, the majority of our study of kidney parenchyma was limited to evaluation at autopsy. The clinical–pathological correlation of this postmortem tissue was challenging because autolysis and global scarring hampered insight into disease processes. The development of the kidney biopsy procedure was essential in the establishment of nephrology as a separate subspecialty in internal medicine.[1] In 1951, Iversen and Brun first introduced the PRB based on their experience performing liver biopsies. Using intravenous pyelography for localization and the liver aspiration needle, they biopsied the right kidney with patients placed in the sitting position. The procedure was successful in only 53% of attempts, with less than adequate tissue for diagnosis in 60% of samples.[2] Despite these limitations, their experience fueled interest in the PRB and led to increased biopsy attempts around the globe. The success rate nevertheless continued to remain unacceptably low. In 1954, Kark and Muehrcke published a modified technique that would change the course of the renal biopsy field. By placing the patient in the prone position and using a Franklin-modified Vim-Silverman needle, as opposed to an aspiration needle, they were able to achieve a success rate of 96% without major complications.[3,4] Although there have been other minor advances in biopsy technique since that time, their approach still remains the foundation of the practice today.

The role of the kidney biopsy in the evaluation of proteinuria, microscopic hematuria, renal manifestations of systemic disease, and unexplained acute kidney injury (AKI) are well established.[5] However, the utility in patients with chronic kidney disease (CKD) is less defined. We review the PRB biopsy procedure, discuss indications, contraindications, and complications with a focus on the role in patients with CKD and consider potential future applications of the procedure.

INDICATIONS AND CONTRAINDICATIONS

The renal biopsy remains the gold standard for diagnosis, therapeutic management, and outcome prediction in patients with renal parenchymal disease. The primary indications for a renal biopsy in the clinical setting include evaluation of proteinuria, microscopic hematuria, renal manifestations of systemic diseases, and unexplained AKI or CKD.[5] The results of the renal biopsy have a significant impact in patient care, in that they change the diagnosis in greater than 60% of cases and affect therapeutic management decisions in a third of patients.[6,7] The impact on management is greatest in patients being evaluated for nephrotic proteinuria, unexplained AKI, and renal involvement with systemic disease.[8] Given the invasive nature of the procedure, nephrologists must weigh the risks of a kidney biopsy in

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00073-5

the context of the perceived benefits a patient may derive from a histologic diagnosis.[9] As such, the indications for renal biopsy may vary among nephrologists based on an individual patient's presentation and the consideration of the risk–benefit ratio.

Despite its utility in establishing a diagnosis and guiding therapeutic management in patients with near-normal renal function, the value of renal biopsy in patients with CKD is more controversial. The indications for renal biopsy in a CKD patient should be the same as that in a patient without CKD, though certain considerations apply. CKD patients have a higher risk of bleeding and a lower chance of diagnostic or therapeutic success, particularly when the kidney size is small.[10] CKD tends to progress in most but not all patients.[11] The rate of progression varies considerably within each diagnostic group and within each patient category.[12] Whatever the mechanism involved in renal disease progression, there is a "point of no return": a stage of structural and functional damage beyond which progression of renal disease occurs independent of pharmacologic intervention.[13] Although different diseases likely have different "points of no return," in adults, a serum creatinine concentration (S[Cr]) value of around 2 mg/dL or estimated glomerular filtration rate of approximately 50 mL/min/1.73 m^2 might be regarded as a critical level discriminating the results of treatment.[13] Institution of currently available therapies with high levels of potential toxicity and narrow therapeutic windows is not advisable if much of the renal parenchyma is already scarred. Patients who present with CKD of unknown etiology or duration, based on clinical and serologic work up can benefit from a renal biopsy to establish a diagnosis, confirm the likelihood of benefit from therapeutic intervention, clarify prognosis, and guide future management regarding transplantation. When considering a renal biopsy in a CKD patient, the challenge for the nephrologist is to weigh the higher risks and the lower benefits of a renal biopsy in the context of the overall clinical setting. Indications for and contraindications to performing a renal biopsy in the native kidney according to clinical presentation will be considered. We have intentionally excluded such discussions in the kidney transplant patient.

ISOLATED GLOMERULAR HEMATURIA

The diagnostic approach to isolated glomerular hematuria changes according to the patient's age. In children, isolated glomerular hematuria is often due to hypercalciuria, hyperuricemia, or glomerular diseases such as IgA and thin basement membrane nephropathy.[14] Thus, in the absence of other abnormal urinary, serologic, or radiographic findings, a metabolic work up is often undertaken and a renal biopsy is deferred given the excellent overall long-term prognosis.[15] In adult patients who present with persistent microscopic hematuria but have no coexisting proteinuria, hypertension, renal insufficiency, or other structural abnormalities of the urinary tract, the etiology of hematuria is often due to a mild glomerular abnormality such as IgA nephropathy (50%) or a form of hereditary nephritis (Alport syndrome or thin basement membrane disease) and a renal biopsy is often deferred.[16] Remarkably, 25% of such patients have normal renal biopsies.[17] Most patients with either IgA nephropathy or hereditary nephritis without proteinuria have a good long-term prognosis. Renal biopsy may be more useful to assess an individual's risk of progressive renal disease (suitability for kidney donation) or inspire the screening of relatives (in the case of Alport syndrome) than to guide management. Thus, renal biopsy should be performed only if defining the source of hematuria is necessary to obviate further expensive or hazardous evaluations, to define the therapeutic approach (including providing no therapy), or to reassure the patient. If the decision has been made not to perform a renal biopsy in a patient with isolated glomerular hematuria, ongoing follow-up to monitor for the development of proteinuria or disease progression is warranted. A general consensus on performing a biopsy occurs when glomerular hematuria coexists with proteinuria.[18]

ISOLATED NONNEPHROTIC PROTEINURIA

Patients who present with low-grade proteinuria of <1 g/day without hematuria, renal insufficiency, or serologic abnormalities may be monitored without undergoing a renal biopsy. The majority of these patients will have a mild form of focal segmental glomerulosclerosis (FSGS).[19] These patients are not presently candidates for immunosuppressive therapy as the clinical significance of this lesion remains uncertain. It must be noted that all glomerular diseases can cause mild to moderate proteinuria as their only manifestation. Tubulointerstitial diseases can also present with mild to moderate proteinuria, but renal biopsy is generally not useful in identifying a specific cause. Most often, the biopsy reveals nonspecific findings such as inflammation and fibrosis. Occasionally, infiltration of the interstitium with eosinophils, deposition of immune complexes, or immunoglobulins in tubules may suggest a specific diagnosis.[20] The rationale for performing a renal biopsy in these patients with low-grade proteinuria is therefore similar to patients with asymptomatic hematuria. Factors such as the presence of abnormal urinary sediment such as hematuria or pyuria, serologic abnormalities, or the presence of

renal insufficiency should be considered in decision-making. Many nephrologists routinely perform renal biopsies in patients who have higher levels of proteinuria (1–3 g/day) unless explained by conditions such as long-standing diabetes mellitus.

NEPHROTIC SYNDROME

Primary nephrotic syndrome in adults is the most universally accepted indication for a renal biopsy. Although the incidence and distribution of primary glomerulopathies vary throughout the world and by race, the most common findings are often FSGS, membranous nephropathy (MN) or minimal change disease (MCD).[21,22] However, diabetic nephropathy, systemic lupus erythematosus (SLE), IgA nephropathy, amyloidosis, or multiple myeloma (MM), among others, are also found. The findings on renal biopsy in patients with the nephrotic syndrome influence therapeutic management in 86% of cases.[7] Establishing a firm diagnosis is especially prudent in the age of novel and targeted therapies to avoid unnecessary side effects. The overall prognosis and response to treatment depend on the severity of the histologic lesion and the potential for reversibility.[23] Glomerulosclerosis, arteriosclerosis, interstitial fibrosis, and tubular atrophy are all suggestive of irreversible changes that are less likely to respond to treatment.

The utility of renal biopsy in children with nephrotic syndrome is more limited. In the original studies of the International Study of Kidney Diseases in Children (ISKDC), biopsies of children between the ages of 1–6 years with nephrotic syndrome, highly selective proteinuria, who did not have microscopic hematuria, hypertension, or renal failure, MCD was the diagnosis in greater than 80% of cases.[24] Those children had a greater than 90% chance of achieving a remission within 4 weeks of initiation of steroid therapy. As such, an initial trial of steroids without pursuing a renal biopsy is warranted. If there is no response to steroids within 8 weeks, then a renal biopsy should be considered to establish the diagnosis. In children under the age of a year, there is a high probability of the congenital nephrotic syndromes. Therefore a renal biopsy should be considered in these infants.

In adult patients who present with nephrotic syndrome, a biopsy may be deferred in certain cases. Patients with diabetes mellitus, who exhibit the expected natural history of diabetic nephropathy along with microvascular complications such as retinopathy, are often not offered a renal biopsy, given that blockade of the renin–angiotensin–aldosterone system is indicated in all stages of CKD, and the histological confirmation of diabetic nephropathy alone does not change therapeutic management.[25] On the other hand, atypical features such as rapid deterioration in renal function, sudden onset of proteinuria, presence of microscopic hematuria, or the onset of nephropathy in patients with diabetes less than 5 years warrant performance of a renal biopsy to exclude nondiabetic or coexisting parenchymal disease.[26] Of the patients with diabetes who underwent a renal biopsy, 37% demonstrated diabetic nephropathy alone, whereas nondiabetic renal disease (NDRD), either alone (36%) or superimposed on diabetic nephropathy (27%) was more common.[27] Duration of diabetes mellitus is the best predictor of the presence of diabetic nephropathy alone on the renal biopsy. IgA nephropathy and MN are among the most frequently observed NDRD lesions.[27]

Anti-phospholipase A2 receptor antibody (anti-PLA2R) has emerged as a reliable biomarker for diagnosis, monitoring of disease activity and response to therapy in primary MN.[28] In cases of nephrotic syndrome with a positive serum anti-PLA2R, the necessity of a renal biopsy has been questioned, as seropositivity for anti-PLA2R has not been found in any proteinuric kidney disease other than membranous nephropathy.[29] Depending on the state of disease activity, characteristics of assay used, and perhaps ethnicity (i.e. Japanese patients with primary membranous have a lower rate of anti-PLA2R positivity), the sensitivity of the anti-PLA2R evaluation is between 50–80%.[30,31] In addition, cases of membranous nephropathy with a positive test result for Anti-PLA2R have been described in patients with cancer, lupus, hepatitis B viral infection, and other inflammatory or autoimmune diseases.[32–34] For now, a renal biopsy remains an integral component of the workup of nephrotic syndrome, even in anti-PLA2R seropositive patients, as histological features such as mesangial or subendothelial deposits may indicate a secondary process.

PARAPROTEINEMIAS

Paraprotein-related kidney disease represents a complex group of diseases caused by an abnormal monoclonal immunoglobulin (Ig) secreted by a clone of B cells. The spectrum ranges from monoclonal gammopathy of undetermined significance (MGUS), by definition a benign condition characterized by abnormal serum paraproteins without any evidence of organ involvement, to the malignant condition MM, characterized by either the possibility or presence of end-organ damage, such as renal failure secondary to cast nephropathy.[35] Monoclonal gammopathy of renal significance (MGRS) is a heterogeneous group of disorders characterized by renal involvement with paraproteins that

are no longer MGUS but also do not meet criteria for the malignant hematologic conditions of MM or Waldenstrom's macroglobulinemia.[36] Paraproteins can play a direct role in pathogenesis of kidney disease independent of their concentration or the tumor burden. The deposition of monoclonal Ig can occur in the glomeruli leading to AL Amyloidosis, cryoglobulinemia, immunotactoid GN, monoclonal immunoglobulin deposition disease, proliferative GN with monoclonal Ig deposits, and C3 GN with monoclonal deposits.[36] Tubulointerstitial diseases resulting from monoclonal deposition include light chain proximal tubulopathy, Fanconi syndrome, and light chain cast nephropathy. Vascular Ig deposition can be in the form of amyloid fibrils, cryoglobulinemia, or crystaloglobulinemia.[37] The decision to treat a paraproteinemia relies heavily on the proof of end-organ damage. The diagnosis of MM can often be established through a combination of bone marrow biopsy and a myeloma defining event (anemia, hypercalcemia, osteolytic bone lesion, or renal failure). If the bone marrow biopsy with or without one of the myeloma-defining events confirm the diagnosis of MM, treatment is often initiated without the need for a renal biopsy. However, in the absence of a definitive MM diagnosis, a renal biopsy should be performed in all patients with the finding of a monoclonal Ig and either urinary abnormalities (proteinuria or hematuria) or abnormal glomerular filtration rate (GFR).[38] One of the critical aspects of the renal biopsy is to correlate the specific Ig found on the biopsy with that found during hematologic workup to ensure a direct link is present. Surprisingly, only 37% of patients with a monoclonal gammopathy who undergo a renal biopsy have a kidney disease associated with the paraprotein.[39] This highlights the importance of a renal biopsy in establishing a correct diagnosis in such patients to avoid prescribing potentially toxic therapies.

NEPHRITIC SYNDROME

The acute nephritic syndrome, characterized by glomerular hematuria, cellular casts, proteinuria, and frequently hypertension and renal insufficiency, is one of the main indications for a renal biopsy. Often, the initial clinical presentation or the subsequent serologic workup suggests a diagnosis, in which case, a renal biopsy is useful in confirming the diagnosis and providing information on the extent of injury and potential response to therapy. For example, the presence of circulating antineutrophil cytoplasmic antibodies (ANCA) or antiglomerular basement membrane (Anti-GBM) antibodies is highly suggestive of the diagnosis of ANCA-associated vasculitis or Anti-GBM disease respectively. In such cases, a renal biopsy is useful to evaluate the extent of inflammation and the likelihood of response to potentially toxic therapies. In other scenarios, the results of the renal biopsy can offer a new diagnosis, which can completely alter management. The presence of AKI with the nephritic syndrome increases the urgency to establish a diagnosis, given the improved outcomes when early treatment is instituted.[40] If rapidly progressive glomerulonephritis is suspected, treatment with glucocorticoids is often initiated while awaiting the renal biopsy.

The kidney biopsy is important to define the nature of renal involvement in patients with SLE. Although immune complex–mediated glomerulonephritis is the most common cause of kidney disease in SLE, other coexisting pathologic processes such as thrombotic microangiopathy (TMA), lupus podocytopathy, pauci-immune glomerulonephritis, or interstitial nephritis may result in renal injury and can only be diagnosed by renal biopsy.[41–44] As treatment of lupus nephritis moves beyond the nontargeted immunosuppressive regimen of high-dose steroids plus cyclophosphamide or MMF, a more detailed knowledge of kidney pathology becomes crucial. Presently, there is little consensus on the duration of maintenance therapy in lupus nephritis. Repeat protocol biopsies in patients with lupus nephritis can inform ongoing treatment decisions and predict long-term renal prognosis, as considerable discordance exists between clinically and histologically defined active disease.[45] Repeat renal biopsy for a flare may be most beneficial for patients with previous class II or V lupus nephritis because there is a reasonable likelihood that therapy may be intensified.[43] On the other hand, rising S[Cr] or proteinuria often do not reflect active lupus nephritis, and a repeat renal biopsy may allow reduction in therapy in inactive disease.

Renal biopsy is usually not performed in patients with a presumptive diagnosis of infection-related glomerulonephritis, unless there are features that make the diagnosis doubtful. This cluster of diagnoses, which includes poststreptococcal GN or IgA-dominant poststaphylococcal GN often present with an episode of infection, resolution of infection, and a latency period followed by an episode of acute GN. Treatment is conservative and the glomerulonephritis often resolves with supportive care. In endocarditis or shunt nephritis, the glomerulonephritis often resolves with control of the underlying infection, and a renal biopsy is not indicated. Persistent hypocomplementemia, progressive worsening of renal function, or recurrent gross hematuria should be indications for a renal biopsy to rule out other diagnoses.

ACUTE KIDNEY INJURY

In most patients with AKI, the cause of renal failure can be determined clinically without a renal biopsy. Urinary obstruction, reduced renal perfusion, acute tubular necrosis, and systemic diseases with renal involvement are often evident from clinical, serologic, radiographic, and urinary sediment examinations. In a small percentage of patients, the initial workup is either unremarkable or misleading. For example, a patient with AKI and urine sediment examination showing red blood cells, white blood cells, renal tubular cells, and granular casts can have a proliferative glomerulonephritis, acute interstitial nephritis, ATN, or a combination of these entities. In such scenarios, a renal biopsy can be very helpful to establish a diagnosis and help guide management, although the risk of a biopsy-related complication in AKI is greater.[46,47] On the other hand, renal biopsy in a patient with a prolonged period of AKI presumed to be due to ATN should be considered, to ascertain prognosis or diagnose an unsuspected disease.

CONTRAINDICATIONS TO PERCUTANEOUS RENAL BIOPSY

Because the percutaneous renal biopsy is an invasive diagnostic procedure that is elective, nephrologists are obligated to assure the safest possible setting that poses the least amount of risk to the patient, particularly because there are alternative ways to procure tissue. Settings in which the risks for the percutaneous renal biopsy are felt to be too great and thus the procedure is absolutely contraindicated are (1) uncontrolled bleeding diathesis, (2) uncontrolled severe hypertension, (3) an uncooperative patient, and (4) a solitary native kidney.[8] Relative contraindications to percutaneous renal biopsy include small hyperechoic kidneys often indicative of chronic irreversible disease, advanced uremia, the presence of multiple bilateral renal cysts, renal tumor, hydronephrosis, active renal or perirenal infection, horseshoe kidney, and inability to provide informed consent.

A major contraindication to performing a percutaneous renal biopsy is a bleeding diathesis. In most circumstances, the bleeding disorder is due to chronic anticoagulation (i.e. warfarin) or drugs that alter hemostasis (salicylates or nonsteroidal antiinflammatory agents) and can be corrected prior to the procedure. Ideally, chronic anticoagulation should be stopped long enough prior to the procedure to allow near normalization of coagulation parameters. It may become necessary to use intravenous heparin as a bridge, while chronic anticoagulation is being held, such as is the case with mechanical heart valves. For patients who require treatment with unfractionated heparin, it should be held at least 6 hours prior to the biopsy procedure to allow normalization of partial thromboplastin time (PTT). After the procedure, anticoagulation should not be resumed for at least 24 hours, but ideally one week after the procedure, given that bleeding may occur several days after the biopsy.[48,49] If the bleeding diathesis cannot be corrected and the biopsy is deemed indispensable, a transvenous or an open surgical biopsy can be considered[50–52] (see below). In such instances, consultation with a hematologist or a cardiologist can provide an assessment of risk stratification.

Uncontrolled hypertension is an absolute contraindication to a percutaneous renal biopsy. Hypertension is a risk factor for spontaneous bleeding in other vascular beds throughout the body, including intracerebral vasculature. In the kidneys, the combination of traumatic injury from the biopsy needle and elevated blood pressure has been linked to an increased risk of bleeding.[53] The risk of bleeding after renal biopsy increased more than seven times when the systolic blood pressure was >170 mm Hg.[54] Patients with history of hypertension have a greater than threefold risk of bleeding after a renal biopsy regardless of their blood pressure at the time of the procedure. The increased risk in patients with a history of hypertension is possibly due to changes in arterial compliance. Monitoring blood pressure the day of the procedure is important, as patients may not take their routine antihypertensive medications if advised to avoid eating before the procedure. In such cases, administration of antihypertensive medications with a goal reduction in blood pressure ideally to <140/90 mm Hg but at minimum systolic blood pressure to <160 mm Hg, diastolic to <100 mm Hg, and MAP <120 mm Hg is sensible prior to the procedure.

The presence of a solitary kidney as an absolute contraindication has been debated.[55] The concern for a percutaneous renal biopsy in a patient with a solitary kidney is the occurrence of a major complication that may lead to loss of renal function or require a nephrectomy, rendering the patient dependent on renal replacement therapy. However, this same reasoning would apply to the routinely performed transplant renal biopsy, although this procedure is known to be safer.[56] The practice of biopsy in a solitary native kidney is based on limited experience, but it has been suggested that it can be performed because advances in technology and techniques, which have improved the safety of the procedure, have minimized the need for such drastic interventions such as nephrectomy.[57] Despite the improvement in safety, the patient would need to be appropriately counseled on the risks, benefits, and alternatives to the percutaneous renal biopsy of a solitary kidney prior to the procedure.

The contraindication to percutaneous renal biopsy in an uncooperative patient also requires clarification. Patients on mechanical ventilation who are unable to follow commands can successfully undergo a percutaneous renal biopsy with temporary bag mask valve ventilation during the procedure.[58] As such, the contraindication is pertinent to a patient that increases risk by interfering with the procedure. Suitability of the procedure should be determined on an individual basis.

Uremic bleeding is a well-recognized complication in patients with renal failure.[59] The pathophysiology of uremic bleeding is not well understood and is thought to be multifactorial, due to platelet dysfunction associated with weakened von Willebrand factor (vWF) interaction with GPIb/IX, increased levels of cyclic AMP leading to reduced thromboxane A_2, anemia, and the action of uremic toxins.[60] Evaluation of bleeding time is arguably the most useful test to assess clinical bleeding in uremic patients (see below).[61] Lowering of uremic toxins with hemodialysis or peritoneal dialysis (PD better than HD) improves platelet aggregation and may normalize bleeding time in certain patients.[62] Desmopressin, through stimulation of factor VIII and increasing vWF activity, is a commonly used first-line agent in patients with active bleeding or who are being prepared for a renal biopsy.[63] Prior to a renal biopsy, assessment of uremic bleeding, either directly through measurement of bleeding time or platelet function analyzers when available, or indirectly through evaluation of S[Cr], blood urea nitrogen (BUN), estimated GFR, and kidney size, should be an integral component of biopsy risk stratification (see below).

SPECIAL CIRCUMSTANCES

When considering a percutaneous renal biopsy, special circumstances require attention. Pregnancy is one such special circumstance, not only because the prone positioning may need to be altered based on gestational age or patient comfort but also because the risk of the biopsy or the underlying disease may affect the mother and her fetus.[54] Although the risk of bleeding complications in pregnant patients is equivalent to that of nonpregnant patients, extreme caution must be exercised to minimize maternal–fetal harm.[64] Ideally, the procedure should be deferred, if possible, until the postpartum period, unless it may alter management during pregnancy.[65]

Another patient factor that influences the risk of a percutaneous renal biopsy is morbid obesity. Though there are no studies directly measuring complication rates in obese patients, it is widely assumed that poor ultrasound visualization would lead to higher bleeding risk.[66] This has resulted in alternative methods of tissue sampling in obese patients, such as CT-guided, transjugular or open renal biopsies (see below). Altering the prone position to the supine anterolateral has also been described as safe and effective.[67]

Kidney disease is highly prevalent among elderly persons. The aging kidney is characterized by structural and functional changes due to age and coexisting systemic disease, which lead to glomerulosclerosis, tubulointerstitial fibrosis, and subsequent loss of renal function leading to CKD.[68] Although in some cases, a renal biopsy cannot differentiate between the sequelae of chronic disease and the aging kidney, there are special conditions, such as those indicated in nonelderly adults, which may require histologic evaluation to establish a clear-cut diagnosis and therapeutic planning.[69] The elderly are more likely to present with decreased renal function, cardiovascular, pulmonary or hematologic comorbidities, and poorer general health. As such, a complete evaluation of risk factors is warranted. However, advanced age is not a contraindication to a renal biopsy. Percutaneous renal biopsy can be safely performed in the elderly (age >60 years) or the very old (age >80 years) with complication rates similar to that of adult patients.[70] Because the most common indications for a renal biopsy in the elderly are AKI or rapid onset nephrotic syndrome, treatable histologic findings such as membranous nephropathy, amyloidosis, ANCA-associated vasculitis, or interstitial nephritis are prevalent.[71,72] The histologic confirmation of diagnosis in the elderly patient leads to targeted and successful treatment in a significant proportion of cases (40–67%).[73,74]

Nephrologists have always addressed renal disease in cancer patients. Due to the explosion of new chemotherapeutic agents and their renal side effects, a new area in nephrology, called onconephrology, is being promoted to specifically address such complex issues. Membranous nephropathy is the most common glomerular pathology seen in patients with solid tumors.[75] MCD is classically associated with Hodgkin's lymphoma and usually presents around the time of diagnosis of malignancy.[76] Patients who present with nephrotic syndrome after an established diagnosis of overt malignancy may not undergo a renal biopsy, as the nephrotic syndrome often resolves with effective treatment of the malignancy. Patients with hematopoietic stem cell transplant (HSCT) can present with nephrotic syndrome due to a spectrum of glomerular diseases including MN, MCD, FSGS, and membranoproliferative glomerulonephritis.[77] There is often a close relationship between the onset of nephrotic syndrome and withdrawal of immunosuppression, leading to the development of chronic graft-versus-host disease (GVHD). Reinstitution of immunosuppression and treatment of GVHD is often the cornerstone of management of nephrotic syndrome in patients with HSCT. In

such cases, a renal biopsy can be deferred unless atypical features are present or treatment is ineffective.

Another group of kidney-related complications in patients with cancer is related to chemotherapy. TMAs have been associated with the use of gemcitabine, mitomycin C, vascular endothelial growth factor (VEGF) inhibitors, and proteosome inhibitors, such as carflizomib.[78–80] Platinum-based chemotherapy (cisplatin more than carboplatin) has long been known to be associated with tubulointerstitial nephrotoxicity and Fanconi syndrome.[81] The newest antineoplastic agents belonging to the class of immune checkpoint inhibitors have also been implicated in acute autoimmune interstitial nephritis.[82] Renal biopsies have allowed determination of the exact mechanism of injury in cancer patients, whether due to the underlying disease or side effects of treatment. In the vast majority of cases, treatment can be instituted by effective treatment of the cancer or withdrawal of the nephrotoxic chemotherapy, without performing a renal biopsy. However, renal biopsy remains a valuable tool for the nephrologist in cases where diagnosis is unclear or when newer chemotherapeutic agents, without known toxicity, are introduced.

PREBIOPSY EVALUATION

The prebiopsy evaluation comprises three major components: patient history, physical examination, and select laboratory tests. A thorough history should be obtained with special attention to a history of bleeding with prior surgeries, along with any family history of bleeding. Active medications need to be reviewed to identify agents that may increase risk of bleeding complications, including aspirin, nonsteroidal antiinflammatory drugs, and anticoagulants. On physical examination, the patient should be alert, oriented, and be able to follow simple directions for the PRB. The overlying skin at the planned biopsy site should be without signs of infection. A comprehensive metabolic panel, complete blood count with platelet count, prothrombin time, PTT, and blood type with antibody screen for cross-matching are routinely recommended prior to the procedure.[8,83]

The value of the bleeding time prior to the PRB is debated due to the lack of randomized prospective studies, operator skill, and variable availability of the test. The College of American Pathologists and American Society of Clinical Pathologists concluded in their 1998 consensus statement that the bleeding time was not clinically beneficial in predicting surgical bleeding and thus is not indicated as a routine preoperative test.[84] However, the bleeding time has been shown to be associated with increased risk of hemorrhage in closed percutaneous liver and kidney biopsies in both prospective and retrospective studies.[85–88] In one prospective study of 1055 biopsies, patients with a bleeding time greater than 7.5 minutes were twice as likely to have a bleeding complication when undergoing real-time ultrasound-guided PRB.[48] Furthermore, major complications (transfusion requirement, invasive radiologic or surgical procedure, severe hypotension, readmission, or death) were twice as likely when the bleeding time was greater than 9 minutes in this study.[48] The issue of bleeding times becomes even more important in the PRB of patients with CKD. Patients with underlying CKD are at a higher risk for having prolonged bleeding times due to platelet dysfunction associated with uremia. Desmopressin (DDAVP), a vasopressin analogue, has been used in patients to correct elevated bleeding times. Although effective in patients with hemophilia and von Willebrand's disease, the use of DDAVP in the setting of patients with prolonged bleeding times undergoing PRB is more controversial. In one randomized, placebo-controlled trial of 162 patients with normal GFR, the indiscriminant use of DDAVP (without checking bleeding times) reduced the incidence of silent postbiopsy hematomas.[89] However, there was no change in the hemoglobin level or major complications between the groups.[90] Furthermore, there still is an increased risk of bleeding despite the correction of the bleeding time with DDAVP based on the observations from several studies.[91,92] Given the added potential risk of thrombosis and hyponatremia with DDAVP use, its application in the PRB remains practice dependent.[93,94]

METHODS OF THE RENAL BIOPSY

The PRB procedure today is performed by both certified nephrologists and radiologists, with an increase in the frequency being done by the latter.[95–98] A major change in the field has been in the development of imaging techniques. Real-time ultrasound guidance has replaced the need for intravenous pyelograms and thus the need for iodinated contrast agents. Furthermore, ultrasound guidance is not dependent on the level of renal function and allows continuous visualization of the kidney and the needle, allowing the procedure to be done at the bedside. Real-time ultrasound guidance also has been shown to provide further benefits in terms of achieving a higher diagnostic yield with lower major hemorrhagic complication rates compared to the "blind" approach in which ultrasound is used for localization purposes only.[99,100] The patient is placed in the prone position and the lower pole of the right kidney is preferentially targeted to avoid the renal vasculature and blood-rich spleen. Rarely, the biopsy may be performed in the seated, lateral decubitus, or supine

anterolateral positions when patients are unable to remain in the prone position, typically due to respiratory issues.[67]

A variety of different needle types and gauges can be used for the PRB procedure. Both manual needles, such as the TruCut, and automated, spring-loaded needles are available, with the latter being used primarily today. The different sizes used for the procedure are the 14-gauge, 16-gauge and 18-gauge.[9] Although the diagnostic yield between the 14-gauge and 16-gauge needles does not differ significantly, these larger needles have consistently been shown to produce better yield than the 18-gauge needle.[8,97,101,102] Despite the larger size, in head to head studies, the 14-gauge and 16-gauge needles do not result in higher complication rates.[8] In one large series of over 9000 renal biopsies done in Norway, there was no difference in the complication rate between the 14-, 16-, or 18-gauge automated needle.[97] However, in a large meta-analysis, the 14-gauge needle has been associated with higher rates of blood transfusion after PRB compared to the 16-gauge needle.[103] Thus, most recommend the use of an automated 16-gauge needle.[9]

Computed tomography (CT) guidance for the PRB can be used in clinical situations when ultrasound imaging does not provide adequate visualization. This route is often used in patients with advanced CKD who may have small, echogenic kidneys that are difficult to visualize by ultrasound. The CT-guided PRB is also preferred in patients who have complex anatomies, such as a horseshoe kidney or in obese patients.[9,66] The CT-guided technique has been shown to be safe, with low complication rates and still provides adequate tissue for diagnosis. In one large retrospective study reviewing 146 outpatient CT-guided biopsies, diagnostic tissue was obtained in 98.6% of cases with only one patient requiring a transfusion.[104]

Immediately after the biopsy, the patient is placed in the supine position with strict bedrest. Vital signs are monitored frequently and the urine is examined for gross hematuria. Although there is debate regarding its value and timing, a repeat renal ultrasound one hour after the biopsy has been shown to predict an uncomplicated procedure. In a study of 162 adult patients who underwent real-time ultrasound renal biopsies, the absence of a hematoma one hour after PRB had a negative predictive value of 95% for clinical complications.[92]

The postprocedural observation duration is also subject to debate. In one prospective study of 750 real-time ultrasound-guided PRBs, 89% of complications were detected when patients were observed for 24 hours, but 33% of complications occurred after 8 hours,[49] proving that complications can present in a delayed fashion and that a prolonged period of observation is warranted. The risks and costs of an overnight hospital admission play a large role in the attempt to shorten the postprocedural observation time. In select patients without a bleeding diathesis, with normal blood pressure, preserved kidney function, stable hematocrit, and a negative one-hour post-PRB ultrasound, same day discharge within 6 hours can be considered.[54] However, the duration of the observation time and criteria for discharge still remain hospital- and nephrologist-dependent. We recommend an observation period of at least 6 hours and ideally up to 24 hours. Patients are also instructed to avoid blood thinners (including aspirin and nonsteroidal antiinflammatory agents), vigorous activity, and heavy lifting for 7–14 days after the biopsy. There are clinical situations that necessitate restarting anticoagulants after PRB. These should be handled in a case-specific manner and typically require consultation with other specialists including hematologists and/or cardiologists.

COMPLICATIONS

Although the percutaneous native kidney biopsy is generally safe, complications can occur and range in severity from minimal to disastrous. Due to the vascular nature of the organ, the most common complications are related to bleeding,[54] which is typically in the perinephric area and/or collection system, but rarely may occur with laceration of a lumbar[105] or mesenteric vessel.[106] Complications have traditionally been divided into two types (Table 73.1). Major complications are defined as requiring a treatment or an intervention to stop the problem. Examples include embolization for persistent or acute bleeding, transfusion of blood products for a significant drop in hemoglobin concentration, or even the occasional case of sepsis[107] or gross hematuria leading to AKI from obstruction.[108] Minor complications are defined as those that spontaneously resolve without the need for intervention or further treatment, such as gross hematuria or a symptomatic hematoma that resolves with time. Rarely (<0.1%), catastrophic complications could occur, such as a nephrectomy or even death.[48,93,109] Relatively routine consequences of the biopsy, but not necessarily complications, include microscopic hematuria (nearly 100%), minor postprocedure lumbar pain lasting up to 12 hours, a mild drop in hemoglobin concentration, or a silent perinephric hematoma detected by routine screening imaging evaluation (up to 90% in prospective series).[110]

The most common major complications are acute anemia requiring a transfusion of blood products and/or a perinephric hematoma that can occasionally require an intervention to stop the bleeding.

Acute anemia, however, can occur in uncomplicated biopsies as well. A fall in hemoglobin concentration of 1 g/dL after PRB has been reported in large series to

TABLE 73.1 Complications after Percutaneous Renal Biopsy

MAJOR COMPLICATIONS
Bleeding
Perinephric hematoma Requiring procedure to stop the bleeding With acute anemia requiring blood transfusion
Nephrectomy
Laceration of aorta, lumbar or mesenteric vessel
Outlet obstruction with acute kidney injury
Hemorrhagic shock
Sepsis
Prolonged hospitalization
Nonkidney organ puncture
Death
MINOR COMPLICATION
Bleeding
Symptomatic perinephric hematoma
Gross hematuria
Acute anemia (>1 g/dL drop in Hgb) without transfusion
Page kidney
Pain (>12 hours)
Local infection
Arteriovenous fistula
CONSEQUENCES
Microscopic hematuria
Pain (<12 hours)
Silent perinephric hematoma

dL, deciliter; *g*, gram; *Hgb*, hemoglobin concentration.

occur in up to 50% of uncomplicated cases.[48,111] In one series of 1055 patients,[48] the average change in hemoglobin concentration was 0.9 ± 0.8 g/dL in patients without complications. However, in the same series, patients with major complications had, on average, a drop in hemoglobin concentration of 2.3 ± 1.7 g/dL ($p < 0.001$ compared with uncomplicated biopsies), suggesting that a minor drop can occur in any biopsy, but a greater degree of acute anemia may herald a major complication. Possible mechanisms to explain why acute anemia may occur in uncomplicated biopsies include a dilutional effect[111] (due to routine administration of intravenous fluids or even resorption of interstitial fluid in patients with nephrosis[112]), or possibly due to the development of undocumented silent hematomas.[110]

Another group of investigators evaluated the change in hematocrit in a retrospective cohort of 83 PRBs.[113] They found that the decrease in hematocrit at 6 hours after PRB had a linear correlation with the hematocrit at 24 hours, implying that if the 6-hour hematocrit was stable, then it would likely remain stable at 24 hours. However, there was no correlation with actual hemorrhage or complications in this study.

Acute anemia can also result in the need for transfusion of erythrocytes. Similar to use of transfusions in patients on hemodialysis,[114] the trigger for transfusion after PRB is closely related to the prebiopsy hemoglobin concentration, as opposed to clinically significant bleeding or drop in hemoglobin level.[115] For example, a patient with a prebiopsy Hgb concentration of 7.5 g/dL who drops 1 g/dL after the biopsy is more likely to get a transfusion, compared to one who starts at 14 g/dL and drops to 11 g/dL, regardless of the development of a hematoma. This has implications regarding the absolute frequency of major complications in the literature, as they are defined by interventions, including the administration of blood products, even in the absence of hemorrhage. Thus, the major complication rate is actually lower than what is reported.

Another common complication is the development of a perinephric hematoma, which can lead to pain, acute anemia, transfusions, and/or procedures to stop the hematoma from expanding. The majority of perinephric hematomas, when detected by routine screening, are small and clinically silent[116] and therefore not considered actual complications. Typically, a hematoma will tamponade and stop enlarging but can continue to expand into a major complication, requiring an intervention or surgical procedure to stop the bleeding. Rarely, Page kidney can occur, where a perinephric hematoma causes renal parenchymal compression and leads to renin-mediated hypertension.[117]

RISK FACTORS FOR COMPLICATIONS

The risk factors for developing a hemorrhagic complication after PRB (Table 73.2) are divided into those that are patient-related (i.e. age, bleeding diathesis, uncontrolled HTN, inpatient vs. outpatient) and those that are related to the technique itself (i.e. needle size or type, use of imaging or not).[54]

One of the most important patient-related clinical risk factors associated with an increased risk of bleeding is an elevated BUN and/or S[Cr].[10,46–48,118–120] Azotemia is strongly associated with bleeding, as well as anemia. In one large prospective series of 910 patients undergoing PRB, the average baseline S[Cr] was 4.0 ± 2.9, 2.9 ± 2.6, and 1.7 ± 1.4 mg/dL in patients with a baseline Hgb of <9.0, 9.0–11.0, and >11.0 g/dL

TABLE 73.2 Features Predictive of Complication after Percutaneous Renal Biopsy

Patient Related	Range	Risk
BP systolic	>170 mm Hg	7×
Hemoglobin concentration	<11 g/dL	3×
S[Cr]	<2.0–3.5 mg/dL	3–5×
Bleeding time	>8 minutes	2×
Platelet count	<200 K/μL	2–4×
Procedure Related		
Needle gauge	14- vs. 16/18-gauge	4×
Number of passes	<3 vs. ≥ 3	NS

dL, deciliter; *g*, gram; *mm Hg*, millimeters of mercury; μL, microliter.
From references 48,97,103,120,137.

($p < 0.0001$), respectively.[115] Using a multivariate analysis of known risk factors, however, both S[Cr] and anemia were independently associated with complications,[48] highlighting the importance of renal dysfunction as an actual risk factor. In this study, patients with a S[Cr] > 3.5 mg/dL were 1.8 times more likely (95% confidence interval (CI) 1.2–2.9, $p = 0.009$) to develop a complication and 2.7 times more likely (95% CI 1.5–5.1, $p = 0.001$) to require an erythrocyte transfusion.[48]

The S[Cr] is elevated in AKI as well as in CKD, and both disease states have been found to be associated with complications. In one study, complications occurred in 11% of patients with AKI compared to 6.7% of patients without AKI, and 10% of patients with AKI required a blood transfusion. Patients with AKI had more risk factors for a complication, including anemia, higher S[Cr], higher blood pressure, and female gender.[46] CKD is also a risk factor for bleeding after a PRB. Joseph et al.[10] evaluated patients undergoing PRB with an elevated S[Cr] in addition to baseline renal function within 6 months prior to the procedure. They found that with prolonged elevations in the S[Cr] (CKD), bleeding after a biopsy was more frequent. In addition, they found that the higher the S[Cr], the greater the likelihood of finding an irreversible or untreatable condition. Thus, AKI and CKD both increase the risk of bleeding after a biopsy, and in more severe stages of CKD, there is less chance of finding a reversible lesion.

Some have suggested that a diagnosis itself may be associated with an increased risk of bleeding. However, this is most likely due to confounding variables, as an increased risk has been reported for diseases such as acute tubular necrosis,[91,121] end-stage renal disease,[91] and hypertensive kidney disease,[121] all which are known to have elevated S[Cr] as well as greater degrees of anemia.

NONPERCUTANEOUS RENAL BIOPSY

Several nonpercutaneous renal biopsy techniques are available when contraindications exist with the percutaneous route, but a biopsy is still required for diagnosis and treatment considerations. This is often the case in patients with bleeding diathesis, patients being mechanically ventilated, or when attempts with the percutaneous method have been unsuccessful.

The transvenous renal biopsy (TVRB), most often transjugular, was first introduced in 1990[122] and is an alternative to the PRB, which is often used when biopsies of multiple organs are required (such as with simultaneous liver and kidney biopsies).[52,123] Studies have demonstrated that the TVRB can provide adequate tissue for diagnosis, and a comparable safety profile as the PRB when contraindications exist for the latter.[52,83,123] The major limitations of this method include the need for administration of contrast with accompanied risk of allergic reactions and nephrotoxicity, variable operator experience, and the potential higher costs associated with this procedure. Capsular perforation resulting in gross hematuria has been reported with TVRB. However, the resulting bleeding is typically self-limiting, owing to the tamponade effect from the perinephric fat and with the return of the blood back into the venous vessels.[9,83,122,124] A potential benefit of the TVRB in patients at higher risk for bleeding complications is the ability of the interventionalist to rapidly apply hemostasis to a bleed if it is identified immediately after the procedure.

The open renal biopsy (ORB) procedure is an established surgical approach for obtaining kidney tissue when contraindications exist with the PRB. Although one of the largest studies with 934 patients showed tissue adequacy of 100% without major complications, the risk of anesthesia and the associated postsurgical recovery time remain significant limitations of this technique.[125] In a recent retrospective study of 115 patients, the mortality rate after the ORB was 0.8%, with a 27% rate of minor complications, including wound infection, pneumonia, and deep vein thrombosis.[126] With advances in laparoscopic techniques, the laparoscopic renal biopsy (LRB) has also been used. Advantages include the reduction of the operation time down to one hour and decrease in mean blood loss to 10 mL.[127] However, the LRB still requires anesthesia and is subject to the same postoperative complications as the ORB. Furthermore, the costs of LRB are also higher than the PRB. Nevertheless, this modality remains a viable alternative to the PRB.

FUTURE APPLICATIONS

Despite the high burden of CKD, there are few effective therapies for management of patients across the CKD spectrum.[128,129] There are fewer clinical trials compared to other medical specialties, and the results are often negative.[130] Even when clinical trials launch, as with many chronic disease states, the low trajectory of meaningful clinical events requires long follow-up times associated with significant financial burden.[131] These setbacks often stem from lack of understanding the pathophysiology of CKD, the weak pipeline of bench to bedside research, and ineffective animal models that do not appropriately mimic human disease or human drug effects.[132,133] To address these challenges, The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has put forward initiatives from the perspective of precision medicine, and pragmatic clinical trials and population health, each supported by efforts in health information technology, to advance kidney health.[134] Part of this project involves the use of 'omics' techniques (genomics, proteomics, metabolomics) on human kidney tissue to gain a deeper understanding of disease process and ultimately develop targeted therapies.[135,136] Given the poor fidelity of animal models and the limitations of tissue from transplant, nephrectomy, and autopsy, obtaining research biopsies from patients with AKI and CKD is a necessary first step in this process.[134] Because kidney biopsies pose a risk of complications and the tissue that is obtained may not provide immediate benefit to the tissue donor, ethical and patient safety considerations are of primary concern.

Ultimately, renal biopsies have the greatest utility in cases where there are available therapies. Lupus nephritis is an excellent example of variability in histology and therapy to the extent that almost all lupus patients with clinical or laboratory evidence of renal involvement should undergo a renal biopsy. On the other hand, acute tubular necrosis is almost never intentionally biopsied as there is no effective therapy at this time. As new therapies emerge, the utility of renal biopsy in different clinical presentations will change.

References

1. Cameron JS, Hicks J. The introduction of renal biopsy into nephrology from 1901 to 1961: a paradigm of the forming of nephrology by technology. *Am J Nephrol* 1997;**17**:347–58.
2. Iversen P, Brun C. Aspiration biopsy of the kidney. *Am J Med* 1951; **11**:324–30.
3. Kark RM, Muehrcke RC. Biopsy of kidney in prone position. *Lancet* 1954;**266**:1047–9.
4. Kark RM, Muehrcke RC, Pirani CL, Pollak VE. The clinical value of renal biopsy. *Ann Intern Med* 1955;**43**:807–47.
5. Clinical competence in percutaneous renal biopsy. Health and Public Policy Committee. American College of Physicians. *Ann Intern Med* 1988;**108**:301–3.
6. Cohen AH, Nast CC, Adler SG, Kopple JD. Clinical utility of kidney biopsies in the diagnosis and management of renal disease. *Am J Nephrol* 1989;**9**:309–15.
7. Richards NT, Darby S, Howie AJ, Adu D, Michael J. Knowledge of renal histology alters patient management in over 40% of cases. *Nephrol Dial Transplant* 1994;**9**:1255–9.
8. Korbet SM. Percutaneous renal biopsy. *Semin Nephrol* 2002;**22**: 254–67.
9. Hogan JJ, Mocanu M, Berns JS. The native kidney biopsy: update and evidence for best practice. *Clin J Am Soc Nephrol* 2016;**11**: 354–62.
10. Joseph AJ, Compton SP, Holmes LH, et al. Utility of percutaneous renal biopsy in chronic kidney disease. *Nephrology* 2010;**15**:544–8.
11. Rutherford WE, Blondin J, Miller JP, Greenwalt AS, Vavra JD. Chronic progressive renal disease: rate of change of serum creatinine concentration. *Kidney Int* 1977;**11**:62–70.
12. Oldrizzi L, Rugiu C, Valvo E, et al. Progression of renal failure in patients with renal disease of diverse etiology on protein-restricted diet. *Kidney Int* 1985;**27**:553–7.
13. Maschio G, Oldrizzi L, Rugiu C. Is there a "point of no return" in progressive renal disease? *J Am Soc Nephrol* 1991;**2**:832–40.
14. Trachtman H, Weiss RA, Bennett B, Greifer I. Isolated hematuria in children: indications for a renal biopsy. *Kidney Int* 1984;**25**:94–9.
15. Zhai Y, Xu H, Shen Q, et al. Renal histological features of school-age children with asymptomatic haematuria and/or proteinuria: a multicenter study. *Nephrology* 2014;**19**:426–31.
16. Fuiano G, Mazza G, Comi N, et al. Current indications for renal biopsy: a questionnaire-based survey. *Am J Kidney Dis* 2000;**35**: 448–57.
17. Copley JB, Hasbargen JA. 'Idiopathic' hematuria. A prospective evaluation. *Arch Intern Med* 1987;**147**:434–7.
18. Hall CL, Bradley R, Kerr A, Attoti R, Peat D. Clinical value of renal biopsy in patients with asymptomatic microscopic hematuria with and without low-grade proteinuria. *Clin Nephrol* 2004;**62**: 267–72.
19. Sinniah R, Pwee HS, Lim CH. Glomerular lesions in asymptomatic microscopic hematuria discovered on routine medical examination. *Clin Nephrol* 1976;**5**:216–28.
20. Madaio MP. Renal biopsy. *Kidney Int* 1990;**38**:529–43.
21. Korbet SM, Genchi RM, Borok RZ, Schwartz MM. The racial prevalence of glomerular lesions in nephrotic adults. *Am J Kidney Dis* 1996;**27**:647–51.
22. Sim JJ, Batech M, Hever A, et al. Distribution of biopsy-proven presumed primary glomerulonephropathies in 2000-2011 among a racially and ethnically diverse US population. *Am J Kidney Dis* 2016;**68**:533–44.
23. Alexopoulos E. How important is renal biopsy in the management of patients with glomerular diseases? *Nephrol Dial Transplant* 2001;**16**(Suppl. 6):83–5.
24. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. *J Pediatr* 1981;**98**:561–4.
25. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993;**329**: 1456–62.
26. Mazzucco G, Bertani T, Fortunato M, et al. Different patterns of renal damage in type 2 diabetes mellitus: a multicentric study on 393 biopsies. *Am J Kidney Dis* 2002;**39**:713–20.
27. Fiorentino M, Bolignano D, Tesar V, et al. Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies. *Nephrol Dial Transplant* 2017;**32**:97–110.

28. Francis JM, Beck Jr LH, Salant DJ. Membranous nephropathy: a journey from bench to bedside. *Am J Kidney Dis* 2016;**68**:138–47.
29. Ronco P, Debiec H. Pathogenesis of membranous nephropathy: recent advances and future challenges. *Nat Rev Nephrol* 2012;**8**: 203–13.
30. Akiyama S, Akiyama M, Imai E, Ozaki T, Matsuo S, Maruyama S. Prevalence of anti-phospholipase A2 receptor antibodies in Japanese patients with membranous nephropathy. *Clin Exp Nephrol* 2015;**19**:653–60.
31. Hofstra JM, Beck Jr LH, Beck DM, Wetzels JF, Salant DJ. Anti-phospholipase A(2) receptor antibodies correlate with clinical status in idiopathic membranous nephropathy. *Clin J Am Soc Nephrol* 2011;**6**:1286–91.
32. Dauvergne M, Moktefi A, Rabant M, et al. Membranous nephropathy associated with immunological disorder-related liver disease: a retrospective study of 10 cases. *Medicine (Baltim)* 2015;**94**:e1243.
33. Huang X, Qin W, Zhang M, Zheng C, Zeng C, Liu Z. Detection of anti-PLA2R autoantibodies and IgG subclasses in post-allogeneic hematopoietic stem cell transplantation membranous nephropathy. *Am J Med Sci* 2013;**346**:32–7.
34. Qin W, Beck Jr LH, Zeng C, et al. Anti-phospholipase A2 receptor antibody in membranous nephropathy. *J Am Soc Nephrol* 2011;**22**: 1137–43.
35. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014;**15**:e538–48.
36. Leung N, Bridoux F, Hutchison CA, et al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. *Blood* 2012;**120**:4292–5.
37. Basnayake K, Stringer SJ, Hutchison CA, Cockwell P. The biology of immunoglobulin free light chains and kidney injury. *Kidney Int* 2011;**79**:1289–301.
38. Rosner MH, Edeani A, Yanagita M, Glezerman IG, Leung N. Paraprotein-related kidney disease: diagnosing and treating monoclonal gammopathy of renal significance. *Clin J Am Soc Nephrol* 2016;**11**:2280–7.
39. Paueksakon P, Revelo MP, Horn RG, Shappell S, Fogo AB. Monoclonal gammopathy: significance and possible causality in renal disease. *Am J Kidney Dis* 2003;**42**:87–95.
40. Booth AD, Almond MK, Burns A, et al. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis* 2003;**41**:776–84.
41. Anders HJ, Weening JJ. Kidney disease in lupus is not always 'lupus nephritis'. *Arthritis Res Ther* 2013;**15**:108.
42. Schwartz MM. The pathology of lupus nephritis. *Semin Nephrol* 2007;**27**:22–34.
43. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. *Clin J Am Soc Nephrol* 2017;**12**:825–35.
44. Song D, Wu LH, Wang FM, et al. The spectrum of renal thrombotic microangiopathy in lupus nephritis. *Arthritis Res Ther* 2013;**15**: R12.
45. Malvar A, Pirruccio P, Alberton V, et al. Histologic versus clinical remission in proliferative lupus nephritis. *Nephrol Dial Transplant* 2017;**32**:1338–44.
46. Korbet SM, Gashti CN, Evans JK, Whittier WL. Risk of percutaneous renal biopsy of native kidneys in the evaluation of acute kidney injury. *Clin Kidney J* 2018;**11**:610–5.
47. Moledina DG, Luciano RL, Kukova L, et al. Kidney biopsy-related complications in hospitalized patients with acute kidney disease. *Clin J Am Soc Nephrol* 2018;**13**:1633–40.
48. Korbet SM, Volpini KC, Whittier WL. Percutaneous renal biopsy of native kidneys: a single-center experience of 1,055 biopsies. *Am J Nephrol* 2014;**39**:153–62.
49. Whittier WL, Korbet SM. Timing of complications in percutaneous renal biopsy. *J Am Soc Nephrol* 2004;**15**:142–7.
50. Bolton WK, Vaughan Jr ED. A comparative study of open surgical and percutaneous renal biopsies. *J Urol* 1977;**117**:696–8.
51. Chodak GW, Gill WB, Wald V, Spargo B. Diagnosis of renal parenchymal diseases by a modified open kidney biopsy technique. *Kidney Int* 1983;**24**:804–6.
52. Thompson BC, Kingdon E, Johnston M, et al. Transjugular kidney biopsy. *Am J Kidney Dis* 2004;**43**:651–62.
53. Eiro M, Katoh T, Watanabe T. Risk factors for bleeding complications in percutaneous renal biopsy. *Clin Exp Nephrol* 2005;**9**:40–5.
54. Whittier WL. Complications of the percutaneous kidney biopsy. *Adv Chron Kidney Dis* 2012;**19**:179–87.
55. Mendelssohn DC, Cole EH. Outcomes of percutaneous kidney biopsy, including those of solitary native kidneys. *Am J Kidney Dis* 1995;**26**:580–5.
56. Whittier WL, Gashti C, Saltzberg S, Korbet S. Comparison of native and transplant kidney biopsies: diagnostic yield and complications. *Clin Kidney J* 2018;**11**:616–22.
57. Schow DA, Vinson RK, Morrisseau PM. Percutaneous renal biopsy of the solitary kidney: a contraindication? *J Urol* 1992;**147**: 1235–7.
58. Conlon PJ, Kovalik E, Schwab SJ. Percutaneous renal biopsy of ventilated intensive care unit patients. *Clin Nephrol* 1995;**43**:309–11.
59. Noris M, Remuzzi G. Uremic bleeding: closing the circle after 30 years of controversies? *Blood* 1999;**94**:2569–74.
60. Hedges SJ, Dehoney SB, Hooper JS, Amanzadeh J, Busti AJ. Evidence-based treatment recommendations for uremic bleeding. *Nat Clin Pract Nephrol* 2007;**3**:138–53.
61. Steiner RW, Coggins C, Carvalho AC. Bleeding time in uremia: a useful test to assess clinical bleeding. *Am J Hematol* 1979;**7**:107–17.
62. Nenci GG, Berrettini M, Agnelli G, Parise P, Buoncristiani U, Ballatori E. Effect of peritoneal dialysis, haemodialysis and kidney transplantation on blood platelet function. I. Platelet aggregation by ADP and epinephrine. *Nephron* 1979;**23**:287–92.
63. Kohler M, Hellstern P, Tarrach H, Bambauer R, Wenzel E, Jutzler GA. Subcutaneous injection of desmopressin (DDAVP): evaluation of a new, more concentrated preparation. *Haemostasis* 1989;**19**:38–44.
64. Chen HH, Lin HC, Yeh JC, Chen CP. Renal biopsy in pregnancies complicated by undetermined renal disease. *Acta Obstet Gynecol Scand* 2001;**80**:888–93.
65. Kuller JA, D'Andrea NM, McMahon MJ. Renal biopsy and pregnancy. *Am J Obstet Gynecol* 2001;**184**:1093–6.
66. Fine DM, Arepally A, Hofmann LV, Mankowitz SG, Atta MG. Diagnostic utility and safety of transjugular kidney biopsy in the obese patient. *Nephrol Dial Transplant* 2004;**19**:1798–802.
67. Gesualdo L, Cormio L, Stallone G, et al. Percutaneous ultrasound-guided renal biopsy in supine antero-lateral position: a new approach for obese and non-obese patients. *Nephrol Dial Transplant* 2008;**23**:971–6.
68. Brown CM, Scheven L, O'Kelly P, Dorman AM, Walshe JJ. Renal histology in the elderly: indications and outcomes. *J Nephrol* 2012;**25**:240–4.
69. Dhaun N, Bellamy CO, Cattran DC, Kluth DC. Utility of renal biopsy in the clinical management of renal disease. *Kidney Int* 2014; **85**:1039–48.
70. Kohli HS, Jairam A, Bhat A, et al. Safety of kidney biopsy in elderly: a prospective study. *Int Urol Nephrol* 2006;**38**:815–20.
71. Haas M, Spargo BH, Wit EJ, Meehan SM. Etiologies and outcome of acute renal insufficiency in older adults: a renal biopsy study of 259 cases. *Am J Kidney Dis* 2000;**35**:433–47.
72. Yokoyama H, Sugiyama H, Sato H, et al. Renal disease in the elderly and the very elderly Japanese: analysis of the Japan Renal Biopsy Registry (J-RBR). *Clin Exp Nephrol* 2012;**16**:903–20.
73. Moutzouris DA, Herlitz L, Appel GB, et al. Renal biopsy in the very elderly. *Clin J Am Soc Nephrol* 2009;**4**:1073–82.

74. Nair R, Bell JM, Walker PD. Renal biopsy in patients aged 80 years and older. *Am J Kidney Dis* 2004;**44**:618–26.
75. Ronco PM. Paraneoplastic glomerulopathies: new insights into an old entity. *Kidney Int* 1999;**56**:355–77.
76. Mallouk A, Pham PT, Pham PC. Concurrent FSGS and Hodgkin's lymphoma: case report and literature review on the link between nephrotic glomerulopathies and hematological malignancies. *Clin Exp Nephrol* 2006;**10**:284–9.
77. Brukamp K, Doyle AM, Bloom RD, Bunin N, Tomaszewski JE, Cizman B. Nephrotic syndrome after hematopoietic cell transplantation: do glomerular lesions represent renal graft-versus-host disease? *Clin J Am Soc Nephrol* 2006;**1**:685–94.
78. Glezerman I, Kris MG, Miller V, Seshan S, Flombaum CD. Gemcitabine nephrotoxicity and hemolytic uremic syndrome: report of 29 cases from a single institution. *Clin Nephrol* 2009;**71**:130–9.
79. Hobeika L, Self SE, Velez JC. Renal thrombotic microangiopathy and podocytopathy associated with the use of carfilzomib in a patient with multiple myeloma. *BMC Nephrol* 2014;**15**:156.
80. Lesesne JB, Rothschild N, Erickson B, et al. Cancer-associated hemolytic-uremic syndrome: analysis of 85 cases from a national registry. *J Clin Oncol* 1989;**7**:781–9.
81. Arany I, Safirstein RL. Cisplatin nephrotoxicity. *Semin Nephrol* 2003;**23**:460–4.
82. Shirali AC, Perazella MA, Gettinger S. Association of acute interstitial nephritis with programmed cell death 1 inhibitor therapy in lung cancer patients. *Am J Kidney Dis* 2016;**68**:287–91.
83. Whittier WL, Korbet SM. Renal biopsy: update. *Curr Opin Nephrol Hypertens* 2004;**13**:661–5.
84. Peterson P, Hayes TE, Arkin CF, et al. The preoperative bleeding time test lacks clinical benefit: College of American Pathologists' and American Society of Clinical Pathologists' position article. *Arch Surg* 1998;**133**:134–9.
85. Boberg KM, Brosstad F, Egeland T, Egge T, Schrumpf E. Is a prolonged bleeding time associated with an increased risk of hemorrhage after liver biopsy? *Thromb Haemostasis* 1999;**81**:378–81.
86. Diaz-Buxo JA, Donadio Jr JV. Complications of percutaneous renal biopsy: an analysis of 1,000 consecutive biopsies. *Clin Nephrol* 1975;**4**:223–7.
87. Nass K, O'Neill WC. Bedside renal biopsy: ultrasound guidance by the nephrologist. *Am J Kidney Dis* 1999;**34**:955–9.
88. Wolf DC, Weher F, Palascak J, et al. Role of the template bleeding time in predicting bleeding complications of percutaneous liver biopsy [abstract]. *Hepatology* 1995;**22**:509A.
89. Manno C, Bonifati C, Torres DD, Campobasso N, Schena FP. Desmopressin acetate in percutaneous ultrasound-guided kidney biopsy: a randomized controlled trial. *Am J Kidney Dis* 2011;**57**:850–5.
90. Whittier WL. Percutaneous kidney biopsy: "the needle and the damage done"? *Am J Kidney Dis* 2011;**57**:808–10.
91. Stratta P, Canavese C, Marengo M, et al. Risk management of renal biopsy: 1387 cases over 30 years in a single centre. *Eur J Clin Investig* 2007;**37**:954–63.
92. Waldo B, Korbet SM, Freimanis MG, Lewis EJ. The value of post-biopsy ultrasound in predicting complications after percutaneous renal biopsy of native kidneys. *Nephrol Dial Transplant* 2009;**24**:2433–9.
93. Lees JS, McQuarrie EP, Mordi N, Geddes CC, Fox JG, Mackinnon B. Risk factors for bleeding complications after nephrologist-performed native renal biopsy. *Clin Kidney J* 2017;**10**:573–7.
94. Lees JS, McQuarrie EP, Mackinnon B. Renal biopsy: it is time for pragmatism and consensus. *Clin Kidney J* 2018;**11**:605–9.
95. Korbet SM. Nephrology and the percutaneous renal biopsy: a procedure in jeopardy of being lost along the way. *Clin J Am Soc Nephrol* 2012;**7**:1545–7.
96. Korbet SM, Whittier WL, Rodby RA. Changing trends in the performance of percutaneous renal biopsy from nephrologist to interventional radiologist: a single-center experience. *Am J Nephrol* 2018;**48**:326–9.
97. Tondel C, Vikse BE, Bostad L, Svarstad E. Safety and complications of percutaneous kidney biopsies in 715 children and 8573 adults in Norway 1988-2010. *Clin J Am Soc Nephrol* 2012;**7**:1591–7.
98. Whittier WL, Korbet SM. Who should perform the percutaneous renal biopsy: a nephrologist or radiologist? *Semin Dial* 2014;**27**:243–5.
99. Maya ID, Maddela P, Barker J, Allon M. Percutaneous renal biopsy: comparison of blind and real-time ultrasound-guided technique. *Semin Dial* 2007;**20**:355–8.
100. Prasad N, Kumar S, Manjunath R, et al. Real-time ultrasound-guided percutaneous renal biopsy with needle guide by nephrologists decreases post-biopsy complications. *Clin Kidney J* 2015;**8**:151–6.
101. Nicholson ML, Wheatley TJ, Doughman TM, et al. A prospective randomized trial of three different sizes of core-cutting needle for renal transplant biopsy. *Kidney Int* 2000;**58**:390–5.
102. Roth R, Parikh S, Makey D, et al. When size matters: diagnostic value of kidney biopsy according to the gauge of the biopsy needle. *Am J Nephrol* 2013;**37**:249–54.
103. Corapi KM, Chen JL, Balk EM, Gordon CE. Bleeding complications of native kidney biopsy: a systematic review and meta-analysis. *Am J Kidney Dis* 2012;**60**:62–73.
104. Margaryan A, Perazella MA, Mahnensmith RL, Abu-Alfa AK. Experience with outpatient computed tomographic-guided renal biopsy. *Clin Nephrol* 2010;**74**:440–5.
105. Kim KT, Kim BS, Park YH, Cho KJ, Shinn KS, Bahk YW. Embolic control of lumbar artery hemorrhage complicating percutaneous renal biopsy with a 3-F coaxial catheter system: case report. *Cardiovasc Interv Radiol* 1991;**14**:175–8.
106. Galloway DC, Tytle T. Laceration of a mesenteric artery: unusual complication of percutaneous renal biopsy. *South Med J* 1980;**73**:1413–4.
107. Dara T, Lohr J. Disseminated intravascular coagulation following percutaneous renal biopsy. *Am J Nephrol* 1991;**11**:343–4.
108. Bergman SM, Frentz GD, Wallin JD. Ureteral obstruction due to blood clot following percutaneous renal biopsy: resolution with intraureteral streptokinase. *J Urol* 1990;**143**:113–5.
109. Huang CC, Kuo CC, Chen YM. The incidence of fatal kidney biopsy. *Clin Nephrol* 2011;**76**:256–8.
110. Ralls PW, Barakos JA, Kaptein EM, et al. Renal biopsy-related hemorrhage: frequency and comparison of CT and sonography. *J Comput Assist Tomogr* 1987;**11**:1031–4.
111. Bolton WK. Nonhemorrhagic decrements in hematocrit values after percutaneous renal biopsy. *J Am Med Assoc* 1977;**238**:1266–8.
112. Clive DM. Postural hemodilution in nephrotic edema: a cause of spurious hemorrhage after renal biopsy. *Am J Kidney Dis* 1997;**29**:627–30.
113. Khajehdehi P, Junaid SM, Salinas-Madrigal L, Schmitz PG, Bastani B. Percutaneous renal biopsy in the 1990s: safety, value, and implications for early hospital discharge. *Am J Kidney Dis* 1999;**34**:92–7.
114. Whitman CB, Shreay S, Gitlin M, van Oijen MG, Spiegel BM. Clinical factors and the decision to transfuse chronic dialysis patients. *Clin J Am Soc Nephrol* 2013;**8**:1942–51.
115. Whittier WL, Sayeed K, Korbet SM. Clinical factors influencing the decision to transfuse after percutaneous native kidney biopsy. *Clin Kidney J* 2016;**9**:102–7.
116. Manno C, Strippoli GF, Arnesano L, et al. Predictors of bleeding complications in percutaneous ultrasound-guided renal biopsy. *Kidney Int* 2004;**66**:1570–7.
117. McCune TR, Stone WJ, Breyer JA. Page kidney: case report and review of the literature. *Am J Kidney Dis* 1991;**18**:593–9.

118. Ishikawa E, Nomura S, Hamaguchi T, et al. Ultrasonography as a predictor of overt bleeding after renal biopsy. *Clin Exp Nephrol* 2009;**13**:325–31.
119. Shidham GB, Siddiqi N, Beres JA, et al. Clinical risk factors associated with bleeding after native kidney biopsy. *Nephrology* 2005; **10**:305–10.
120. Simard-Meilleur MC, Roy L, Troyanov S, Brachemi S. Risk factors and timing of native kidney biopsy complications [abstract]. *J Am Soc Nephrol* 2012;**23**:541A.
121. Parrish AE. Complications of percutaneous renal biopsy: a review of 37 years' experience. *Clin Nephrol* 1992;**38**:135–41.
122. Zhuo L, Wang H, Chen D, Lu H, Zou G, Li W. Alternative renal biopsies: past and present. *Int Urol Nephrol* 2018;**50**:475–9.
123. Cluzel P, Martinez F, Bellin MF, et al. Transjugular versus percutaneous renal biopsy for the diagnosis of parenchymal disease: comparison of sampling effectiveness and complications. *Radiology* 2000;**215**:689–93.
124. Navuluri R, Ahmed O. Complications of transjugular biopsies. *Semin Intervent Radiol* 2015;**32**:42–8.
125. Nomoto Y, Tomino Y, Endoh M, et al. Modified open renal biopsy: results in 934 patients. *Nephron* 1987;**45**:224–8.
126. Stec AA, Stratton KL, Kaufman MR, et al. Open renal biopsy: comorbidities and complications in a contemporary series. *BJU Int* 2010;**106**:102–6.
127. Anas CM, Hattori R, Morita Y, et al. Efficiency of laparoscopic-assisted renal biopsy. *Clin Nephrol* 2008;**70**:203–9.
128. Appel LJ, Wright Jr JT, Greene T, et al. Long-term effects of renin-angiotensin system-blocking therapy and a low blood pressure goal on progression of hypertensive chronic kidney disease in African Americans. *Arch Intern Med* 2008;**168**:832–9.
129. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;**345**:851–60.
130. Inrig JK, Califf RM, Tasneem A, et al. The landscape of clinical trials in nephrology: a systematic review of Clinicaltrials.gov. *Am J Kidney Dis* 2014;**63**:771–80.
131. Levin A, Lancashire W, Fassett RG. Targets, trends, excesses, and deficiencies: refocusing clinical investigation to improve patient outcomes. *Kidney Int* 2013;**83**:1001–9.
132. Bonventre JV, Boulware LE, Dember LM, et al. The kidney research national dialogue: gearing up to move forward. *Clin J Am Soc Nephrol* 2014;**9**:1806–11.
133. Yang HC, Zuo Y, Fogo AB. Models of chronic kidney disease. *Drug Discov Today Dis Model* 2010;**7**:13–9.
134. Norton JM, Ketchum CJ, Narva AS, Star RA, Rodgers GP. Complementary initiatives from the NIDDK to advance kidney health. *Clin J Am Soc Nephrol* 2017;**12**:1544–7.
135. Sharma K, Pasa-Tolic L. Toward individual glomerular phenotyping: advent of precision medicine in kidney biopsies. *Kidney Int* 2018;**93**:1265–7.
136. Sui W, Zhang R, Chen J, et al. Comparative proteomic analysis of membranous nephropathy biopsy tissues using quantitative proteomics. *Exp Ther Med* 2015;**9**:805–10.
137. Augusto JF, Lassalle V, Fillatre P, et al. Safety and diagnostic yield of renal biopsy in the intensive care unit. *Intensive Care Med* 2012; **38**:1826–33.

QUESTIONS AND ANSWERS

Question 1

What is the mortality rate associated with a renal biopsy?

A. 0.001%
B. 0.01%
C. 0.1%
D. 1%
E. 10%

Answer: C

The established mortality rate is 1/1000 in the largest series which followed complications, making C the correct choice.[48]

Question 2

A patient has nephrotic range proteinuria and progressive reduction in his GFR over the last year (S [Cr] 1.3 mg/dL one year ago, now 2.2 mg/dL). He refused a renal biopsy one year ago but now is willing to have the procedure. What is true regarding his risk of complication?

A. His risk is the same now as it was one year ago
B. His risk is lower now than one year ago
C. His risk is higher than it was one year ago
D. His risk is dependent on his biopsy diagnosis
E. His risk is dependent on the degree of proteinuria

Answer: C

Patients with reduced GFR have higher rates of complication, both in the acute and chronic setting. Patients with CKD more commonly have azotemia, anemia, and bleeding diathesis as shown by the template bleeding time, but in the studies using multivariate analysis of risk factors, patients with a S [Cr] of 2.0−3.5 mg/dL are 2−5 times more likely to experience a complication. Cause of CKD and degree of proteinuria have not been linked to complications. Thus, C is the correct answer.[48,97,103,120,137]

Question 3

A percutaneous renal biopsy is considered in all the cases below EXCEPT:

A. A 32-year-old woman with recent diagnosis of SLE and hematuria
B. A 60-year-old man with 20-year history of diabetes, CKD with rapidly progressive diminution in renal function, 10 g/24 h proteinuria, and new onset hematuria
C. A 50-year-old man with sudden onset nephrotic syndrome and normal renal function
D. A 45-year-old IV drug abuser with history of HIV infection and rapidly rising S[Cr]
E. A 70-year-old Chinese male with microscopic hematuria, no proteinuria and normal renal function

Answer: E

Renal biopsy is often deferred in patients with isolated glomerular hematuria in the absence of proteinuria or renal insufficiency as the etiology is often due to IgA nephropathy or a hereditary form of nephritis such as Alport's or thin basement membrane disease, all of which have good prognoses. In a 70-year-old Chinese man who is more likely to have IgA nephropathy, conservative management without undergoing a renal biopsy is acceptable.[16,17]

Question 4

A 65-year-old woman presents for evaluation of proteinuria of 6 g/24 h and normal renal function. As part of the initial serologic workup, a serum PLA2R antibody was ordered. Results are positive. Which one of the following statements is correct?

A. A renal biopsy is not indicated as the positive serum PLA2R is an indication of primary membranous nephropathy
B. A renal biopsy is indicated as there are cases of membranous nephropathy secondary to malignancy in patients with positive serum PLA2R
C. Serum PLA2R levels do not correlate with response to therapy in primary membranous nephropathy
D. Japanese patients with positive PLA2R have a much higher finding of primary membranous nephropathy on the renal biopsy
E. A renal biopsy is indicated to determine alternative diagnoses as serum PLA2R antibodies are also found in primary focal segmental glomerular sclerosis

Answer: B

Serum anti-PLA2R has been recognized as a good biomarker for primary membranous nephropathy. However, positivity has been reported in patients with membranous nephropathy secondary to malignancy, autoimmune diseases, Hepatitis B virus infection, and other inflammatory diseases. As such, a renal biopsy is still indicated to establish a histologic diagnosis and remains an integral component of the evaluation of nephrotic syndrome despite seropositivity of PLA2R. Serum levels of PLA2R correlate with response to therapy, where a reduction in proteinuria is seen after decrease in serum PLA2R levels. Japanese patients with primary membranous nephropathy have a lower rate of anti-PLA2R positivity.[28–34]

Question 5

A patient is referred to you for evaluation of AKI and microscopic hematuria. It is determined that the patient requires a kidney biopsy. A renal ultrasound is done but demonstrates poor visualization of the kidneys due to the patient's obese body habitus. Thus, a CT-guided kidney biopsy is recommended. Which of the following is the *best true* statement?

A. A kidney biopsy is contraindicated and thus empiric treatment should be initiated
B. An ORB is the preferred alternative in this patient
C. The CT-guided approach represents a safe and viable alternative to obtain tissue in this patient
D. The CT-guided approach has a much higher complication rate when compared to the ultrasound-guided technique
E. The CT-guided approach results in insufficient tissue for a diagnosis compared to the ultrasound-guided technique

Answer: C

The CT-guided technique has been shown to be a safe alternative to the ultrasound-guided approach with low complication rates. CT-guided approaches provide adequate tissue for a diagnosis (thus choices D and E are incorrect). The CT route is typically pursued in patients with complex anatomies (such as horseshoe kidney), obese patients, as well as in patients with CKD with smaller, echogenic kidneys. The ORB represents an alternative to obtain tissue, but would not be the preferred route given the unnecessary risk of general anesthesia in this setting (B is incorrect). Obesity is not an absolute contraindication to a kidney biopsy (Choice A is incorrect).[9,66,104]

Question 6

Which of the following patients would be the best candidate for a PRB?

A. A patient with a history of von Willebrand disease presenting with nephrotic syndrome
B. A patient with a history of chronic cellulitis presenting for evaluation of proteinuria; the patient's cellulitis involves the bilateral flank regions
C. A patient with new AKI and hematuria. Patient's BP is 220/120 mm Hg
D. An elderly patient (age 84) presenting with unexplained AKI and hematuria
E. An uncooperative patient with new onset of HTN, AKI, and hematuria

Answer: D

Patients with uncontrolled bleeding diathesis or uncontrolled severe hypertension are at higher risk for complications, and thus the procedure is generally avoided until the modifiable diseases can be managed. Percutaneous biopsies in solitary native kidneys have been performed safely in a small subset of series but are relatively contraindicated due to the possibility of having to perform a nephrectomy if complications develop. An uncooperative patient is also not the best candidate due to the potential for complication or movement during the procedure. Therefore, Choices A, C, and E are incorrect. Patients with evidence of infection overlying the area of the potential biopsy site are also not good candidates for the percutaneous route as the needle may need to traverse the infected area (Choice B is incorrect). Age alone is not a restriction to the percutaneous renal biopsy.[8,70]

CHAPTER

74

Pregnancy and Kidney Disease

Sharon E. Maynard[a], *Ravi Thadhani*[b,c]

[a]University of South Florida Morsani College of Medicine, Lehigh Valley Health Network, Allentown, PA, United States; [b]Cedars-Sinai Medical Center, Los Angeles, CA, United States; [c]Harvard Medical School, Boston, MA, United States

Abstract

Chronic kidney disease (CKD) affects almost 4% of women of childbearing age. In women with early stage CKD (serum creatinine concentration [S[Cr]] less than 1.4 mg/dL) and well-controlled blood pressure, the likelihood of successful pregnancy is high and of pregnancy-associated deterioration in kidney function is low. Nevertheless, CKD is associated with several adverse maternal and neonatal outcomes, including preeclampsia, intrauterine growth restriction, and preterm delivery. Pregnancy in more advanced CKD (S[Cr] > 2.0 mg/dL) can result in an accelerated and often irreversible decline in renal function. CKD can present *de novo* during pregnancy. Management and outcomes must be individualized based on the severity, etiology, and gestational age at presentation. Medical management of kidney disease and its complications during pregnancy is affected by the impact of therapy on the developing fetus. This chapter reviews the evaluation and management of pregnant women with CKD.

PHYSIOLOGY AND PATHOPHYSIOLOGY

Important changes in renal physiology occur in pregnancy. Glomerular filtration rate (GFR) increases by 40–65%, due primarily to a large increase in renal blood flow.[1] This pregnancy-induced increase in renal plasma flow and GFR is mediated by a variety of hormones, including relaxin, which is secreted by the corpus luteum, placenta, and decidua.[2] Creatinine clearance also increases in pregnancy in women with CKD.[3] The plasma volume expands by 30–50%,[4] resulting in hemodilution. As a result, the normal serum creatinine concentration (S[Cr]) in pregnancy is 0.4–0.7 mg/dL,[5] approximately 0.4 mg/dL below nonpregnant values. Other blood chemistries are also altered in pregnancy (Table 74.1).[5] Both kidneys increase by 1.0–1.5 cm in length, and kidney volume increases by up to 30%[6] during normal pregnancy. Urinary protein excretion during normal pregnancy rises[7] due to a combination of increased GFR and increased permeability of the glomerular filtration barrier.[8]

Endocrine and hormonal functions of the kidney are also affected by pregnancy. Erythropoietin production increases, resulting in increased RBC mass. Due to an even larger increase in plasma volume, the hemoglobin concentration in healthy pregnancy falls, with a nadir in the second trimester.[9] Blood pressure (BP) falls during normal pregnancy due to generalized vasodilation, mediated by relaxin and vascular resistance to the effects of angiotensin II and other vasoconstrictors.[2,10] There is a physiologic increase in plasma renin activity, angiotensin 2 concentration, and aldosterone concentration, which contribute to plasma volume expansion and the tendency for edema formation.[11]

Fertility is maintained in mild CKD. As CKD progresses, the uremic milieu often results in infertility by CKD stage 5, and spontaneous pregnancies in women on conventional renal replacement therapy are unusual. This may be mediated by hypothalamic anovulation, with absent normal cyclicity of gonadotrophin release.[12] Fertility is typically restored after kidney transplantation.[13]

DIAGNOSIS

Estimating GFR in Pregnancy

Estimation of GFR is important in the diagnosis and management of CKD in pregnancy. CKD affects almost 4% of women of childbearing age.[14] Methods to estimate GFR include creatinine clearance by 24-hour urine collection and estimating equations based on S[Cr] measurement. The 24-hour urine collection for creatinine clearance (24-hour CrCl) is cumbersome and has several limitations, including inaccuracy due to overcollection or incomplete collection. Use of the 24-hour CrCl

https://doi.org/10.1016/B978-0-12-815876-0.00074-7

TABLE 74.1 Normal Ranges of Common Laboratory Results in Pregnancy

	Normal Range (2.5th–97.5th percentile)[5]		
	7–17 weeks of Gestation	17–28 weeks of Gestation	28–38 weeks of Gestation
Sodium (mEq/L)	133.2–140.5	128.9–139.7	128.0–139.8
Potassium (mEq/L)	3.24–4.86	3.27–4.61	3.36–5.00
Chloride (mEq/L)	100–107	98–108	98–108
BUN (mg/dL)	5.80–11.79	4.57–12.16	4.60–10.50
Creatinine (mg/dL)	0.41–0.70	0.37–0.68	0.37–0.66
Calcium (mg/dL)	8.72–10.12	8.24–9.70	8.21–9.60
Magnesium (mg/dL)	1.70–2.34	1.61–2.12	1.53–2.21
Phosphate (mg/dL)	2.63–5.11	2.55–4.52	2.54–4.50
Uric acid (mg/dL)	2.04–5.28	2.45–5.15	2.67–5.70
Albumin (g/dL)	3.22–4.32	2.75–3.58	2.42–3.37
Hemoglobin (g/dL)	>10.6	>10.7	>11.4

requires assessment of the completeness of the collection by comparing measured compared with predicted creatinine excretion. Normal creatinine excretion has not been studied in pregnancy, and it is unknown whether prepregnancy weight or current (lean) body weight should be used to estimate creatinine excretion. A study of pregnant women with hypertensive disorders found 54% of 24-hour urine collections were incomplete, using 15–20 mg/kg/day and prepregnancy weight to estimate creatinine excretion. Inaccurate collections were evenly split between overcollections and incomplete collections.[15]

The MDRD study equation[16] and the CKD-EPI equation[17] are creatinine-based methods that are widely used to estimate GFR. Both equations were derived from patient populations that excluded pregnant women. In pregnancy, the MDRD and CKD-EPI estimating equations underestimate true GFR by 12–40 mL/min/1.73 m^2.[18–20] Based on the lack of validation data, guidelines on the use of the MDRD and CKD-EPI formulas specifically exclude use in pregnant women. Despite its limitations, 24-hour CrCl remains the preferred method for estimating renal function in pregnancy.

Proteinuria in Pregnancy

Because of the physiologic increase in proteinuria during pregnancy, urinary protein excretion is considered pathologic only when >300 mg/day.[21] Even higher levels of proteinuria occur in normal multiple gestation pregnancies.[22]

Routine antepartum care includes dipstick urine protein testing at each prenatal visit. The purpose is detection of urinary tract infection and preeclampsia. Although inexpensive and commonly used, the urinary dipstick has a high false-positive and false-negative rate for proteinuria screening in pregnancy.[23] Thus, positive dipstick testing for proteinuria should always be followed by a quantitative method, such as 24-hour urine collection, or determination of a random urine protein:creatinine ratio (UPCR) or albumin:creatinine ratio (ACR).

As with the 24-hour creatinine clearance, the 24-hour urine protein excretion in pregnant women is frequently inaccurate.[15] The adequacy of collection should be assessed by comparing the observed with expected 24-hour creatinine excretion (15–20 mg/kg prepregnancy body weight). In addition to the high rate of inaccurate and/or incomplete collections, the 24-hour urine collection is cumbersome for ambulatory patients, and the result is not available for at least 24 hours. Hence, there has been longstanding interest in alternative methods to quantify urine protein excretion in pregnancy.

The UPCR measured on a random urine sample has become the preferred method for the quantification of proteinuria in the nonpregnant population due to high accuracy, reproducibility, and convenience. Most studies evaluating the accuracy of the protein:creatinine ratio (PCR) in pregnancy have focused on women with hypertensive pregnancy undergoing evaluation for preeclampsia. A systematic review, which included 2790 women from 15 studies, concluded that a PCR <0.13 mg protein/mg creatinine has good sensitivity (89–90%) for excluding proteinuria (>300 mg/day) in hypertensive pregnancy.[24] There are no data validating the use of the PCR to follow changes in proteinuria in pregnant patients with CKD, but based on

TABLE 74.2 Criteria for Diagnosis of Preeclampsia and Superimposed Preeclampsia

PREECLAMPSIA	
In a woman without preexisting hypertension or proteinuria	Blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation AND the new onset of one or more of the following:
	Proteinuria (any one of the following): ≥300 mg/24 hours (or this amount extrapolated from a timed collection) Protein:creatinine ratio ≥0.3 mg protein/mg creatinine Dipstick proteinuria 1+ or greater (if quantitative methods are unavailable)
	Thrombocytopenia (platelet count <100,000/mcl)
	Renal insufficiency (S[Cr] >1.1 mg/dL or doubling from baseline in the absence of other renal disease)
	Impaired liver function (≥twofold increase in transaminase levels)
	Pulmonary edema
	Cerebral or visual symptoms
SUPERIMPOSED PREECLAMPSIA	
In a woman with chronic hypertension that was previously well controlled	New onset of proteinuria or end-organ dysfunction (see above) after 20 weeks gestation
In a women with proteinuria prior to, or early in, pregnancy	New, worsening, or resistant hypertension or end-organ dysfunction (see above), after 20 weeks gestation

Adapted from report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. Obstet Gynecol *2013;**122**:1122–31.*

strong data supporting its use in the nonpregnant population, we recommend its use in pregnancy for this purpose.

The urine albumin:creatinine ratio (UACR) may be used as an alternative to the UPCR to quantify proteinuria in pregnancy. The ACR may be performed using an automated analyzer, allowing immediate point-of-care testing that could be utilized in an antenatal clinic. An ACR >2.5–8.0 mg/mmol is strongly predictive of proteinuria in high-risk pregnant patients[25] and in women with hypertensive pregnancies.[26] Although more data are needed, the ACR has the potential to supplant the urinary dipstick as a rapid and accurate screening method for proteinuria in routine obstetric care.

When proteinuria is first documented after 20 weeks gestation, preeclampsia is the most likely cause. In women without kidney disease or chronic hypertension, preeclampsia is usually diagnosed by the new onset of hypertension (BP > 140/90 mm Hg) and proteinuria (24-hour urine protein >300 mg, or spot UPCR >0.3 mg/mg) after 20 weeks gestation. Current guidelines from the American College of Obstetrics and Gynecology no longer require proteinuria for the diagnosis of preeclampsia if other severe preeclampsia features are present (Table 74.2). In women with CKD or chronic hypertension, the diagnosis of preeclampsia can be challenging, as diagnostic criteria are less clear-cut.

If preeclampsia has been excluded, diagnostic evaluation of proteinuria proceeds similarly to nonpregnant individuals. In women with mild proteinuria and intact or stable renal function, conservative management is often prudent, with consideration of renal biopsy and/or RAAS blockade after delivery. In patients with nephrotic syndrome or rapid loss of renal function, particularly early in pregnancy, renal biopsy should be considered. A multicenter cohort study of 173 women who underwent kidney biopsy during pregnancy or during the first postpartum year reported the most common diagnoses were focal segmental glomerulosclerosis (FSGS), lupus nephritis, IgA nephropathy, interstitial nephritis, membranous nephropathy (MN), and minimal change disease.[27]

MANAGEMENT

Counseling

Ideally, women with CKD who are considering pregnancy should be counseled regarding pregnancy and renal risks prior to conception. Careful attention to timing of pregnancy and transition to medications that are safe in pregnancy are important preparatory steps that maximize the likelihood of a healthy, successful pregnancy. Counseling women with CKD who are pregnant or considering pregnancy should include education regarding potential adverse pregnancy outcomes, the impact of pregnancy on kidney disease and overall maternal health, and interventions and monitoring to

TABLE 74.3 Risk of Adverse Pregnancy Outcomes in Chronic Kidney Disease

	Preeclampsia	Preterm Birth (<37 weeks)	Extremely Preterm Birth (<34 weeks)	SGA[a]	Perinatal Mortality
Normal renal function	3–5%	5–10%	1.5%	10.5%	0.1%
CKD1-2[30,58,124]	14–22%	13–40%	13–15%	13–25%	1%
CKD3-5[29–31]	40–60%	59–90%	50–55%	37–65%	4–7%
Diabetic microalbuminuria[125,126]	40–42%	62%	13%	4%	n/a
Diabetic nephropathy (>300 mg/day proteinuria)[41,127]	41–65%	22–60%	n/a	25–50%	5%
Lupus nephritis[81,90]	23%	31–48%	n/a	24–28%	6–11.3%
IgA nephropathy[99,100]	9%[c]	8.4–10%	n/a	14–25%[b]	3%
Kidney transplant recipients	27%	45.6%	n/a	n/a	2.5%

[a]*SGA, Small for gestational age defined as birthweight below the 10th percentile.*
[b]*Low birthweight (<2500 g).*
[c]*severe preeclampsia.*

minimize these risks and maximize the probability of a good pregnancy outcome.

CKD confers an increased risk of preeclampsia, preterm birth, cesarean section, small for gestational age (SGA) infant, and perinatal mortality (Table 74.3). Women with CKD are at increased risk for adverse pregnancy outcomes even when renal function is normal (stage 1 CKD due to isolated proteinuria, microscopic hematuria, or congenital urinary tract abnormalities).[28] However, risks are highest with more advanced CKD,[29] hypertension, or urinary protein excretion greater than 1 g/day.[30–32] Among women with chronic hypertension, the presence and severity of proteinura is correlated with adverse perinatal outcomes.[33]

Most pregnancies in women with CKD result in live births. However, more than half are preterm, with associated neonatal morbidity.[30] Notably, preterm offspring have an increased risk of hypertension and CKD later in life.[34] Although late preterm infants (delivery between 34 and 37 weeks gestation) usually do well with appropriate neonatal care, they still have a sixfold increase in neonatal death and fourfold increase in infant death in the first year after delivery.[35]

Women who enter pregnancy with mild CKD, absent or well-controlled hypertension, and mild or absent proteinuria have a low risk for pregnancy-associated loss of renal function.[32,36] In women with advanced CKD, pregnancy may lead to an accelerated decline in renal function.[31] Physicians should anticipate increased proteinuria during gestation, which must be distinguished from superimposed preeclampsia.

The physiologic increase in GFR characteristic of normal pregnancy is attenuated in CKD, and absent in women with severe renal dysfunction.[37] Hyperfiltration of remaining intact nephrons may exacerbate renal damage in this setting. Indeed, women who enter pregnancy with S[Cr] greater than 2.0 mg/dL have a high likelihood (>30%) for accelerated decline in renal function, with progression to end-stage renal disease (ESRD) within 1 year postpartum.[29] For women with moderate CKD prior to pregnancy (S[Cr] 1.4–2.0 mg/dL), the risk for rapid progression to ESRD is lower (2%), but loss of renal function is still observed in 30–40% of cases. Whether this loss of function is accelerated by pregnancy remains uncertain. Imbasciati et al. studied renal function in 49 pregnant women with CKD stage 3–5. They found no difference in the rate of estimated glomerular filtration rate (eGFR) decline before, during, or after pregnancy.[31] However, a pregnancy-associated acceleration in the rate of eGFR loss was observed in the subgroup with both prepregnancy eGFR <40 mL/min/1.73 m^2 and proteinuria greater than 1 g/day.[31]

Risks of adverse pregnancy outcomes are lowest when women with CKD enter pregnancy with well-controlled BP, minimal proteinuria, and stable renal function. For women with glomerular disease, pregnancy outcomes are better when the renal disease is stable or in remission on medications that are safe in pregnancy.

KDIGO (Kidney Disease: Improving Global Outcomes) and NICE (the National Institute for Health and Care Excellence) guidelines recommend that women with CKD without proteinuria achieve stable BP less than 140/90 mm Hg prior to conception. For women with proteinuria (ACR >70 mg/mmol per NICE, ACR >30 mg/mmol per KDIGO) or diabetes, a

TABLE 74.4 Treatment of Hypertension in Pregnancy

	Advantages	Disadvantages/Side Effects
FIRST-LINE AGENTS		
Nifedipine (PO)	Extended release formulation/once-daily dosing	Edema, headache
Labetalol (PO or IV)	Theoretical benefit of α-blockade on placental blood flow	May exacerbate reactive airway disease
Methyldopa (PO)	Extensive safety data	Fatigue, sedation, poor efficacy, short duration of action
SECOND-LINE AGENTS		
Verapamil, Diltiazem		Limited safety data
Metoprolol (PO or IV)	Extended release formulation/once-daily dosing	Limited safety data
Hydralazine (PO or IV)	Extensive clinical experience	Maternal tachycardia, delayed maternal hypotension
Nicardipine (IV)	Extensive clinical experience as tocolytic	Requires intravenous administration in a monitored setting
AVOIDED		
Thiazide, loop diuretics	No known adverse fetal effects	May interfere with physiologic increase in maternal plasma volume
Spironolactone	Effective in primary aldosteronism	Theoretical risk of feminization of male fetuses
Atenolol		Associated with fetal growth restriction
Nitroprusside (IV)	Rapidly effective for short-term use if other agents fail or are contraindicated.	Risk of cyanide poisoning to fetus
CONTRAINDICATED		
ACE inhibitors	May be safe in the early first trimester	Multiple fetal defects with second and third trimester exposure
Angiotensin receptor antagonists	Similar to ACEI	Simiar to ACEI

IV, intravenous; *PO*, by mouth.

lower BP target of <130/80 mm Hg is recommended. Medications should be reviewed to ensure they are safe in pregnancy, including avoidance of ACE inhibitors and angiotensin receptor antagonists (ACEIs/ARBs) in most cases (Table 74.4).

Prevention of Preeclampsia

Low-dose aspirin (ASA) reduces preeclampsia risk, with the greatest benefit in high-risk women. For example, a 2017 randomized controlled trial of 1776 women with singleton pregnancies at high risk for preeclampsia showed 150 mg ASA daily started before 14 weeks gestation reduced the risk of preterm preeclampsia from 4.3% in the placebo group to 1.6% in the aspirin group ($p = 0.004$).[38] However, the authors did not report whether patients with CKD were included in the study population. Similarly, a 2018 meta-analysis of trials of aspirin in average-risk pregnancies showed that when ASA is initiated prior to 16 weeks gestation at a dose of at least 100 mg daily, the risk of preterm preeclampsia was reduced by almost 80% (relative risk, 0.33; 95% confidence interval, 0.19–0.57).[39] Hence, low-dose ASA is recommended in women at high risk for preeclampsia—a category that includes women with CKD and chronic hypertension—by several national and international organizations, including the US Preventive Services Task Force, the American College of Obstetrics and Gynecology, NICE, the World Health Organization, and the American Heart Association.

Calcium supplementation reduces preeclampsia risk in women with low baseline dietary calcium intake.[40] A benefit in women with adequate dietary calcium intake has not been demonstrated. Therefore, oral calcium supplementation (1–2 g/day) is recommended in women with dietary calcium intake less than the recommended daily allowance of 1000 mg/day.

Available data do not support the use of anticoagulation, vitamin C, vitamin E, vitamin D, folate, diuretics, or antihypertensive medications for the prevention of preeclampsia.

Hypertension

Hypertension is associated with adverse maternal and neonatal outcomes among women with CKD,[30] so hypertension control prior to conception is recommended.[41] BP usually falls in early pregnancy, sometimes allowing medications to be reduced or discontinued. BP rises again toward term, frequently requiring uptitration of antihypertensive medications.

BP treatment targets in women with hypertension in pregnancy are controversial. A 2015 randomized trial comparing intensive (DBP target 90 mm Hg) vs. less-tight (DBP target 100 mm Hg) BP control in 987 women with chronic or gestational hypertension showed no difference in preeclampsia or neonatal outcomes.[42] However, women in the intensive control group had a lower rate of several maternal complications, including severe hypertension (BP > 160/110 mm Hg), thrombocytopenia, and elevated liver function tests. For pregnant women with CKD and diabetes mellitus, KDOQI (Kidney Disease Outcomes Quality Initiative) recommends pharmacologic treatment when BP is greater than 140/90 mm Hg.[41]

Preferred medications for treatment of hypertension in pregnancy include long-acting nifedipine, labetalol, and methyldopa (Table 74.4). Severe hypertension (systolic BP >160 mm Hg or diastolic BP >110 mm Hg) requires urgent treatment, often in a monitored setting. Oral nifedipine, intravenous nicardipine, and oral and intravenous labetalol are safe and effective for rapid BP lowering in this setting.[43] Nicardipine is a tocolytic and should not be used during labor.

ACEIs/ARBs are contraindicated in the second and third trimesters of pregnancy. Exposure during this time leads to major fetal malformations including renal dysgenesis, perinatal renal failure, oligohydramnios, pulmonary hypoplasia, hypocalvaria, and intrauterine growth restriction.[44,45] Evidence for teratogenicity with first trimester exposure is less compelling. In a large population-based study, Cooper et al. reported congenital malformations of the central nervous and cardiovascular systems were higher among women with first-trimester exposure to ACEIs.[46] However, this study has been criticized for the presence of potential confounders and ascertainment bias. Subsequent studies have failed to confirm evidence of teratogenicity with first-trimester ACEI exposure when controlling for potential confounders.[47] Women with a compelling indication for ACEIs/ARBs (such as diabetic nephropathy) can probably continue these agents while attempting conception, with discontinuation as soon as pregnancy is diagnosed. However, risks and benefits of this strategy should be discussed with the patient, with shared and individualized decision-making. Women inadvertently exposed in early pregnancy can be reassured by a normal mid-trimester ultrasound examination.

Atenolol has been linked to decreased placental perfusion and subsequent fetal growth restriction.[48] Therefore, pure beta-agonists are generally avoided in pregnancy. Although thiazide diuretics are not typically initiated during pregnancy, some have supported their continuation in women on stable doses prior to pregnancy.[49] Spironolactone is avoided in pregnancy due to the potential for ambiguous genitalia in male infants.[50] There are case reports of the successful use of eplerenone, which has fewer antiandrogenic effects, in patients with primary aldosteronism and Gitelman's syndrome during pregnancy.[51]

Edema

Edema is common in the third trimester of pregnancy. Women entering pregnancy with proteinuric CKD can develop severe edema as pregnancy progresses, affecting functional status and quality of life. Worsening edema after 20 weeks gestation should always prompt consideration of superimposed preeclampsia, especially when accompanied by high or worsening BP, increasing proteinuria, or other symptoms of severe preeclampsia (Table 74.2). Diuretics are contraindicated in preeclampsia, where there is already contraction of the intravascular volume.

Initial management of edema should include conservative measures, such as low sodium diet, compression stockings, and elevation of the legs. Diuretics are avoided unless symptoms are severe, due to theoretical interference with the normal pregnancy-associated increase in plasma volume. Although safety data are limited, loop and thiazide diuretics do not appear to cause fetal harm[52] and may be used cautiously to manage severe edema in pregnancy. The amniotic fluid index should be monitored, and diuretics stopped if oligohydramnios develops.

Anemia

There is a physiologic fall in hemoglobin concentration during pregnancy (Table 74.1). Iron requirements increase due to fetal demands. Iron deficiency is common and should be treated using oral or intravenous iron supplementation. Intravenous iron is safe and widely used when oral iron is ineffective or not tolerated. Women with advanced CKD, and especially ESRD, may require treatment with erythropoietin. Recombinant erythropoietin does not appear to cross the

placenta and is safe in pregnancy.[53] Increased doses are often required to maintain hemoglobin levels within the target range (Hb 10–11 g/dL).[54]

Secondary Hyperparathyroidism

Adequate vitamin D levels are important in pregnancy for fetal skeletal mineralization and growth.[55] In normal pregnancy, maternal 1,25-dihydroxyvitamin D increases substantially. In CKD, it is reasonable to measure and replace 25-hydroxyvitamin D if low, and to administer active vitamin D (i.e. calcitriol) if PTH remains elevated despite adequate 25-hydroxyvitamin D stores. There are inadequate safety data to support the use of vitamin D analogs (i.e. paracalcitol) in pregnancy. Calcium-containing phosphate binders are probably safe but may reduce absorption of some vitamins. Sevelamer has been associated with irregular ossification of fetal bones in animal studies and should be avoided in pregnancy. There is inadequate safety data regarding the use of cinacalcet in pregnancy.

Venous Thromboembolism

Pregnancy is a prothrombotic state, and women with nephrotic syndrome in pregnancy are at particularly high risk for thromboembolic complications. Prophylactic anticoagulation should be considered in women with nephrotic-range proteinuria in pregnancy, particularly in the setting of severe hypoalbuminemia, MN, the presence of anticardiolipin antibodies, or prescribed bed rest. Warfarin crosses the placenta and is associated with a high rate of fetal loss.[56] Heparin (including low-molecular weight heparin) does not cross the placenta and is considered safe.

Superimposed Preeclampsia

Preeclampsia is a pregnancy-specific disorder of hypertension, proteinuria, and thrombotic microangiopathy, which affects 3–5% of all pregnancies.[57] Women with CKD are at increased risk for preeclampsia, with an overall preeclampsia rate of 14–33%.[58] For women with advanced CKD (S[Cr] > 2.5 mg/dL), the risk of preeclampsia is over 40%.[29] Complications can include seizures (eclampsia), cerebral hemorrhage, liver failure, acute renal failure, pulmonary edema, and maternal death. Neonatal complications include intrauterine growth restriction and consequences of preterm delivery, which is often necessary when the maternal status is deteriorating.

Distinguishing superimposed preeclampsia from exacerbation of (or *de novo*) underlying kidney disease can be challenging. Standard diagnostic criteria for preeclampsia—which include the new onset of hypertension and proteinuria after 20 weeks gestation—often cannot be applied, and diagnosis rests on astute clinical judgment and close evaluation of BP and proteinuria trends throughout gestation. In women with preexisting proteinuria, the diagnosis of superimposed preeclampsia is suggested by new, worsening, or resistant hypertension after 20 weeks gestation, with or without severe preeclampsia features (Table 74.2).

Women with CKD should have proteinuria quantified frequently throughout gestation, using UPCR, ACR, or 24-hour urine protein measurement. Increasing proteinuria in the context of worsening hypertension can signify preeclampsia. Uterine artery Doppler flow may be useful in distinguishing CKD and preeclampsia among pregnant women with proteinuria and hypertension.[59] Alterations in maternal serum levels of angiogenic biomarkers, such as placental growth factor and soluble fms-like tyrosine kinase-1, may distinguish preeclampsia from CKD in pregnancy.[60] Further studies are needed before angiogenic biomarkers can be recommended for routine clinical practice, and angiogenic markers are not yet approved by the US Food and Drug Administration (FDA) for use in pregnancy.

Treatment of preeclampsia is supportive and ultimately requires delivery, particularly when there is clinical deterioration of the mother or fetus. When preeclampsia is diagnosed, urgent consultation with an obstetrician is imperative. Mild preeclampsia remote from term can sometimes be managed with bed rest, antihypertensive medication, and close maternal and fetal monitoring.[61] However, progression to severe preeclampsia over days to weeks is typical, requiring hospitalization, intensive fetal monitoring, antihypertensive medication, intravenous magnesium sulfate, and—if preterm—antenatal corticosteroids to accelerate fetal lung maturity. Delivery remains the only definitive treatment and should be undertaken immediately with women who develop even mild preeclampsia at or near term.[62]

Dialysis

Pregnant patients with advanced CKD may require dialysis initiation during pregnancy if progressive loss of kidney function occurs. Women who initiate dialysis after conception have relatively high live birth rates, compared to women who are already on dialysis at the time of conception (91% vs. 63%).[63] This difference may be attributable to the effect of residual renal function. Although there are no data to guide timing of dialysis initiation at a specific GFR or BUN threshold, dialysis should probably be started well before uremic symptoms develop. According to the Toronto experience, pregnant women with ESRD requiring dialysis who received intensive dialysis (6–8 hours, 6–7 times

per week, totaling >36 hours/week) had markedly better pregnancy outcomes compared to women from an American registry who received conventional dialysis (<20 hours per week). Women from the Canadian cohort had a higher live birth rate (86.4% vs. 61.4%, $p = 0.03$) and higher median gestational age at delivery (36 weeks vs. 27 weeks, $p = 0.002$).[64] A meta-analysis that included 681 pregnancies in women with ESRD confirmed that rates of preterm birth and SGA are lower with greater dialysis intensity.[65] To achieve >35 hours/week of dialysis, most pregnant women will require nocturnal and/or home hemodialysis. Late in gestation, dialysis may be performed in a hospital setting with continuous fetal monitoring. Peritoneal dialysis is usually avoided in pregnancy, with some data suggesting an increased incidence of SGA infants as compared with hemodialysis[65]

DISEASE-SPECIFIC CONSIDERATIONS

Diabetic Nephropathy

Women with diabetes in pregnancy are at increased risk for preeclampsia, macrosomia, and preterm birth. Women with diabetic nephropathy (proteinuria >300 mg/24 hour) are at highest risk, with very high rates of preterm delivery (34–60%) and SGA infants (25–50%).[66,67] Table 74.3 outlines the incidence of several adverse pregnancy outcomes among women with diabetic albuminuria and nephropathy. Although the majority of studies focus on women with type 1 diabetes, pregnancy risks in type 1 and type 2 diabetic nephropathy appear to be similar.[68]

Data are reassuring regarding the impact of pregnancy on progression of diabetic kidney disease. Pregnancy itself does not lead to progression from microalbuminuria to diabetic nephropathy (proteinuria >300 mg/day) or deterioration in renal function in women with diabetic nephropathy,[69] so long as pre-pregnancy renal function is preserved (S[Cr] <1.4 mg/dL).[70] There is a higher likelihood (32–45%) of pregnancy-associated deterioration in renal function in women with moderate or severe renal dysfunction (S[Cr] >1.4 mg/dL) prior to pregnancy,[71] possibly related to the inability to use ACEIs/ARBs in pregnancy.

ACEI/ARB use after the first trimester leads to severe fetal malformations. Because women frequently have their first prenatal visit weeks after pregnancy self-diagnosis, education of diabetic women of childbearing age regarding the teratogenic effects of ACEIs/ARBs is an important provider responsibility. Although preconception use of ACEIs/ARBs is probably safe, women must be educated to discontinue these agents as soon as pregnancy is suspected (i.e. after first missed period or positive pregnancy test).[41] These medications should be resumed immediately postpartum in women with diabetic nephropathy and are safe in breastfeeding.

The American Diabetes Association recommends a target HbA1c of 6–6.5% in most pregnant women.[72] Higher HbA1c before and during pregnancy is associated with several adverse outcomes, including preeclampsia, macrosomia, and fetal malformations.[73–75] Insulin is the preferred agent for management of type 1 and type 2 diabetes mellitus and (when pharmacologic therapy is needed) gestational diabetes mellitus in pregnancy.

Intensive BP control in early pregnancy (target BP <135/85 mm Hg) is associated with lower risk of preterm delivery among women with diabetic nephropathy in uncontrolled studies.[76,77] Hence, it is reasonable to aim for tighter BP control in women with diabetic nephropathy than in women with uncomplicated essential hypertension. Unfortunately, randomized controlled trials are lacking and controversy remains regarding appropriate BP goals in pregnancy. As with all women at high risk for preeclampsia, low-dose aspirin is recommended beginning in the first or early second trimester.[78]

Lupus Nephritis

Systemic lupus erythematosus (SLE) is one of the most common autoimmune diseases in women of childbearing age. Pregnant women with SLE are at increased risk for preterm birth, intrauterine growth restriction, spontaneous abortions, and preeclampsia.[79] A history of lupus nephritis, and especially active lupus nephritis at the time of conception, increases the risk of these complications even further.[79–81] Recent improvements in disease management and perinatal monitoring have improved rates of pregnancy loss and preterm delivery,[82] although outcomes remain suboptimal in developing countries.[83] With careful planning, monitoring, and management, most patients with SLE, particularly those with normal baseline renal function, can have successful pregnancies without serious maternal or fetal complications.[84]

There are conflicting data regarding whether pregnancy itself increases the risk for lupus flare.[85] The likelihood of renal flare during pregnancy is highest when there is evidence of active renal disease (proteinuria greater than 0.5 g/day or active urinary sediment) at the time of conception.[86,87] Predictors of poor obstetric outcomes include previous lupus nephritis, active renal disease at conception, poor renal function at conception, hypertension, and presence of the antiphospholipid syndrome.[85,86,88–90] Proliferative (WHO class III or IV) lupus nephritis carries a higher risk of preeclampsia

and delivery of a low–birthweight infant than mesangial (class II) or membranous (class V) lupus nephritis.[91]

According to guidelines from the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association, pregnancy may be safely planned in stable patients with inactive lupus and no more than minimal proteinuria for at least six months.[92] Women receiving mycophenolic acid or mycophenolate mofetil as maintenance therapy for lupus nephritis should be switched to azathioprine at least 3 months prior to conception.[92] It is recommended that use of biologic agents, such as rituximab, be avoided for at least 4 months prior to conception.[92] Steroids, azathioprine, and hydroxychloroquine are useful in pregnant women with SLE, particularly for the management of extrarenal symptoms.[85] Women receiving these drugs prior to pregnancy should be continued on them during pregnancy, as their withdrawal can precipitate a lupus flare.

The most important intervention to minimize pregnancy-associated risk in women with lupus nephritis is to delay pregnancy until renal disease is in remission on a medication regimen that is safe in pregnancy. If remission cannot be attained, consideration should be given to delaying pregnancy until after renal transplantation. Although steroids can be safely continued during pregnancy, prophylactic steroid therapy does not reduce the risk of a lupus flare during pregnancy.[93] Low-dose aspirin is recommended to reduce preeclampsia risk.[92] Women with the antiphospholipid syndrome and SLE are at particularly high risk for developing thrombosis.[94] Anticoagulation with low-molecular weight heparin should be considered in women with SLE and the antiphospholipid syndrome.[92]

Women with pregnancy in the setting of prior lupus nephritis need careful and close monitoring before, during, and after pregnancy by a multidisciplinary team, including an obstetrician, rheumatologist, and nephrologist.[87] Prenatal care should include frequent monitoring of urinalysis for hematuria, quantification of proteinuria, and regular measurement of renal function and serum complement levels. BP should be closely monitored, particularly after 20 weeks gestation, for detection of preeclampsia.

Lupus nephritis flare and preeclampsia share many clinical features, including hypertension, proteinuria, thrombocytopenia, and renal impairment. Though challenging, accurate diagnosis is critical because treatments for these entities differ.[95] Several clinical clues can suggest the correct diagnosis, and the approach will vary based on gestational age at the time of presentation. For women presenting with worsening proteinuria and hypertension prior to 20 weeks gestation, preeclampsia is very unlikely, and the diagnosis of lupus nephritis should be strongly considered. For women presenting after 37 weeks gestation, consider immediate delivery, with timely renal biopsy postpartum if clinical and serologic features suggest lupus nephritis. Clinical clues suggesting lupus nephritis include hypocomplementemia, increased anti-dsDNA titer, neutropenia, hematuria, active urinary sediment, and the presence of extrarenal lupus symptoms.[52,87] As for nonpregnant individuals, renal biopsy is necessary for definitive diagnosis of lupus nephritis in pregnancy and should precede initiation of immunosuppressive treatment. Although data on the safety of renal biopsy during pregnancy are limited, clinical experience suggests it is safe if undertaken prior to approximately 30 weeks gestation.[96] As gestation progresses, kidney biopsy becomes technically difficult as the gravid uterus precludes usual prone positioning. In these cases, the lateral decubitus or seated position may be used.

Treatment of lupus nephritis in pregnancy is challenging, as conventional induction therapies are contraindicated due to risk of congenital malformations associated with mycophenolate[97] and fetal loss associated with cyclophosphamide.[98] In severe proliferative lupus nephritis early in pregnancy, cyclophosphamide or mycophenolate should be considered despite adverse fetal effects because untreated or inadequately treated severe lupus nephritis may result in both maternal and fetal jeopardy. Maternal counseling regarding the fetal effects of treatment, including the option of pregnancy termination, should be provided in these cases. Calcineurin inhibitors are nonteratogenic and can be used to treat lupus nephritis in pregnancy, with some data to support their efficacy in the nonpregnant population.[92] Tacrolimus may increase the risk of gestational diabetes, and screening with a glucose tolerance test is recommended at 28 weeks or earlier. Rituximab lacks safety data in pregnancy, and it is not recommended for use in pregnancy.[92] Azathioprine, despite assignment to category "D" (evidence for human fetal risk based on human studies) by the FDA, is considered relatively safe in pregnancy and can be used as adjunctive or maintenance therapy in pregnant patients with lupus nephritis.

IgA Nephropathy

Pregnancy-associated risks in patients with IgA nephropathy and other forms of chronic glomerulonephritis appear to parallel the risks for CKD more generally (Table 74.3). Women with IgA nephropathy who enter pregnancy with normal renal function have a low risk of pregnancy-associated deterioration in kidney function.[99] Persistent proteinuria at the time of conception may be associated with more rapid decline in renal function postpartum.[100]

There are no clinical trials to guide the treatment of IgA nephropathy in pregnancy. The same treatment principles used in nonpregnant individuals can generally be applied to pregnant patients, with a few important caveats. RAS inhibitors are contraindicated in pregnancy and should be discontinued at pregnancy diagnosis. Prednisone, azathioprine, tacrolimus, and cyclosporine can be safely used in pregnancy.

IgA nephropathy sometimes presents during pregnancy, possibly because screening urinalysis is routinely performed. When renal function is stable, kidney biopsy can usually be safely deferred until after delivery.

Focal Segmental Glomerulosclerosis

FSGS is the most common cause of kidney disease diagnosed by kidney biopsy during or within 1 year of pregnancy.[27] Nevertheless, published literature on treatment and pregnancy outcomes among women with FSGS in pregnancy is very limited. The rate of eGFR decline and need for RRT was not different when comparing 31 women with FSGS diagnosed during or within 1 year of pregnancy, to control women of childbearing age.[27] Glucocorticoids are first-line when treatment is necessary. Risks include development of gestational diabetes mellitus. *De novo* diagnosis of FSGS has been described after preeclampsia, and it has been suggested that podocyte damage in preeclampsia may contribute to the pathogenesis of FSGS in these cases.[101,102]

Membranous Nephropathy

There are few case reports and no large clinical studies of MN in pregnancy. Early reports suggested women with MN have a lower rate of fetal loss than women with other forms of glomerulonephritis. Treatment is generally supportive; ACEIs/ARBs are contraindicated. Standard first-line agents for MN (chlorambucil, cyclophosphamide) should be avoided during pregnancy. There are minimal data on potential fetal effects of rituximab, and it should be avoided in pregnancy.

Polycystic Kidney Disease

In most women with autosomal dominant polycystic kidney disease (ADPKD), renal function usually remains intact until after completion of childbearing, and pregnancy outcomes are generally favorable. Chapman and colleagues compared pregnancy outcomes in 485 women with ADPKD and 205 unaffected family members.[103] Most ADPKD subjects had S[Cr] $\leq$1.2 mg/dL before pregnancy. Women with ADPKD were more likely to experience preeclampsia (11% vs. 4% of controls) and new or worsening hypertension (23% vs. 7% of controls), but there were no significant differences in adverse fetal or neonatal outcomes. Subsequent studies have reported similar results.[104] Prepregnancy hypertension is an important risk factor for maternal complications.

Screening for intracranial aneurysms by magnetic resonance angiography, if indicated by a family history of cerebral aneurysm or intracranial hemorrhage, should be performed prior to term. If an aneurysm is detected, labor should be avoided and Cesarean section planned because pushing during labor can result in aneurysm rupture.[105]

Genetic counseling is an important component of pregnancy care in women with polycystic kidney disease, ideally prior to conception. Offspring of individuals with ADPKD have a 50% chance of having the disease. Prenatal genetic diagnosis is available for both ADPKD and autosomal recessive PKD, particularly when the specific genetic mutation has been identified in a proband.[106] Preimplantation genetic diagnosis is an option among couples receiving *in vitro* fertilization and other assisted reproductive technologies.[107]

Alport Syndrome

Of women with X-linked Alport syndrome (AS), 15–30% may develop renal failure and hearing loss, and autosomal recessive AS affects men and women equally. The literature on AS in pregnancy is largely limited to case reports, and little is known about pregnancy risks. A case series of seven pregnancies in six women with AS reported a high incidence of low birthweight and worsening proteinuria, especially among those with proteinuria prior to pregnancy.[108]

As with ADPKD, genetic counseling is an important component of pregnancy management. For pregnant female carriers of X-linked AS, male fetuses have a 50% chance of being affected, and female fetuses have a 50% risk of being carriers. For pregnant women whose partner has X-linked AS, male fetuses will not be affected, whereas female fetuses have a 100% chance of being carriers.

Kidney Transplant Recipients

Pregnancy outcomes are generally favorable in kidney transplant recipients, compared to women with ESRD on dialysis or with advanced CKD. For this reason, women with advanced CKD who desire pregnancy are sometimes advised to wait until after kidney transplantation. Nevertheless, transplant recipients are at risk for adverse pregnancy outcomes, including preeclampsia, preterm birth, intrauterine growth restriction, cesarean section, and perinatal mortality.[109–111]

The risk of preterm delivery is highest when the eGFR is <90 mL/min/1.72 m^2, or if hypertension is present.[112]

Women are usually advised to wait at least 12 months after kidney transplantation before pursuing pregnancy, because the early posttransplant period has a higher risk of acute rejection and requires more intensive immunosuppression. A 2011 systematic review and meta-analysis that included data from 4706 pregnancies in 3570 kidney transplant recipients found a higher risk of obstetric complications in women with a shorter interval between transplant and pregnancy.[109] Because kidney transplantation rapidly restores fertility in women with ESRD and advanced CKD, patients should be counseled on the importance of using appropriate contraception until pregnancy is desired and safe. The American Society of Transplantation Consensus Conference suggests transplantation can be safely pursued if all the following conditions are met[113]:

- No rejection in the past year
- Adequate and stable graft function (S[Cr] <1.5 mg/dL)
- No acute infections are present that may impact the fetus (e.g. CMV, toxoplasmosis)
- Stable maintenance immunosuppression is present

Maintenance immunosuppression usually includes a calcineurin inhibitor, azathioprine, and/or glucocorticoids (e.g. prednisone). Cyclosporine and tacrolimus are both safe in pregnancy, though increased metabolism often requires an increase in dosage, requiring frequent therapeutic monitoring.[114] Mycophenolate and rapamycin are teratogenic and should be stopped at least 6 weeks prior to conception.[115] There are few data on the safety of antithymocyte globulin, alemtuzumab, belatacept, bortezomib, and eculizumab in pregnancy, so these agents are generally avoided.

The indications for transplant kidney biopsy in pregnancy are similar to those in nonpregnant individuals. Worsening graft function during pregnancy should generally be evaluated by kidney biopsy, which is generally well-tolerated. The incidence of acute rejection in pregnancy is about 4%, similar to that in nonpregnant individuals.[109] High-dose glucocorticoids are the first-line treatment for acute cellular rejection. Intravenous immunoglobulin and therapeutic plasma exchange can be safely used for the treatment of antibody-mediated rejection in pregnancy.

Pregnancy does not appear to have a negative effect on the rate of graft loss. For example, in one Norwegian study, women who had pregnancy after kidney transplantation had a 50% lower risk of graft loss compared to women who did not have a pregnancy after kidney donation.[116]

DRUGS AND LACTATION

Breastfeeding is recommended by the American Academy of Pediatrics and the World Health Organization as the preferred form of infant nutrition during the first 6 months of life. Women should be encouraged to breastfeed whenever feasible, but women receiving medications for CKD should be advised on the safety and appropriateness of medications in breastfeeding. The LactMed database, freely available online at the National Library of Medicine's TOXNET system, is a useful clinical resource that provides updated information from multiple sources (https://toxnet.nlm.nih.gov, accessed 8/30/2018).

Antihypertensive Agents

There are few well-designed studies of the safety of antihypertensive medications in breastfeeding women. In general, agents considered safe during pregnancy are considered safe when breastfeeding. Methyldopa and nifedipine are safe. β-Blockers with high protein binding, such as labetalol and propranolol, are preferred over atenolol and metoprolol, which are concentrated in breast milk. Most diuretics decrease milk production and should be avoided in breastfeeding mothers.[117] Spironolactone is safe.[21,118] Captopril and enalapril are poorly excreted in breast milk and generally considered safe in lactating women.[119] Hence, in women with proteinuric renal disease, reinitiation of ACEIs/ARBs should be considered immediately after delivery. There are presently no data on the safety of angiotensin receptor antagonists in lactation.

Immunosuppressive Agents

Because of lack of definitive data, breastfeeding is generally discouraged in women taking immunosuppressive drugs. Studies on transfer of calcineurin inhibitors to the babies of breastfeeding mothers are inconsistent, with some studies reporting undetectable levels,[120,121] but one reporting infant blood levels in the therapeutic range.[122] There are no reports on adverse neonatal effects with cyclosporine use in breastfeeding. Limited data suggest tacrolimus levels are very low in breast milk. Investigators from the National Transplantation Pregnancy Registry suggest that breastfeeding should not be discouraged in women taking tacrolimus.[123] When cyclosporine or tacrolimus is used in a lactating mother, consideration should be given to monitoring neonatal blood concentrations for potential toxicity. Theoretically, mycophenolic acid should be safe in breastfeeding because the active

metabolite secreted in breast milk, methylmalonic acid, is not bioavailable. Human evidence of safety is lacking, however.

CONCLUSIONS

Pregnancy offers unique challenges in the evaluation and management of women with CKD. The assessment of renal function and proteinuria in pregnancy requires an understanding of the physiologic changes of pregnancy. CKD, even in its early stages, is associated with an increased risk of preeclampsia, preterm birth, and fetal growth restriction. However, women with early stage CKD and well-controlled BP usually have good pregnancy outcomes, with minimal risk of pregnancy-associated deterioration in kidney function. Pregnancy outcomes in kidney transplant recipients are generally favorable, so long as graft function is stable and immunosuppression is adjusted appropriately. Management of CKD and hypertension in pregnancy and the postpartum period requires a recognition of maternal and fetal effects of pharmacologic agents.

References

1. Dunlop W. Serial changes in renal haemodynamics during normal human pregnancy. *Br J Obstet Gynaecol* 1981;**88**(1):1–9.
2. Conrad KP, et al. Role of relaxin in maternal renal vasodilation of pregnancy. *Ann N Y Acad Sci* 2005;**1041**:147–54.
3. Katz AI, et al. Pregnancy in women with kidney disease. *Kidney Int* 1980;**18**(2):192–206.
4. Lund CJ, Donovan JC. Blood volume during pregnancy. Significance of plasma and red cell volumes. *Am J Obstet Gynecol* 1967; **98**(3):394–403.
5. Larsson A, et al. Reference values for clinical chemistry tests during normal pregnancy. *BJOG* 2008:874–81. England.
6. Bailey RR, Rolleston GL. Kidney length and ureteric dilatation in the puerperium. *J Obstet Gynaecol Br Commonw* 1971;**78**(1):55–61.
7. Kattah A, et al. Spot urine protein measurements in normotensive pregnancies, pregnancies with isolated proteinuria and preeclampsia. *Am J Physiol Regul Integr Comp Physiol* 2017;**313**(4): R418–24.
8. Roberts M, Lindheimer MD, Davison JM. Altered glomerular permselectivity to neutral dextrans and heteroporous membrane modeling in human pregnancy. *Am J Physiol* 1996;**270**(2 Pt 2): F338–43.
9. Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 1998;**47**(RR-3):1–29.
10. Gant NF, et al. The nature of pressor responsiveness to angiotensin II in human pregnancy. *Obstet Gynecol* 1974;**43**(6):854.
11. Elsheikh A, et al. The renin-aldosterone system during normal and hypertensive pregnancy. *Arch Gynecol Obstet* 2001;**264**(4): 182–5.
12. Lim VS, et al. Ovarian function in chronic renal failure: evidence suggesting hypothalamic anovulation. *Ann Intern Med* 1980;**93**(1): 21–7.
13. Gill JS, et al. The pregnancy rate and live birth rate in kidney transplant recipients. *Am J Transplant* 2009;**9**(7):1541–9.
14. Coresh J, et al. Prevalence of chronic kidney disease in the United States. *J Am Med Assoc* 2007;**298**(17):2038–47.
15. Cote AM, et al. The 24-hour urine collection: gold standard or historical practice? *Am J Obstet Gynecol* 2008;**199**(6):625. e1–e6.
16. Levey AS, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;**130**(6):461–70.
17. Levey AS, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**(9):604–12.
18. Smith MC, et al. Assessment of glomerular filtration rate during pregnancy using the MDRD formula. *BJOG* 2008;**115**(1): 109–12.
19. Alper AB, et al. Estimation of glomerular filtration rate in preeclamptic patients. *Am J Perinatol* 2007;**24**(10):569–74.
20. Smith MC, Moran P, Davison JM. EPI-CKD is a poor predictor of GFR in pregnancy. *Arch Dis Child Fetal Neonatal Ed* 2011;**96**(Suppl. 1):Fa99. Fa99.
21. Higby K, et al. Normal values of urinary albumin and total protein excretion during pregnancy. *Am J Obstet Gynecol* 1994; **171**(4):984–9.
22. Smith NA, Lyons JG, McElrath TF. Protein:creatinine ratio in uncomplicated twin pregnancy. *Am J Obstet Gynecol* 2010;**203**(4):381. e1–e4.
23. Waugh JJ, et al. Accuracy of urinalysis dipstick techniques in predicting significant proteinuria in pregnancy. *Obstet Gynecol* 2004; **103**(4):769–77.
24. Morris RK, et al. Diagnostic accuracy of spot urinary protein and albumin to creatinine ratios for detection of significant proteinuria or adverse pregnancy outcome in patients with suspected pre-eclampsia: systematic review and meta-analysis. *BMJ* 2012;**345**: e4342.
25. Kyle PM, et al. Comparison of methods to identify significant proteinuria in pregnancy in the outpatient setting. *BJOG* 2008;**115**(4): 523–7.
26. Gangaram R, Naicker M, Moodley J. Comparison of pregnancy outcomes in women with hypertensive disorders of pregnancy using 24-hour urinary protein and urinary microalbumin to creatinine ratio. *Int J Gynaecol Obstet* 2009;**107**(1):19–22.
27. Webster P, et al. A multicenter cohort study of histologic findings and long-term outcomes of kidney disease in women who have been pregnant. *Clin J Am Soc Nephrol* 2017;**12**(3):408–16.
28. Piccoli GB, et al. Risk of adverse pregnancy outcomes in women with CKD. *J Am Soc Nephrol* 2015;**26**(8):2011–22.
29. Jones DC, Hayslett JP. Outcome of pregnancy in women with moderate or severe renal insufficiency. *N Engl J Med* 1996;**335**(4): 226–32.
30. Piccoli GB, et al. Pregnancy and chronic kidney disease: a challenge in all CKD stages. *Clin J Am Soc Nephrol* 2010;**5**(5):844–55.
31. Imbasciati E, et al. Pregnancy in CKD stages 3 to 5: fetal and maternal outcomes. *Am J Kidney Dis* 2007;**49**(6):753–62.
32. Zhang JJ, et al. A systematic review and meta-analysis of outcomes of pregnancy in CKD and CKD outcomes in pregnancy. *Clin J Am Soc Nephrol* 2015;**10**(11):1964–78.
33. Morgan JL, et al. Association of baseline proteinuria and adverse outcomes in pregnant women with treated chronic hypertension. *Obstet Gynecol* 2016;**128**(2):270–6.
34. Abitbol CL, Rodriguez MM. The long-term renal and cardiovascular consequences of prematurity. *Nat Rev Nephrol* 2012;**8**(5): 265–74.
35. Teune MJ, et al. A systematic review of severe morbidity in infants born late preterm. *Am J Obstet Gynecol* 2011;**205**(4):374.e1–9.
36. Jungers P, et al. Influence of pregnancy on the course of primary chronic glomerulonephritis. *Lancet* 1995;**346**(8983):1122–4.
37. Cunningham FG, et al. Chronic renal disease and pregnancy outcome. *Am J Obstet Gynecol* 1990;**163**(2):453–9.

38. Rolnik DL, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med* 2017;**377**(7): 613−22.
39. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. *Am J Obstet Gynecol* 2018;**218**(3):287−293.e1.
40. Hofmeyr GJ, et al. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database Syst Rev* 2014;**6**:CD001059.
41. National Kidney Foundation. KDOQI clinical practice guidelines for diabetes and CKD: 2012 update. *Am J Kidney Dis* 2012;**60**(5): 850−86.
42. Magee LA, et al. Less-tight versus tight control of hypertension in pregnancy. *N Engl J Med* 2015;**372**(5):407−17.
43. Raheem IA, et al. Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial. *BJOG* 2012;**119**(1):78−85.
44. GG B, Freeman RK. *Drugs in Pregnancy and Lactation: a reference guide to fetal and neonatal risk*. 9th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2011.
45. Bullo M, et al. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. *Hypertension* 2012; **60**(2):444−50.
46. Cooper WO, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006;**354**(23): 2443−51.
47. Bateman BT, et al. Angiotensin-converting enzyme inhibitors and the risk of congenital malformations. *Obstet Gynecol* 2017;**129**(1): 174−84.
48. Lydakis C, et al. Atenolol and fetal growth in pregnancies complicated by hypertension. *Am J Hypertens* 1999;**12**(6):541−7.
49. Nielsen LR, et al. Reduced prevalence of early preterm delivery in women with Type 1 diabetes and microalbuminuria–possible effect of early antihypertensive treatment during pregnancy. *Diabet Med* 2006;**23**(4):426−31.
50. Groves TD, Corenblum B. Spironolactone therapy during human pregnancy. *Am J Obstet Gynecol* 1995;**172**(5):1655−6.
51. Cabassi A, et al. Eplerenone use in primary aldosteronism during pregnancy. *Hypertension* 2012;**59**(2):e18−9.
52. Collins R, Yusuf S, Peto R. Overview of randomised trials of diuretics in pregnancy. *Br Med J* 1985;**290**(6461):17−23.
53. Cyganek A, et al. Anemia treatment with erythropoietin in pregnant renal recipients. *Transplant Proc* 2011;**43**(8):2970−2.
54. Hladunewich M, et al. Pregnancy in end stage renal disease. *Semin Dial* 2011;**24**(6):634−9.
55. Marshall I, Mehta R, Petrova A. Vitamin D in the maternal-fetal-neonatal interface: clinical implications and requirements for supplementation. *J Matern Fetal Neonatal Med* 2013;**26**(7):633−8.
56. Basude S, et al. Low-molecular-weight heparin or warfarin for anticoagulation in pregnant women with mechanical heart valves: what are the risks? A retrospective observational study. *BJOG* 2012;**119**(8):1008−13. discussion 1012-3.
57. World Health Organization. *World Health Report: make every mother and child count*. 2005. Geneva.
58. Nevis IF, et al. Pregnancy outcomes in women with chronic kidney disease: a systematic review. *Clin J Am Soc Nephrol* 2011; **6**(11):2587−98.
59. Piccoli GB, et al. Pre-eclampsia or chronic kidney disease? The flow hypothesis. *Nephrol Dial Transplant* 2013;**28**(5):1199−206.
60. Rolfo A, et al. Chronic kidney disease may be differentially diagnosed from preeclampsia by serum biomarkers. *Kidney Int* 2013; **83**(1):177−81.
61. Sibai BM, et al. Aggressive versus expectant management of severe preeclampsia at 28 to 32 weeks' gestation: a randomized controlled trial. *Am J Obstet Gynecol* 1994;**171**(3):818−22.
62. Koopmans CM, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet* 2009;**374**(9694):979−88.
63. Jesudason S, Grace BS, McDonald SP. Pregnancy outcomes according to dialysis commencing before or after conception in women with ESRD. *Clin J Am Soc Nephrol* 2014;**9**(1):143−9.
64. Hladunewich MA, et al. Intensive hemodialysis associates with improved pregnancy outcomes: a Canadian and United States cohort comparison. *J Am Soc Nephrol* 2014;**25**(5):1103−9.
65. Piccoli GB, et al. Pregnancy in dialysis patients in the new millennium: a systematic review and meta-regression analysis correlating dialysis schedules and pregnancy outcomes. *Nephrol Dial Transplant* 2016;**31**(11):1915−34.
66. Vääräsmäki MS, et al. Factors predicting peri- and neonatal outcome in diabetic pregnancy. *Early Hum Dev* 2000;**59**(1):61−70.
67. Biesenbach G, et al. Perinatal complications and three-year follow up of infants of diabetic mothers with diabetic nephropathy stage IV. *Ren Fail* 2000;**22**(5):573−80.
68. Dunne F. Type 2 diabetes and pregnancy. *Semin Fetal Neonatal Med* 2005;**10**(4):333−9.
69. Rossing K, et al. Pregnancy and progression of diabetic nephropathy. *Diabetologia* 2002;**45**(1):36−41.
70. Miodovnik M, et al. Does pregnancy increase the risk for development and progression of diabetic nephropathy? *Am J Obstet Gynecol* 1996;**174**(4):1180−9. discussion 1189-91.
71. Mathiesen ER, et al. Obstetric nephrology: pregnancy in women with diabetic nephropathy–the role of antihypertensive treatment. *Clin J Am Soc Nephrol* 2012;**7**(12):2081−8.
72. Association AD. 13. Management of diabetes in pregnancy. *Diabetes Care* 2018;**41**(Suppl. 1):S137−43.
73. Nielsen GL, et al. Glycosylated hemoglobin as predictor of adverse fetal outcome in type 1 diabetic pregnancies. *Acta Diabetol* 1997;**34**(3):217−22.
74. Hiilesmaa V, Suhonen L, Teramo K. Glycaemic control is associated with pre-eclampsia but not with pregnancy-induced hypertension in women with type I diabetes mellitus. *Diabetologia* 2000;**43**(12):1534−9.
75. Holmes VA, et al. Optimal glycemic control, pre-eclampsia, and gestational hypertension in women with type 1 diabetes in the diabetes and pre-eclampsia intervention trial. *Diabetes Care* 2011; **34**(8):1683−8.
76. Carr DB, et al. Diabetic nephropathy in pregnancy: suboptimal hypertensive control associated with preterm delivery. *Am J Hypertens* 2006;**19**(5):513−9.
77. Nielsen LR, Damm P, Mathiesen ER. Improved pregnancy outcome in type 1 diabetic women with microalbuminuria or diabetic nephropathy: effect of intensified antihypertensive therapy? *Diabetes Care* 2009;**32**(1):38−44.
78. Duley L, et al. Antiplatelet drugs for prevention of pre-eclampsia and its consequences: systematic review. *BMJ* 2001;**322**(7282): 329−33.
79. Wagner SJ, et al. Maternal and foetal outcomes in pregnant patients with active lupus nephritis. *Lupus* 2009;**18**(4):342−7.
80. Gladman DD, et al. The effect of lupus nephritis on pregnancy outcome and fetal and maternal complications. *J Rheumatol* 2010;**37**(4):754−8.
81. Saavedra MA, et al. Impact of previous lupus nephritis on maternal and fetal outcomes during pregnancy. *Clin Rheumatol* 2012;**31**(5):813−9.
82. Clark CA, Spitzer KA, Laskin CA. Decrease in pregnancy loss rates in patients with systemic lupus erythematosus over a 40-year period. *J Rheumatol* 2005;**32**(9):1709−12.
83. Chandran V, Aggarwal A, Misra R. Active disease during pregnancy is associated with poor foetal outcome in Indian patients with systemic lupus erythematosus. *Rheumatol Int* 2005;**26**(2):152−6.

84. Erkan D, Sammaritano L. New insights into pregnancy-related complications in systemic lupus erythematosus. *Curr Rheumatol Rep* 2003;**5**(5):357–63.
85. Bramham K, Soh MC, Nelson-Piercy C. Pregnancy and renal outcomes in lupus nephritis: an update and guide to management. *Lupus* 2012;**21**(12):1271–83.
86. Moroni G, Ponticelli C. Pregnancy after lupus nephritis. *Lupus* 2005;**14**(1):89–94.
87. Stanhope TJ, et al. Obstetric nephrology: lupus and lupus nephritis in pregnancy. *Clin J Am Soc Nephrol* 2012;**7**(12):2089–99.
88. Soubassi L, et al. Pregnancy outcome in women with pre-existing lupus nephritis. *J Obstet Gynaecol* 2004;**24**(6):630–4.
89. Dhar JP, et al. Pregnancy outcomes before and after a diagnosis of systemic lupus erythematosus. *Am J Obstet Gynecol* 2005;**193**(4): 1444–55.
90. Imbasciati E, et al. Pregnancy in women with pre-existing lupus nephritis: predictors of fetal and maternal outcome. *Nephrol Dial Transplant* 2009;**24**(2):519–25.
91. Carmona F, et al. Class III-IV proliferative lupus nephritis and pregnancy: a study of 42 cases. *Am J Reprod Immunol* 2005;**53**(4): 182–8.
92. Bertsias GK, et al. Joint European League against rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Ann Rheum Dis* 2012;**71**(11):1771–82.
93. Khamashta MA, Ruiz-Irastorza G, Hughes GR. Systemic lupus erythematosus flares during pregnancy. *Rheum Dis Clin N Am* 1997; **23**(1):15–30.
94. Ruiz-Irastorza G, Khamashta MA. Management of thrombosis in antiphospholipid syndrome and systemic lupus erythematosus in pregnancy. *Ann N Y Acad Sci* 2005;**1051**:606–12.
95. Williams Jr WW, et al. Case records of the Massachusetts General Hospital. Case 38-2005. A 29-year-old pregnant woman with the nephrotic syndrome and hypertension. *N Engl J Med* 2005; **353**(24):2590–600.
96. Day C, et al. The role of renal biopsy in women with kidney disease identified in pregnancy. *Nephrol Dial Transplant* 2008;**23**(1): 201–6.
97. Hoeltzenbein M, et al. Teratogenicity of mycophenolate confirmed in a prospective study of the European Network of Teratology information Services. *Am J Med Genet* 2012;**158A**(3): 588–96.
98. Østensen M, Förger F. How safe are anti-rheumatic drugs during pregnancy? *Curr Opin Pharmacol* 2013;**13**(3):470–5.
99. Liu Y, et al. A systematic review and meta-analysis of kidney and pregnancy outcomes in IgA nephropathy. *Am J Nephrol* 2016;**44**(3): 187–93.
100. Oh HJ, et al. Reduced pre-pregnancy proteinuria is associated with improving postnatal maternal renal outcomes in IgA nephropathy women. *Clin Nephrol* 2011;**76**(6):447–54.
101. Kwiatkowski S, et al. Development of a focal segmental glomerulosclerosis after pregnancy complicated by preeclampsia: case report and review of literature. *J Matern Fetal Neonatal Med* 2016; **29**(10):1566–9.
102. Shiiki H, et al. Focal and segmental glomerulosclerosis in preeclamptic patients with nephrotic syndrome. *Am J Nephrol* 1990; **10**(3):205–12.
103. Chapman AB, Johnson AM, Gabow PA. Pregnancy outcome and its relationship to progression of renal failure in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 1994;**5**(5): 1178–85.
104. Wu M, et al. Pregnancy outcomes in autosomal dominant polycystic kidney disease: a case-control study. *J Matern Fetal Neonatal Med* 2016;**29**(5):807–12.
105. Rubin SM, Jackson GM, Cohen AW. Management of the pregnant patient with a cerebral venous angioma: a report of two cases. *Obstet Gynecol* 1991;**78**(5 Pt 2):929–31.
106. Vora N, Perrone R, Bianchi DW. Reproductive issues for adults with autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 2008;**51**(2):307–18.
107. Murphy EL, et al. Preimplantation genetic diagnosis counseling in autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 2018;**72**(6):866–72.
108. Brunini F, et al. Alport syndrome and pregnancy: a case series and literature review. *Arch Gynecol Obstet* 2018;**297**(6):1421–31.
109. Deshpande NA, et al. Pregnancy outcomes in kidney transplant recipients: a systematic review and meta-analysis. *Am J Transplant* 2011;**11**(11):2388–404.
110. Coscia LA, et al. Report from the national transplantation pregnancy registry (NTPR): outcomes of pregnancy after transplantation. *Clin Transpl* 2010:65–85.
111. Bramham K, et al. Pregnancy in renal transplant recipients: a UK national cohort study. *Clin J Am Soc Nephrol* 2013;**8**(2):290–8.
112. Piccoli GB, et al. Outcomes of pregnancies after kidney transplantation: lessons learned from CKD. a comparison of transplanted, Nontransplanted chronic kidney disease patients and low-risk pregnancies: a multicenter nationwide analysis. *Transplantation* 2017;**101**(10):2536–44.
113. McKay DB, et al. Reproduction and transplantation: report on the AST Consensus conference on reproductive issues and transplantation. *Am J Transplant* 2005;**5**(7):1592–9.
114. Kim H, et al. The optimal therapy of calcineurin inhibitors for pregnancy in kidney transplantation. *Clin Transplant* 2015;**29**(2): 142–8.
115. Moritz MJ, et al. Mycophenolate and pregnancy: teratology principles and national transplantation pregnancy registry experience. *Am J Transplant* 2017;**17**(2):581–2.
116. Majak GB, et al. The effect of pregnancy on the long-term risk of graft loss, cardiovascular disease and death in kidney transplanted women in Norway: a retrospective cohort study. *Transplantation* 2018;**102**(9):e391–6.
117. Podymow T, August P, Umans JG. Antihypertensive therapy in pregnancy. *Semin Nephrol* 2004;**24**(6):616–25.
118. Phelps DL, Karim A. Spironolactone: relationship between concentrations of dethioacetylated metabolite in human serum and milk. *J Pharm Sci* 1977;**66**(8):1203.
119. Beardmore KS, Morris JM, Gallery ED. Excretion of antihypertensive medication into human breast milk: a systematic review. *Hypertens Pregnancy* 2002;**21**(1):85–95.
120. Danesi R, Del Tacca M. Teratogenesis and immunosuppressive treatment. *Transplant Proc* 2004;**36**(3):705–7.
121. Munoz-Flores-Thiagarajan KD, et al. Breast-feeding by a cyclosporine-treated mother. *Obstet Gynecol* 2001;**97**(5):816–8.
122. Moretti ME, et al. Cyclosporine excretion into breast milk. *Transplantation* 2003;**75**(12):2144–6.
123. Armenti VT, Moritz MJ, Davison JM. Breastfeeding and tacrolimus: is it a reasonable approach? *Expert Rev Clin Immunol* 2013; **9**(7):623–6.
124. Fink JC, et al. Increased risk of adverse maternal and infant outcomes among women with renal disease. *Paediatr Perinat Epidemiol* 1998;**12**(3):277–87.
125. Ekbom P, et al. Pregnancy outcome in type 1 diabetic women with microalbuminuria. *Diabetes Care* 2001;**24**(10):1739–44.
126. Jensen DM, et al. Microalbuminuria, preeclampsia, and preterm delivery in pregnant women with type 1 diabetes: results from a nationwide Danish study. *Diabetes Care* 2010;**33**(1):90–4.
127. Reece EA, Leguizamon G, Homko C. Pregnancy performance and outcomes associated with diabetic nephropathy. *Am J Perinatol* 1998;**15**(7):413–21.

QUESTIONS AND ANSWERS

Question 1

A 25-year-old woman with a history of lupus nephritis and chronic hypertension is evaluated for worsening kidney function. She is currently 32 weeks gestation with a singleton pregnancy. She was diagnosed with class 4 lupus nephritis several years ago. She had received induction therapy with mycophenolate mofetil and was in full remission at the time of conception on azathioprine. Her current medications include nifedipine, labetalol, and azathioprine. Her BP is 150/86 mm Hg, increased from 132/68 mm Hg at her last visit 4 weeks ago. The physical examination is otherwise normal, except for mild lower extremity edema. She denies joint complaints or skin rash. She denies headache, vision changes, or abdominal pain.

Laboratory studies:

S[Cr] 1.0 mg/dL (increased from 0.5 mg/dL 1 month ago)
C3 34 mg/dL (normal 55−120)
C4 8 mg/dL (normal 15−48)
WBC 5900/μL
Hemoglobin 8.8 g/dL
Platelets 76,000/μL
24-hour urine protein excretion 1255 mg/day (increased from 260 mg/day 1 month ago)
Urinalysis 3+ blood, 2+ protein
The urine sediment examination reveals 10−20 RBC/hpf

Which ONE of the following findings MOST favors the diagnosis of relapse of lupus nephritis, rather than severe preeclampsia?

A. Low hemoglobin
B. Thrombocytopenia
C. Proteinuria
D. Hematuria
E. Increasing S[Cr]

Answer: D

Hematuria is a characteristic finding in lupus nephritis but is not typically seen in preeclampsia. An active urinary sediment, with dysmorphic RBCs and/or cellular casts, would further support the diagnosis of lupus nephritis. Anemia, thrombocytopenia, hypertension, worsening renal function, and increasing proteinuria can all be seen in both lupus nephritis flare and in the preeclampsia/HELLP syndrome. The presence of extrarenal lupus symptoms, hypocomplementemia, and a positive anti−double-stranded DNA antibody titer are other clinical clues favoring the diagnosis of lupus nephritis flare.

Question 2

A 36-year-old woman with chronic hypertension and CKD stage 3 (eGFR 55 mL/min/1.73 m^2) presents after a positive pregnancy test. Ultrasound confirms 10 week singleton gestation. Prior to pregnancy she was taking hydrochlorothiazide and lisinopril, which she stopped when she noted her positive pregnancy test. Her BP in the office is 155/95 mm Hg.

Which of the following is the most appropriate agent to treat this patient's hypertension?

A. Labetalol
B. Candesartan
C. Hydrochlorthiazide
D. Atenolol
E. No pharmacologic therapy; repeat visit for BP check in 4 weeks

Answer: A

KDOQI recommends maintaining BP <140/90 mm Hg in pregnant women with CKD. Hence, pharmacologic therapy is indicated in this patient. Labetalol is a safe and appropriate antihypertensive agent for use in pregnancy. Methyldopa and dihydropyridine calcium-channel blockers, such as long-acting nifedipine, are also appropriate for use in pregnancy. ACEIs/ARBs are contraindicated in pregnancy, as they cause birth defects with second and third trimester exposure. Hydrochlorothiazide and other loop and thiazide diuretics are not teratogenic, but can theoretically interfere with the normal plasma volume expansion of pregnancy, and are generally avoided in pregnancy. Atenolol has been associated with impaired fetal growth in some studies. Agents with combined alpha- and beta-blockade, such as labetalol, maintain placental perfusion and are not associated with this adverse effect.

Question 3

A 28-year-old woman with a history of IgA nephropathy presents at 30 weeks gestation with the new onset of edema in her hands and face. Her BP, previously normal, is 168/105 mm Hg. Physical examination shows edema in her upper and lower extremities bilaterally. Two months ago, S[Cr] was 0.8 mg/dL and UPCR was 0.10 mg/mg. Which of the following findings would establish the diagnosis of preeclampsia?

A. Uric acid >8 mg/dL
B. Urine protein excretion >150 mg on a 24-hour urine collection
C. Total bilirubin >2.0 mg/dL.
D. Platelet count <100,000/mm^3
E. Microscopic hematuria

Answer: D

The 2013 ACOG diagnostic criteria for preeclampsia include the new onset of hypertension after 20 weeks gestation and either proteinuria (see below) or another feature of severe preeclampsia. Severe diagnostic features include thrombocytopenia (platelet count $<100{,}000/mm^3$), elevated liver enzymes, acute kidney injury, cerebral symptoms, or visual symptoms. Hence, the new onset of thrombocytopenia, together with the new onset of hypertension, would be considered diagnostic of preeclampsia.

The diagnosis of preeclampsia based on proteinuria requires >300 mg/day on 24-hour collection, PCR > 0.3 mg/mg on a random urine sample, or dipstick urinalysis 1+ or greater if quantitative methods are unavailable. Hyperuricemia is common in preeclampsia but is not reliable for diagnosis. Transaminitis is a diagnostic feature of preeclampsia, but hyperbilirubinemia is not. Microscopic hematuria is not a feature of preeclampsia, and if present would likely be due to this patient's underlying IgA nephropathy.

Question 4

A 32-year-old woman with diabetic nephropathy and hypertension is evaluated 3 months postpartum. During her pregnancy, her ACE-inhibitor was held, and her hypertension was well controlled on 100 mg labetalol twice daily. She reports no headache or blurry vision. On physical examination, her BP is 150/95 mm Hg, and there is no edema. S[Cr] is 1.2 mg/dL, and UPCR is 1.8 mg/mg, unchanged from last measurement. She is currently breastfeeding.

Which one of the following is the MOST appropriate treatment?

A. Start hydrochlorthiazide
B. Increase labetalol dose
C. Start enalapril
D. No medication changes
E. Admit to the hospital for management of postpartum preeclampsia

Answer: C

ACEI are recommended for breastfeeding women with proteinuria and hypertension. Enalapril, captopril, and quinapril are poorly excreted in breast milk and are considered safe. Diuretics, such as hydrochlorthiazide, may decrease breast milk production and are usually avoided in breastfeeding women. Postpartum preeclampsia is an important cause of worsening hypertension between 2 days and 6 weeks postpartum but does not occur this long after delivery.

Question 5

A 37-year-old woman with CKD stage 3 due to vesicoureteral reflux is currently 14 weeks gestation. She had preeclampsia during her last pregnancy 3 years ago. Her only medication is a prenatal vitamin. The BP is 130/80 mm Hg.

Which one of the following is MOST effective to reduce her risk of recurrent preeclampsia?

A. Dietary sodium restriction
B. Vitamin C and E supplementation
C. Labetalol
D. Low-dose aspirin
E. Calcium carbonate

Answer: D

This patient is at high risk for preeclampsia, due to the presence of CKD and prior preeclampsia. Low-dose aspirin reduces the risk of preterm preeclampsia and its complications and is recommended in all high-risk women.

Low-sodium diet, antihypertensive medication, and vitamin C and E do not reduce the risk of preeclampsia. Calcium supplementation (>1 g/day) appears to reduce the risk of severe hypertensive disorders in patients with low baseline dietary calcium intake, but a benefit has not been shown in US populations with a well-balanced Western diet. Hence, calcium supplementation is recommended only if dietary history suggests intake is less than the recommended 1000 mg/day elemental calcium.

CHAPTER

75

Chronic Kidney Disease in Children

Susan L. Furth[a], *Marva Moxey-Mims*[b], *Rebecca Ruebner*[c]

[a]The Children's Hospital of Philadelphia, Philadelphia, PA, United States; [b]Children's National Health System, The George Washington University School of Medicine, Washington, DC, United States; [c]Johns Hopkins University School of Medicine, Baltimore, MD, United States

Abstract

Chronic kidney disease (CKD) in children has unique etiologies compared to adults, with the majority of pediatric CKD caused by congenital anomalies of the kidney and urinary tract (CAKUT). Additional etiologies include primary and secondary glomerular disorders and cystic and hereditary kidney diseases. The natural history of CKD in children is characterized by a steady decline in kidney function over time, although children with CAKUT tend to have a slower decline compared to children with glomerular disorders. Interventions to slow progressive kidney disease in children and diminish CVD risk factors include strict control of blood pressure and correction of anemia, dyslipidemia, and calcium–phosphate balance. When children with CKD progress to ESRD, preemptive transplantation is the preferred method of renal replacement therapy, but HD remains the most common initial therapeutic modality. CKD has a multitude of effects on childhood health including CVD, impaired nutrition and growth, anemia, bone disease, and neurocognitive deficits. Children with CKD have an increased risk of early mortality.

CKD IN CHILDREN

Progressive CKD in children is a devastating illness. Although mortality rates in children treated with dialysis in the US have decreased over the last 20 years, the expected remaining lifetime for children aged less than 14 years with end-stage renal disease (ESRD) in the US is only 21.7 years on dialysis and 57.8 years with a kidney transplant, compared to 72.4 years for the general age-matched population.[1,2] The diagnostic and therapeutic approach to CKD must therefore emphasize early detection and management to slow CKD progression to ESRD and prevent complications.

Although the definition of CKD in adults is generally applicable to children, there are some very specific differences. One important factor is the age of the child. The time frame defining chronicity as greater than 3 months cannot be used for newborns, or infants less than 3 months of age. Additionally, normal glomerular filtration rate (GFR) increases over time in the newborn and infant. Even the normal GFR in infants and young children would qualify as CKD by adult standards (i.e. less than 60 mL/min/1.73 m^2). Alternatively, a normal S[Cr] or eGFR for age may be associated with structural abnormalities, and the diagnosis of CKD may be made on that basis. By 2 years of age, the normal GFR (accounting for body size) in children is comparable to that of adults. There are numerous equations for estimating GFR in children. The most well-known creatinine-based one is the Schwartz formula. This equation has evolved over time to the current recommended bedside formula[3]:

$$\text{eGFR}\left(\frac{\text{mL/min}}{1.73\ \text{m}^2}\right) = 0.413 \times \left(\frac{\text{height}}{\text{S[Cr]}}\right)$$

$$-\ \text{height in cm},\ \frac{\text{S[Cr]in mg}}{\text{dL}}$$

The staging of CKD by GFR described for adults is probably applicable to children older than 2 years,[4] but there is no comparable GFR staging for children under 2 years of age. The most recent KDIGO Guidelines suggest that the latter group has three categories—normal, moderate, or severely reduced GFR—based on the normal range and standard deviations (SD). Those with GFR values >1 SD but <2 SD below the mean would be in the moderately reduced range, whereas those with values >2 SD below the mean would be in the severely reduced range.[5]

The most recent recommendations for the definition of CKD in adults also include albuminuria categories due to the strong association of urinary albumin excretion and prognosis.[5] However, there is not yet sufficient evidence

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00075-9

to use albuminuria, as opposed to proteinuria, in children. A recent study comparing albuminuria to proteinuria in the Chronic Kidney Disease in Children Study showed that albuminuria did not add any predictive value compared with proteinuria.[6] There may be some value to albuminuria in the adolescent age group, as shown in a recent NHANES study.[7] Prospective cohort studies in children report a faster decline in kidney function in children with higher levels of proteinuria[8,9] As with GFR, normal urinary protein excretion varies with age and height, but sex, weight, and Tanner (pubertal physical development) stage also have an impact.[10] A retrospective followup study from the ESCAPE trial suggests that minimizing proteinuria can slow CKD progression.[11] Immature proximal tubular function results in higher urinary protein excretion in infants and young children with normal renal function,[12] so this will need to be accounted for in future analyses evaluating the association of levels of albuminuria or proteinuria and kidney function decline in very young children.

HISTORY OF CKD IN CHILDREN

CKD in children was described in the literature as early as the late 19th century. In 1897 in the *Lancet*, Dr. L. Guthrie reported on "Chronic Interstitial Nephritis in Childhood."[13] This report as well as other early descriptions of CKD characterized fairly normal intellectual development in these children as well as the main sequelae of CKD in childhood: pallor (due to anemia), growth failure (referred to as "infantilism"), rickets "associated with albuminuria," appetite dysregulation, delayed puberty, and sequellae of hypertension, including headaches, vomiting, and left ventricular hypertrophy (LVH). In late stages, "dropsy" or edema was noted, as well as seizures, tetany, and death due to uremia or stroke. From the earliest reports, astute clinicians noted differences between CKD in childhood and in adults. Although in children polyuria was frequently described, with low specific gravity urine, "in adults with granular nephritis the symptom (polyuria) is rarely the subject of a complaint," as usually low urine output was noted.[14] This pointed to the differences between predominant causes of CKD in children and adults. In children, structural urologic diseases, as opposed to acquired glomerular disorders, are the most common causes of CKD both then and now.[15–21]

EPIDEMIOLOGY OF CKD IN CHILDREN

Reports of the incidence and prevalence of childhood CKD are not available from many areas of the world, and those that are reported from different geographical areas are often not directly comparable due to methodological differences in ascertainment and reporting. In Europe, the ItalKid project provides comprehensive data on the epidemiology of CKD in children. The ItalKid project is a prospective, population-based registry started in 1990, including all incident and prevalent cases of CKD (C_{Cr} <75 mL/min/1.73 m^2) in children younger than 20 years from throughout Italy (total population base: 16.8 million children).[15] The ItalKid project reported a mean incidence of preterminal CKD (C_{Cr} <75 mL/min/1.73 m^2) of 12.1 cases per year per million of the age-related population (marp) with a point prevalence of 74.7 per marp in children younger than 20 years of age.[15] The national survey performed in Sweden from 1986 to 1994 included children (ages 6 months to 16 years) with more severe preterminal CKD (C_{Cr} <30 mL/min/1.73 m^2) and reported a median annual incidence and prevalence of 7.7 and 21 per marp, respectively.[18] Similarly, the incidence rate of severe preterminal CKD in Lorraine, France, has been estimated as 10.5 per marp in children less than 16 years, with a prevalence rate of 66 per marp.[17] In Latin America, the Chilean survey from 1996 reported incidence and prevalence rates of 5.7 and 42.5 per marp, respectively, in children younger than 18 years of age with C_{Cr} <30 mL/min/1.73 m^2, including patients with ESRD. There are now data emerging from regions in the world that report CKD of unknown origin, the etiology of which is thought to be related to environmental contaminants. One example is Mexico, where CKD of unknown origin is endemic in some areas, with a recent report of prevalence rates as high as 45.7%, defined by persistent albuminuria.[22] In Turkey, the estimated incidence of GFR <75 mL/min/1.73 m^2 in children less than 19 years of age is 11.9 per marp.[16] Data are also emerging from the African continent showing high prevalence levels. One recent report from Cameroon showed a CKD prevalence of 15.5% in hospitalized children, consistent with levels reported from other developing countries.[23]

In the US, population-based epidemiologic data are not available, and estimates of the distribution of causes of CKD in children are primarily derived from the CKiD study, and the registry of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) organization. The CKiD study is an observational cohort study funded by the National Institutes of Health (NIH) in which individuals with mild to moderate CKD (estimated GFR 30–90 mL/min/1.73 m^2) aged 1–16 years are recruited from over 50 sites in the US and Canada.[19] The NAPRTCS is a voluntary registry, with data entered by participating centers. In 1994, it was expanded to include data from patients with CKD, characterized by a Schwartz estimated creatinine clearance of ≤75 mL/min/1.73 m^2.[21]

DIAGNOSIS OF CKD IN CHILDREN

Summarized data on the demographics and underlying causes of CKD in children from a number of published reports from different geographic areas are presented in Table 75.1. In general, the three largest categories of causes of kidney disease in children are congenital anomalies of the kidney and urinary tract (CAKUT), glomerulonephritis (GN), and cystic and hereditary disorders. The incidence and prevalence rates of CKD are greater for boys than girls.[20] This gender distribution reflects the higher incidence of CAKUT, including obstructive uropathy, renal dysplasia, and prune belly syndrome in boys than girls.[15] CAKUT causes can be isolated renal anomalies, or part of a variety of genetic syndromes. While congenital causes are the most common reported etiology from developed countries where CKD is diagnosed in its earlier stages, infectious or acquired causes predominate in developing countries where patients are referred in the later stages of CKD.

As the majority of pediatric CKD results from CAKUT, many cases are detected prenatally due to the ubiquitous use of prenatal ultrasound.[24] Reduced amniotic fluid is a common finding when there is poor kidney function resulting in reduced urine production.[25] Abnormal findings in the fetal kidneys (cysts, hydronephrosis, hyperechogenic, hypoplastic, or absent kidneys) must be confirmed after birth, as hydronephrosis detected prenatally sometimes resolves spontaneously.[26] Normative data on fetal kidney lengths exist and are used to diagnose hypoplastic kidneys.[27]

Postnatally, renal dysplasia is identified by radionuclide scanning using technetium-99m-labeled dimercaptosuccinic acid (DMSA), which concentrates only in functional renal tissue. This test is used in cases of suspected multicystic dysplastic kidney (MCDK), as well as for assessing renal damage in the presence of vesicoureteral reflux (VUR). Posterior urethral valves (PUV) and VUR, which can both result in hydronephrosis, are diagnosed by voiding cystourethrography. Although unilateral kidney anomalies (such as renal agenesis, MCDK, and hypoplastic kidneys) carry a lower risk for kidney failure in childhood, there is potentially increased risk for hypertension, proteinuria, and renal impairment in adulthood.[28] CAKUT has a definite genetic basis through various molecular mechanisms that share common pathways and affect kidney development. This is a rapidly growing area of research, but there are currently no specific genetic tests routinely recommended for most CAKUT phenotypes because of varied presentation and varied penetrance.

Glomerular etiologies of CKD in children can be primary or secondary, and their incidence differs by geographic region and the race and ethnicity of the population. In the US CKiD study, focal segmental glomerulosclerosis (FSGS) is the most common glomerular cause of CKD reported. Possibly related to increased vulnerability due to genetic risk factors, specifically coding sequence variants in the APOL1 gene, FSGS is three times more common in Blacks than in Whites (18% vs. 6%) and is particularly common among Black adolescents with CKD.[29] GN due to hemolytic uremic syndrome, systemic lupus erythematosus, and IgA nephropathy are the next most common glomerular diagnoses after FSGS in the US-based CKiD study. "Chronic" GN, idiopathic crescentic GN, membranoproliferative GN, membranous nephropathy, and pauci-immune GN are uncommon in the young, but do occur, and have been reported as causes of CKD in youth in multiple reports. Cystic and hereditary disorders account for a substantial proportion of CKD in children. Autosomal recessive and dominant polycystic kidney disease and the nephronophthisis (NPHP)/medullary cystic disease complex are the predominant cystic disorders, whereas Alport syndrome, congenital nephrotic syndrome (CNS), cystinosis, and oxalosis are the primary genetic disorders causing CKD in childhood.

Ultrasonography is the most common imaging modality used to diagnose autosomal dominant polycystic kidney disease (ADPKD) as in adults. It is not uncommon for children to show asymmetric cyst distribution, or even isolated unilateral cysts.[30] If there is no family history of ADPKD, ultrasonography of both parents is recommended. However, if the ultrasounds of the parents are normal and they are less than 30 years old, ultrasonography of the grandparents may be indicated. Up to 50% of children with autosomal recessive polycystic kidney disease (ARPKD) are diagnosed prenatally.[31] There are clear clinical criteria for the diagnosis of ARPKD—the presence of enlarged, echogenic kidneys, with one or more additional findings (the absence of renal cysts in both parents, history of a previously affected sibling, parental consanguinity, and clinical, laboratory, or pathologic features of hepatic fibrosis).[32,33]

Genetic Testing

ADPKD is caused by mutations in either the PKD1 or PKD2 gene, with PKD1 mutations accounting for about 85% of ADPKD cases.[34] Genetic testing is available but is not necessary in patients who have a positive family history of ADPKD and the typical radiographic appearance of bilateral renal cysts. Additionally, even in families known to have ADPKD, mutation analysis may detect only 85% of mutations and will not change clinical management. One exception may be for the exclusion of family members as potential kidney donors when evaluating living donor candidates for an

TABLE 75.1 Demographics and Underlying Causes of CKD in Children From Different Geographic Areas

Reference	**21**	**15**	**19**	**151**	**16**	**152**	**153**	**154**	**155**	**156**
Geographic Region	**North America**	**Italy**	**North America**	**Spain**	**Turkey**	**South Africa**	**Vietnam**	**England**	**Belgian Registry**	**Serbia**
Level of kidney function	GFR<75	GFR<75	GFR 30–90	CKD 2–5	GFR≤75	CKD 2–5	Inpatient	CKD 3–5	CKD 3–5	CKD 2–4
Age (years)	≤20	≤19	1–16	≤18	≤18	≤15	≤17	≤17	≤19	≤18
Number of cases	7037	1197	868	603	290	126	152	288	143	239
Etiology										
CAKUT	3560 (51%)	757 (63%)	522 (60%)	356 (59%)	163 (56%)	27 (21%)	17 (11%)	182 (63%)	89 (62%)	152 (64%)
Glomerulonephritis*	1310 (19%)	111 (9%)	216 (25%)	19 (3%)	46 (16%)	30 (24%)	101 (66%)	47 (16%)	19 (13%)	19 (8%)
Cystic & hereditary	685 (10%)	199 (17%)	85 (10%)	86 (14%)	49 (17%)	46 (37%)	4 (3%)	33 (12%)	27 (19%)	32 (13%)
Vascular	158 (2%)	49 (4%)	26 (3%)	67 (11%)	–	–	–	19 (7%)	6 (4%)	–
Other	1142 (16%)	41 (3%)	19 (2%)	75 (13%)	10 (4%)	23 (18%)	–	–	5 (3%)	32 (13%)
Unknown	182 (3%)	40 (3%)	–	–	22 (8%)	–	30 (20%)	7 (2%)	–	4 (2%)

CAKUT, congenital anomalies of the kidney and urinary tract; *CKD*, chronic kidney disease; *GFR*, glomerular filtration rate.
Note: Due to variant classification techniques between studies, etiologic numbers should be taken as approximate.
** Primary and secondary to systemic disease.*
Modified from Harambat (2012).[20]

ADPKD-transplant recipient.[32] ARPKD is caused by mutations in the polycystic kidney and hepatic disease-1 gene.[35,36] Genetic diagnosis is possible through linkage analysis in families who have already had an affected child or through direct mutation analysis. However, mutation analysis through gene sequencing detects mutations in only 60–75% of patients with known ARPKD.

NPHP encompasses genetically heterogeneous conditions with autosomal recessive inheritance associated with identified mutations in a number of genes that encode proteins involved in the function of primary cilia, basal bodies, and centrosomes. Children with NPHP demonstrate reduced urinary concentrating ability with a bland urinary sediment and chronic tubulointerstitial nephritis with progression to ESRD generally before the age of 20 years. Kidneys in NPHP are of normal or diminished size, cysts are concentrated at the corticomedullary junction, and tubulointerstitial fibrosis is dominant. NPHP can be associated with retinitis pigmentosa (Senior–Løken syndrome), liver fibrosis, and cerebellar vermis aplasia (Joubert syndrome), among other conditions.

CNS, which presents in the first 3 months of life, is a recessively inherited disorder characterized by massive proteinuria detectable at birth, a large placenta, marked edema, and characteristic radial dilatations of the proximal tubules noted on histologic examination. Treatment usually includes bilateral nephrectomy to stop the protein losses, necessitating subsequent dialysis treatment. NPHS1 has been identified as the major gene involved,[37] but other gene mutations including NPHS2, PLCE1, and WT1 have also been detected in patients presenting with CNS. NPHS2 mutations are responsible for most cases of infantile nephrotic syndrome (NS developing between 4 and 12 months of age), as well as a significant proportion of childhood-onset steroid resistant NS, which can lead to early CKD and progression to ESRD.[38,39] An increasing number of genes have been identified as contributors to a variety of kidney diseases in childhood, and newer genetic tests will likely become more widely available and part of clinical care.[40]

In all the reports on etiology of CKD in children, "other" diagnoses comprise a substantial category. Particularly as survival of serious systemic illness in childhood has improved, CKD has become increasingly recognized as a complication of other systemic pediatric illnesses.

ONCOLOGY AND HEMATOPOIETIC STEM CELL TRANSPLANTATION

CKD is a common complication in survivors of pediatric malignancies, with up to 30% having impaired GFR, tubular dysfunction, and/or proteinuria. The long-term burden of such illnesses will likely increase as survival rates continue to improve for patients with pediatric cancers.[41,42] Children with malignancy may develop CKD due to nephrotoxic chemotherapeutic agents, radiation, surgical interventions (as in the case of Wilms' tumors), and exposure to other nephrotoxic medications such as antimicrobials. Hematopoietic stem cell transplantation (HSCT) poses a particularly high risk for long-term kidney dysfunction, with cumulative incidence of CKD reported as high as 66% in adult and 62% in pediatric studies.[43–45] Risk factors for CKD after HSCT include AKI, acute and chronic graft vs. host disease, and lower GFR before transplantion.[46,47] Renal manifestations can also include nephrotic syndrome and thrombotic microangiopathy.[44] CKD in patients after HSCT is associated with a high prevalence of hypertension and proteinuria.[48,49] Among survivors after HSCT, there is a significantly increased risk of ESRD compared to the general population.[50]

NONRENAL SOLID ORGAN TRANSPLANTATION

CKD is a well-described complication after solid organ transplantation.[51] The etiology is multifactorial in most cases, including pretransplant factors (underlying CKD, diabetes, hypertension, and use of nephrotoxic medications), peritransplant factors (hypovolemia, hepatorenal syndrome, and impaired cardiac output), and posttransplant factors (diabetes, hypertension, and long-term exposure to calcineurin inhibitors).[52] The prevalence of CKD in pediatric liver transplant recipients has been reported as 21–33%[53–56] and even higher in other studies based on varying definitions of CKD and followup time. CKD has been reported to occur in as many as 67% of children after heart or lung transplantation.[57–64] The risk of long-term renal dysfunction after intestinal and multivisceral transplants is less well described. The burden of kidney disease in this population may, however, continue to grow as there has been a steady rise in these transplants in recent years.[65–67] Recipients of solid organ transplants who develop CKD may progress to ESRD. In a 20-year national cohort study of over 16,000 pediatric solid organ transplant recipients, 3% developed ESRD, with the highest risk among intestinal and lung transplant recipients.[68] The development of ESRD is associated with increased morbidity and mortality. In a study of almost 9000 pediatric liver transplant recipients, children who developed ESRD had an almost twofold increased risk of mortality.[69] Screening for kidney disease, managing CKD-associated comorbidities, and avoiding additional renal injury are critical in these patients to prevent progressive CKD.

SICKLE CELL DISEASE

CKD due to sickle cell nephropathy is a common complication in adults with sickle cell disease, with up to 12% progressing to ESRD.[70] However, evidence of glomerular hyperfiltration and injury can be present early in childhood, as evidenced by up to 21% of young children with sickle cell disease having albuminuria.[71] Additional renal manifestations of sickle cell disease in children include gross or microscopic hematuria, renal infarction and papillary necrosis, membranoproliferative GN, impaired renal concentrating ability due to tubular injury, and renal tubular acidosis. Children with sickle cell trait may also have kidney involvement including microscopic hematuria, exertional rhabdomyolysis, and papillary necrosis.[72] Sickle cell trait has also been associated with increased risk of albuminuria and CKD.[73] Renal medullary cell carcinoma is a rare but important complication that may present in adolescence or early adulthood with hematuria, flank pain, or abdominal mass, most commonly in African American males with sickle cell trait.[74,75]

PROGRESSION OF PEDIATRIC CKD AND TREATMENT STRATEGIES TO SLOW PROGRESSION

Progression of CKD in children may be the result of ongoing activity of the underlying disease, repeated renal insults such as infections, AKI, and medications, and/or glomerular hyperfiltration. The Brenner hypothesis of renal injury suggests that reduction in functioning nephron mass, either due to congenital or acquired disease, leads to increased filtration in the remaining nephrons through increased glomerular capillary plasma flow rate and increased intraglomerular pressure.[76] This adaptive glomerular hyperfiltration in theory initially leads to preservation of GFR, but subsequently causes progressive glomerular sclerosis, proteinuria, and eventually interstitial inflammation and fibrosis.

The natural history of CKD in children is characterized by a steady decline in kidney function over time. However, the rate of progression of CKD in children is highly affected by the underlying disease process, with a more rapid decline seen in children with glomerular etiologies of CKD compared to congenital anomalies of the kidney and urinary tract. In the CKiD study, children with glomerular disease had a median decline in GFR of 4.3 mL/min/1.73 m^2 per year compared to children with nonglomerular disease whose median decline in GFR was only 1.5 mL/min/1.73 m^2 per year.[77] The rate of CKD progression in children is also affected by periods of rapid growth, as evidenced by a steeper decline in kidney function during infancy and puberty.[78]

As in adults, hypertension and proteinuria are key determinants of CKD progression in children. Hypertension mediates kidney damage through increased glomerular pressure and glomerular hyperfiltration. Large cohort studies of children with CKD have demonstrated the association between hypertension and CKD progression.[79–81] Proteinuria is a marker of disease progression but may contribute to further kidney injury through proinflammatory and prosclerotic effects resulting in further glomerular and tubulointerstitial injury. Proteinuria has been shown to predict renal disease progression in children with CKD, even in those children who have nonglomerular etiologies of CKD.[8,79] Lowering of proteinuria early in the disease process is associated with long-term kidney function preservation.[11] The renin–angiotensin–aldosterone system (RAAS) is an important mediator of CKD progression in children. Angiotensin II increases intraglomerular pressure, activates inflammatory pathways, and may contribute to glomerular and tubulointerstitial fibrosis through cytokines, including transforming growth factor beta.[82]

Many other factors have been implicated in CKD progression in children. In a retrospective cohort study of over 4000 children with CKD from the NAPRTCS registry, anemia, hypocalcemia, hyperphosphatemia, and hypoalbuminemia were independently associated with CKD progression adjusted for age, hypertension, and underlying diagnosis.[81] In the CKiD study, additional risk factors for CKD progression have been identified, including hyperuricemia and elevated plasma fibroblast growth factor 23 (FGF-23).[83,84] Additional mediators of CKD progression in children may include metabolic acidosis, dyslipidemia, chronic inflammation, poor nutrition, and oxidative stress.[85,86] Oxidative stress in CKD is mediated through an increase in reactive oxygen species and a decrease in antioxidative factors including nitric oxide synthase and L-arginine and an increase in nitric oxide inhibitors leading to endothelial dysfunction and a profibrotic state.[87] This oxidative stress may be exacerbated by anemia and chronic inflammation.

Although certain variables contributing to disease progression are uncontrollable, treatments targeted at the potentially modifiable factors can be effective in slowing decline in kidney function in children. Similar to adult studies that have shown a benefit of blood pressure control in slowing progressive kidney damage, the ESCAPE trial (Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of Chronic Renal Failure in Pediatric Patients) demonstrated a benefit of intensified blood pressure control in children. In this randomized controlled trial of 385 children with CKD, all subjects received angiotensin-converting enzyme inhibitor (ACEI), then were randomized to conventional (BP 50th–90th percentile) or intensified (BP<50th

percentile) blood pressure control, with additional blood pressure control achieved through non-RAAS antihypertensive therapies. Children randomized to the intensified arm had significantly lower rates of CKD progression or need for renal replacement therapy (RRT) than children in the conventional arm over 5 years (29.9% of intensified vs. 41.7% in conventional).[88] In addition to their effects on lowering blood pressure, antagonists of the RAAS pathway including ACEIs and angiotensin receptor blockers (ARBs) have other benefits for children with CKD. RAAS inhibitors have antiproteinuric effects mediated primarily by lowering intraglomerular pressure. Numerous studies in adults have shown that RAAS blockade leads to decline in proteinuria and delayed renal disease progression. Similarly, in the ESCAPE trial, subjects who achieved an initial 50% reduction in proteinuria within the first 2 months after initiating ACEI therapy had significantly decreased risk of progressive renal disease.[88] RAAS inhibitors may also have antifibrotic effects by decreasing circulating cytokines involved in glomerular and tubulointerstitial inflammation and fibrosis. ACEIs and ARBs are generally well-tolerated in children but can cause a decline in GFR and/or hyperkalemia in children with more advanced CKD.

Additional interventions that may slow CKD progression in children include correction of anemia, dyslipidemia, and calcium–phosphate balance. In adults, treatment with erythropoietin has been suggested to slow renal disease progression, potentially through decreased oxidative stress and a decrease in tubulointerstitial injury.[89] Treatment of dyslipidemia is important for preventing cardiovascular morbidity but may also slow disease progression. Statins may have renoprotective properties, independent of their lipid-lowering effects, potentially through antiinflammatory and antioxidative effects. There have been conflicting reports in adults on the effects of statins on decreasing proteinuria and slowing CKD progression, with some studies showing a beneficial effect on slowing decline in renal function.[90–93]

However, the SHARP study did not show a benefit of statins on slowing progression of kidney disease.[94] The effects of statins on CKD progression have not been studied in the pediatric CKD population, and statins are not indicated in young children. Correction of hypovitaminosis D may also slow renal disease progression, as vitamin D may suppress renin and renal Klotho expression. Data from the ESCAPE trial showed that lower 25-hydroxyvitamin D levels were associated with greater proteinuria, higher diastolic BP, and greater annualized loss of eGFR.[95] Finally, in adults with diabetes, dietary protein restriction has been shown to be effective in slowing CKD progression in some studies. However, reduced protein intake has not been shown to slow CKD progression in children,[96,97] and protein restriction may impact nutrition and growth. Children with CKD should be given the age-appropriate recommended daily allowance for protein intake.

TREATMENT OF CKD COMORBIDITIES

Cardiovascular Disease

The American Heart Association's guidelines for reduction of cardiovascular risk in pediatrics stratified the child with CKD to the highest risk category.[98] In fact, cardiovascular mortality is the leading cause of death in children with CKD. The most common causes of death in pediatric CKD patients are cardiac arrest and arrhythmia.[1,99] In the CKiD cohort there are high prevalence rates of four traditional cardiovascular risk factors—hypertension, dyslipidemia, abnormal glucose metabolism, and obesity.[100] LVH is the most common cardiac abnormality in children with CKD.[101–103] However, there remains some debate over the ideal way to define pediatric LVH—left ventricular mass index (LVMI) or left ventricular wall thickness z-score. A recent Korean study showed poor concordance between the two methods, which would affect the reported prevalence depending on which is used.[104] Vascular changes such as increased carotid intimal media thickness and arterial stiffness (increased pulse wave velocity) start during mild to moderate CKD stages and progressively worsen as kidney function deteriorates.[105,106] Data support an independent association of cystatin C with increasing LVMI and deteriorating diastolic function, including prediction of the latter in children with CKD.[107]

It is unclear whether lipid-lowering strategies are beneficial in children with CKD and elevated lipid levels. A very small pilot trial of a statin in eight children with CKD resulted in a significant decrease in total cholesterol and LDL, but no change in brachial artery endothelium-dependent flow-mediated dilatation (FMD).[108] However, FMD was in the normal range at baseline. It seems reasonable, however, that the use of statins should be considered for pediatric CKD patients with hyperlipidemia, with age- and renal function–adjusted dosing taken into account. There is no literature on the use of antiplatelet agents for atherosclerotic disease in children with CKD.

Growth and Nutrition

Growth failure in children with CKD is not simply an aesthetic issue. Impaired growth is associated with impaired psychosocial maturation and health-related quality of life,[109] as well as increased morbidity and

mortality.[110,111] The definition of malnutrition, particularly protein-energy wasting (PEW) is not well characterized in children. In adults the components of PEW are low serum albumin concentration or low cholesterol concentration, decreased body mass, decreased muscle mass, and decreased protein intake. It has been suggested that the definition in children should include a growth component, either growth failure or poor growth velocity.[112] The etiology of growth failure in children with CKD is multifactorial—etiology and treatment of the CKD, malnutrition, fluid and electrolyte disturbances, metabolic acidosis, anemia, renal osteodystrophy, and inflammation all have effects.[113–116] Data from the CKiD study indicate that birthweight and gestational age also significantly influence growth in children with CKD.[117] Decreased growth is particularly problematic in infancy because about one-third of a child's postnatal growth occurs in the first 2 years. The improvement of growth as a result of nutritional enhancement from enteral feeding during this critical period has long been advocated. Evidence from very small studies was first published in the 1980s.[118,119] Larger, more recent studies, as well as the KDOQI guidelines recommend early, intensive nutritional management in this group.[120,121] Numerous studies of infants with CKD have shown a significant increase in growth velocity once adequate calories are provided through a nasogastric or gastrostomy tube.[122] Therefore, appropriate nutrition, attention to fluid and sodium balance, along with treatment of metabolic acidosis and hyperparathyroidism, are usually adequate for growth in infants with CKD, with supplemental growth hormone seen as a secondary therapeutic approach.[120] Few, very small studies report a benefit from the use of growth hormone in infants, usually when growth is inadequately responsive to optimized nutrition.[123,124] In children with CKD, there are not many reports of the use and impact of appetite stimulants, although these have proven useful in other chronic diseases in children such as HIV infection, cancer, and cystic fibrosis, as well as in adult dialysis patients. A small retrospective study reported improved weight gain with use of the appetite-stimulant megestrol acetate in pediatric CKD patients,[125] but there are no studies reported on the efficacy of cyproheptadine in children with CKD. Beyond infancy, recombinant human growth hormone (rhGH) use in children with CKD has become a relatively common (although not universal) practice over the past 20 years, as growth hormone resistance is known to be yet another factor contributing to poor growth.[126] Despite concerns about the potential for rhGH to accelerate the decline of renal function in children with CKD, study data have not supported such notions.[127] Puberty is another problematic time—often delayed, and associated with an attenuated growth spurt in patients with CKD.[128–130] There are, however, discrepancies in how adolescents with CKD view the impact of their short stature compared with their parents.[109]

Chronic Kidney Disease—Mineral and Bone Disorder

Chronic kidney disease—mineral and bone disorder (CKD-MBD) is a syndrome that includes biochemical mineral abnormalities, bone fragility, and vascular calcification (even in children) and is associated with increased morbidity and mortality. The biochemical mineral abnormalities include elevated serum phosphate concentration (S[P]) and low serum calcium concentration (S[Ca]), which lead to increased FGF-23 and increased parathyroid hormone (PTH) levels. Bone deformities and fractures are common in children with CKD, and as with poor growth, impaired bone accrual in this population is multifactorial. Contributors include poor growth, decreased physical activity, abnormal mineral metabolism, muscle deficits, and secondary hyperparathyroidism.

Managing pediatric CKD-MBD is quite complex, as one is dealing with the growing skeleton, during the time when calcium accrual in the skeleton has not yet reached its peak. The first line of treatment is dietary phosphate restriction and use of phosphate binders, both of which are generally associated with poor adherence. The most recent KDIGO guidelines recommend that the choice of phosphate-lowering agent should be based on the S[Ca], to avoid development of hypercalcemia and vascular calcification.[131] However, hypercalcemia can result from numerous factors, including both low and high PTH levels and low and high 1,25 hydroxyvitamin D levels, not just calcium-based phosphate binders.[132] The pros and cons of phosphate binders currently on the market for children as well as those under study, including iron-based binders, are still being debated. There are ongoing studies to determine whether the first line of treatment should be to target FGF-23 levels before overt hyperphosphatemia manifests.

Vitamin D levels are low in a majority of children with CKD for a multitude of reasons, including urinary losses of vitamin D binding protein, along with increased renal losses of all vitamin D metabolites in those with proteinuria. The KDIGO guidelines recommend consideration of use of calcitriol and vitamin D analogs to maintain age-appropriate calcium levels, confirming prior recommendations.[131,133] We should also be aware that sodium bicarbonate and proton pump inhibitors, which are prescribed for many children with CKD, inhibit calcium absorption from the gut.[133] The treatment of pediatric CKD-MBD should not target only one metabolic

derangement but must consider the many interacting factors to optimize bone health and growth, while minimizing negative cardiovascular effects.

Optimal noninvasive evaluation of pediatric CKD-MBD is still being studied. Imaging with dual-energy X-ray absorptiometry (DEXA) has been shown to underestimate volumetric bone mineral density in children with growth failure. Evaluation with peripheral quantitative computed tomography may provide more accurate assessments.[134] Although bone biopsy provides the most definitive assessment, it is invasive and not performed routinely at many pediatric CKD programs.

Neurocognitive Function

Apart from the impact of CKD on physical growth, another concern is the impact of CKD on brain development, neurocognition, and behavior. This is known to be particularly problematic in cases of early onset CKD and severe disease or ESRD.[135,136] Compared to healthy controls, children with CKD have poorer performance in multiple areas of neurocognition including attention, memory, and inhibitory control.[137] Studies have also demonstrated lower intelligence quotient (IQ) scores among children with ESRD compared to their unaffected siblings or the general population.[138] In the CKiD study, a large proportion of children with mild to moderate CKD were identified as being at risk for neurocognitive dysfunction, defined as test performance greater than one SD below the normative mean for age in measures of IQ, academic achievement, attention regulation, and executive functioning.[139] These deficits may persist into adulthood. A study in the Netherlands identified persistent difficulties with knowledge, memory, and concentration into adulthood, as well as lower educational attainment in adults with childhood onset of ESRD.[140] Compared to age-matched individuals, adult patients with childhood ESRD were more often involuntarily unemployed at about twice the rate of the age-matched population.[141] Children with CKD have also reported poorer overall health-related quality of life with poorer physical, emotional, and school functioning compared to healthy children.[142]

Risk factors for neurocognitive dysfunction in children with CKD include increased disease severity, longer duration of CKD, and younger age at CKD onset.[143,144] Elevated blood pressure, ambulatory hypertension, and increased blood pressure variability have been associated with decreased IQ scores and neurocognitive dysfunction in children with CKD.[137,145,146]

These data support the need for ongoing neurodevelopmental surveillance of children with CKD and implementation of early targeted interventions to improve school performance and health-related quality of life among those identified at risk. Formal transition programs from pediatric to adult CKD care are critical to provide optimal care and improve overall health-related quality of life for patients with childhood-onset CKD.

TIMING AND INDICATIONS FOR RENAL REPLACEMENT THERAPY

Indications for initiating RRT in children include fluid overload, electrolyte or metabolic derangements that are resistant to medical therapies, fluid restriction limiting adequate nutrition, impairment in growth, and/or refractory hypertension. Preemptive transplantation is the renal replacement modality of choice for pediatric patients with ESRD, given improved survival among pediatric transplant recipients compared to dialysis patients.[147–150] Transplantation also obviates medical and psychosocial comorbidities associated with dialysis. However, preemptive transplantation is not always an option given medical issues precluding transplantion (such as lack of a living donor or insufficient time to prepare for transplant). In those cases, the choice between peritoneal dialysis (PD) and hemodialysis (HD) is guided by both medical and psychosocial considerations.

PD is the preferred modality in most children, particularly for infants and young children in whom HD is technically challenging. PD is associated with decreased mortality compared to HD[2] and allows children to be in their home environments and attend school on a regular basis. However, PD may not be feasible due to abdominal pathologies, peritoneal membrane failure, or insufficient family support. HD remains the more common dialysis modality in children with ESRD in the US.[2]

CONCLUSION

Pediatric CKD has unique etiologies and comorbidities compared to adults. Children with CKD require close monitoring by a pediatric nephrologist with particular focus on cardiovascular health, growth and nutrition, and neurocognition. Despite improvements in survival, children with CKD still face an increased risk of early mortality.

References

1. Mitsnefes MM, Laskin BL, Dahhou M, Zhang X, Foster BJ. Mortality risk among children initially treated with dialysis for end-stage kidney disease, 1990-2010. *J Am Med Assoc* 2013;**309**(18):1921–9.

2. United States Renal Data System. 2017 USRDS annual data report. National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD.
3. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009;**20**(3): 629–37.
4. Hogg RJ, Furth S, Lemley KV, et al. National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guidelines for chronic kidney disease in children and adolescents: evaluation, classification, and stratification. *Pediatrics* 2003;**111**(6 Pt 1):1416–21.
5. Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group. KcpgfteamockdCdaco. *Kidney Int Suppl* 2013.
6. Fuhrman DY, Schneider MF, Dell KM, et al. Albuminuria, proteinuria, and renal disease progression in children with CKD. *Clin J Am Soc Nephrol* 2017;**12**(6):912–20.
7. Saydah SH, Xie H, Imperatore G, Burrows NR, Pavkov ME. Trends in albuminuria and GFR among adolescents in the United States, 1988-2014. *Am J Kidney Dis* 2018;**72**(5):644–52.
8. Ardissino G, Testa S, Dacco V, et al. Proteinuria as a predictor of disease progression in children with hypodysplastic nephropathy. Data from the Ital Kid Project. *Pediatr Nephrol* 2004;**19**(2):172–7.
9. Wong CS, Pierce CB, Cole SR, et al. Association of proteinuria with race, cause of chronic kidney disease, and glomerular filtration rate in the chronic kidney disease in children study. *Clin J Am Soc Nephrol* 2009;**4**(4):812–9.
10. Trachtenberg F, Barregard L. The effect of age, sex, and race on urinary markers of kidney damage in children. *Am J Kidney Dis* 2007;**50**(6):938–45.
11. van den Belt SM, Heerspink HJL, Gracchi V, et al. Early proteinuria lowering by angiotensin-converting enzyme inhibition predicts renal survival in children with CKD. *J Am Soc Nephrol* 2018;**29**(8):2225–33.
12. Brem AS. Neonatal hematuria and proteinuria. *Clin Perinatol* 1981; **8**(2):321–32.
13. Guthrie LG. Chronic interstitial nephritis in childhood. *Lancet* 1897;**149**:728–32.
14. Fletcher HM. Infantilism with polyuria and chronic renal disease. *Proc Roy Soc Med* 1911;**4**:95. Sect Study Dis Child.
15. Ardissino G, Dacco V, Testa S, et al. Epidemiology of chronic renal failure in children: data from the ItalKid project. *Pediatrics* 2003; **111**(4 Pt 1):e382–387.
16. Bek K, Akman S, Bilge I, et al. Chronic kidney disease in children in Turkey. *Pediatr Nephrol* 2009;**24**(4):797–806.
17. Deleau J, Andre JL, Briancon S, Musse JP. Chronic renal failure in children: an epidemiological survey in Lorraine (France) 1975-1990. *Pediatr Nephrol* 1994;**8**(4):472–6.
18. Esbjorner E, Berg U, Hansson S. Epidemiology of chronic renal failure in children: a report from Sweden 1986-1994. Swedish Pediatric Nephrology Association. *Pediatr Nephrol* 1997;**11**(4): 438–42.
19. Furth SL, Cole SR, Moxey-Mims M, et al. Design and methods of the chronic kidney disease in children (CKiD) prospective cohort study. *Clin J Am Soc Nephrol* 2006;**1**(5):1006–15.
20. Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. *Pediatr Nephrol* 2012;**27**(3): 363–73.
21. *North American pediatric renal transplant cooperative study (NAPRTCS)*. Rockville, MD: ArTEC; 2008.
22. Lozano-Kasten F, Sierra-Diaz E, de Jesus Celis-de la Rosa A, et al. Prevalence of albuminuria in children living in a rural agricultural and fishing subsistence community in lake chapala, Mexico. *Int J Environ Res Public Health* 2017;**14**(12).
23. Halle MP, Lapsap CT, Barla E, et al. Epidemiology and outcomes of children with renal failure in the pediatric ward of a tertiary hospital in Cameroon. *BMC Pediatr* 2017;**17**(1):202.
24. Wiesel A, Queisser-Luft A, Clementi M, Bianca S, Stoll C, Group ES. Prenatal detection of congenital renal malformations by fetal ultrasonographic examination: an analysis of 709,030 births in 12 European countries. *Eur J Med Genet* 2005;**48**(2): 131–44.
25. Cromie WJ, Lee K, Houde K, Holmes L. Implications of prenatal ultrasound screening in the incidence of major genitourinary malformations. *J Urol* 2001;**165**(5):1677–80.
26. Small MJ, Copel JA. Practical guidelines for diagnosing and treating fetal hydronephrosis. *Contemp Ob/Gyn* 2004;**49**:59–77.
27. Hill LM, Nowak A, Hartle R, Tush B. Fetal compensatory renal hypertrophy with a unilateral functioning kidney. *Ultrasound Obstet Gynecol* 2000;**15**(3):191–3.
28. Sanna-Cherchi S, Ravani P, Corbani V, et al. Renal outcome in patients with congenital anomalies of the kidney and urinary tract. *Kidney Int* 2009;**76**(5):528–33.
29. Pollak MR, Genovese G, Friedman DJ. APOL1 and kidney disease. *Curr Opin Nephrol Hypertens* 2012;**21**(2):179–82.
30. Fick-Brosnahan G, Johnson AM, Strain JD, Gabow PA. Renal asymmetry in children with autosomal dominant polycystic kidney disease. *Am J Kidney Dis* 1999;**34**(4):639–45.
31. Guay-Woodford LM, Desmond RA. Autosomal recessive polycystic kidney disease: the clinical experience in North America. *Pediatrics* 2003;**111**(5 Pt 1):1072–80.
32. Dell KM. The spectrum of polycystic kidney disease in children. *Adv Chron Kidney Dis* 2011;**18**(5):339–47.
33. Sweeney Jr WE, Avner ED. Diagnosis and management of childhood polycystic kidney disease. *Pediatr Nephrol* 2011;**26**(5): 675–92.
34. Pei Y. Practical genetics for autosomal dominant polycystic kidney disease. *Nephron Clin Pract* 2011;**118**(1):c19–30.
35. Onuchic LF, Furu L, Nagasawa Y, et al. PKHD1, the polycystic kidney and hepatic disease 1 gene, encodes a novel large protein containing multiple immunoglobulin-like plexin-transcription-factor domains and parallel beta-helix 1 repeats. *Am J Hum Genet* 2002;**70**(5):1305–17.
36. Ward CJ, Hogan MC, Rossetti S, et al. The gene mutated in autosomal recessive polycystic kidney disease encodes a large, receptor-like protein. *Nat Genet* 2002;**30**(3):259–69.
37. Kestila M, Lenkkeri U, Mannikko M, et al. Positionally cloned gene for a novel glomerular protein–nephrin–is mutated in congenital nephrotic syndrome. *Mol Cell* 1998;**1**(4):575–82.
38. Benoit G, Machuca E, Antignac C. Hereditary nephrotic syndrome: a systematic approach for genetic testing and a review of associated podocyte gene mutations. *Pediatr Nephrol* 2010; **25**(9):1621–32.
39. Boute N, Gribouval O, Roselli S, et al. NPHS2, encoding the glomerular protein podocin, is mutated in autosomal recessive steroid-resistant nephrotic syndrome. *Nat Genet* 2000;**24**(4): 349–54.
40. Jayasinghe K, Quinlan C, Stark Z, et al. Renal genetics in Australia: kidney medicine in the genomic age. *Nephrology* 2019;**24**(3):279–86.
41. Geenen MM, Cardous-Ubbink MC, Kremer LC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *J Am Med Assoc* 2007;**297**(24):2705–15.
42. Knijnenburg SL, Jaspers MW, van der Pal HJ, et al. Renal dysfunction and elevated blood pressure in long-term childhood cancer survivors. *Clin J Am Soc Nephrol* 2012;**7**(9):1416–27.
43. Ellis MJ, Parikh CR, Inrig JK, Kanbay M, Patel UD. Chronic kidney disease after hematopoietic cell transplantation: a systematic review. *Am J Transplant* 2008;**8**(11):2378–90.
44. Hingorani S. Chronic kidney disease in long-term survivors of hematopoietic cell transplantation: epidemiology, pathogenesis, and treatment. *J Am Soc Nephrol* 2006;**17**(7):1995–2005.
45. Weiss AS, Sandmaier BM, Storer B, Storb R, McSweeney PA, Parikh CR. Chronic kidney disease following non-myeloablative

hematopoietic cell transplantation. *Am J Transplant* 2006;**6**(1): 89–94.
46. Hingorani S, Guthrie KA, Schoch G, Weiss NS, McDonald GB. Chronic kidney disease in long-term survivors of hematopoietic cell transplant. *Bone Marrow Transplant* 2007;**39**(4):223–9.
47. Kersting S, Hene RJ, Koomans HA, Verdonck LF. Chronic kidney disease after myeloablative allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2007;**13**(10):1169–75.
48. Glezerman IG, Jhaveri KD, Watson TH, et al. Chronic kidney disease, thrombotic microangiopathy, and hypertension following T cell-depleted hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2010;**16**(7):976–84.
49. Hingorani S. Chronic kidney disease after liver, cardiac, lung, heart-lung, and hematopoietic stem cell transplant. *Pediatr Nephrol* 2008;**23**(6):879–88.
50. Cohen EP, Drobyski WR, Moulder JE. Significant increase in end-stage renal disease after hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2007;**39**(9):571–2.
51. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003;**349**(10):931–40.
52. Bloom RD, Reese PP. Chronic kidney disease after nonrenal solid-organ transplantation. *J Am Soc Nephrol* 2007;**18**(12):3031–41.
53. Bartosh SM, Alonso EM, Whitington PF. Renal outcomes in pediatric liver transplantation. *Clin Transplant* 1997;**11**(5 Pt 1):354–60.
54. Campbell KM, Yazigi N, Ryckman FC, et al. High prevalence of renal dysfunction in long-term survivors after pediatric liver transplantation. *J Pediatr* 2006;**148**(4):475–80.
55. Harambat J, Ranchin B, Dubourg L, et al. Renal function in pediatric liver transplantation: a long-term follow-up study. *Transplantation* 2008;**86**(8):1028–34.
56. Kivela JM, Raisanen-Sokolowski A, Pakarinen MP, et al. Long-term renal function in children after liver transplantation. *Transplantation* 2011;**91**(1):115–20.
57. Benden C, Kansra S, Ridout DA, et al. Chronic kidney disease in children following lung and heart-lung transplantation. *Pediatr Transplant* 2009;**13**(1):104–10.
58. Bharat W, Manlhiot C, McCrindle BW, Pollock-BarZiv S, Dipchand AI. The profile of renal function over time in a cohort of pediatric heart transplant recipients. *Pediatr Transplant* 2009; **13**(1):111–8.
59. Hmiel SP, Beck AM, de la Morena MT, Sweet S. Progressive chronic kidney disease after pediatric lung transplantation. *Am J Transplant* 2005;**5**(7):1739–47.
60. Phan V, West LJ, Stephens D, Hebert D. Renal complications following heart transplantation in children: a single-center study. *Am J Transplant* 2003;**3**(2):214–8.
61. Ross M, Kouretas P, Gamberg P, et al. Ten- and 20-year survivors of pediatric orthotopic heart transplantation. *J Heart Lung Transplant* 2006;**25**(3):261–70.
62. Sachdeva R, Blaszak RT, Ainley KA, Parker JG, Morrow WR, Frazier EA. Determinants of renal function in pediatric heart transplant recipients: long-term follow-up study. *J Heart Lung Transplant* 2007;**26**(2):108–13.
63. Sigfusson G, Fricker FJ, Bernstein D, et al. Long-term survivors of pediatric heart transplantation: a multicenter report of sixty-eight children who have survived longer than five years. *J Pediatr* 1997; **130**(6):862–71.
64. Smith RR, Wray J, Khaghani A, Yacoub M. Ten year survival after paediatric heart transplantation: a single centre experience. *Eur J Cardiothorac Surg* 2005;**27**(5):790–4.
65. Cai J. Intestine and multivisceral transplantation in the United States: a report of 20-year national registry data (1990-2009). *Clin Transpl* 2009:83–101.
66. Mangus RS, Tector AJ, Kubal CA, Fridell JA, Vianna RM. Multivisceral transplantation: expanding indications and improving outcomes. *J Gastrointest Surg* 2013;**17**(1):179–86. discussion 186–177.
67. OPTN Data Report as of March 1. http://optn.transplant.hrsa.gov/. Accessed March 5 2014.
68. Ruebner RL, Reese PP, Denburg MR, Abt PL, Furth SL. End-stage kidney disease after pediatric nonrenal solid organ transplantation. *Pediatrics* 2013;**132**(5):e1319–1326.
69. Ruebner RL, Reese PP, Denburg MR, Rand EB, Abt PL, Furth SL. Risk factors for end-stage kidney disease after pediatric liver transplantation. *Am J Transplant* 2012;**12**(12):3398–405.
70. Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. *Medicine (Baltim)* 2005;**84**(6):363–76.
71. McPherson Yee M, Jabbar SF, Osunkwo I, et al. Chronic kidney disease and albuminuria in children with sickle cell disease. *Clin J Am Soc Nephrol* 2011;**6**(11):2628–33.
72. Tsaras G, Owusu-Ansah A, Boateng FO, Amoateng-Adjepong Y. Complications associated with sickle cell trait: a brief narrative review. *Am J Med* 2009;**122**(6):507–12.
73. Naik RP, Derebail VK, Grams ME, et al. Association of sickle cell trait with chronic kidney disease and albuminuria in African Americans. *J Am Med Assoc* 2014;**312**(20):2115–25.
74. Hakimi AA, Koi PT, Milhoua PM, et al. Renal medullary carcinoma: the Bronx experience. *Urology* 2007;**70**(5):878–82.
75. Swartz MA, Karth J, Schneider DT, Rodriguez R, Beckwith JB, Perlman EJ. Renal medullary carcinoma: clinical, pathologic, immunohistochemical, and genetic analysis with pathogenetic implications. *Urology* 2002;**60**(6):1083–9.
76. Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. *Kidney Int* 1996;**49**(6):1774–7.
77. Furth SL, Abraham AG, Jerry-Fluker J, et al. Metabolic abnormalities, cardiovascular disease risk factors, and GFR decline in children with chronic kidney disease. *Clin J Am Soc Nephrol* 2011;**6**(9):2132–40.
78. Ardissino G, Testa S, Dacco V, et al. Puberty is associated with increased deterioration of renal function in patients with CKD: data from the ItalKid Project. *Arch Dis Child* 2012;**97**(10):885–8.
79. Fathallah-Shaykh SA, Flynn JT, Pierce CB, et al. Progression of pediatric CKD of nonglomerular origin in the CKiD cohort. *Clin J Am Soc Nephrol* 2015;**10**(4):571–7.
80. Mitsnefes M, Ho PL, McEnery PT. Hypertension and progression of chronic renal insufficiency in children: a report of the North American pediatric renal transplant cooperative study (NAPRTCS). *J Am Soc Nephrol* 2003;**14**(10):2618–22.
81. Staples AO, Greenbaum LA, Smith JM, et al. Association between clinical risk factors and progression of chronic kidney disease in children. *Clin J Am Soc Nephrol* 2010;**5**(12):2172–9.
82. Brewster UC, Perazella MA. The renin-angiotensin-aldosterone system and the kidney: effects on kidney disease. *Am J Med* 2004;**116**(4):263–72.
83. Rodenbach KE, Schneider MF, Furth SL, et al. Hyperuricemia and progression of CKD in children and adolescents: the chronic kidney disease in children (CKiD) cohort study. *Am J Kidney Dis* 2015; **66**(6):984–92.
84. Portale AA, Wolf MS, Messinger S, et al. Fibroblast growth factor 23 and risk of CKD progression in children. *Clin J Am Soc Nephrol* 2016;**11**(11):1989–98.
85. Wuhl E, Schaefer F. Therapeutic strategies to slow chronic kidney disease progression. *Pediatr Nephrol* 2008;**23**(5):705–16.
86. Harambat J, Kunzmann K, Azukaitis K, et al. Metabolic acidosis is common and associates with disease progression in children with chronic kidney disease. *Kidney Int* 2017;**92**(6):1507–14.
87. Karamouzis I, Sarafidis PA, Karamouzis M, et al. Increase in oxidative stress but not in antioxidant capacity with advancing stages of chronic kidney disease. *Am J Nephrol* 2008;**28**(3): 397–404.

88. Wuhl E, Trivelli A, et al. Strict blood-pressure control and progression of renal failure in children. *N Engl J Med* 2009;**361**(17): 1639–50.
89. Gouva C, Nikolopoulos P, Ioannidis JP, Siamopoulos KC. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. *Kidney Int* 2004;**66**(2): 753–60.
90. Shepherd J, Kastelein JJ, Bittner V, et al. Effect of intensive lipid lowering with atorvastatin on renal function in patients with coronary heart disease: the Treating to New Targets (TNT) study. *Clin J Am Soc Nephrol* 2007;**2**(6):1131–9.
91. Tonelli M, Isles C, Craven T, et al. Effect of pravastatin on rate of kidney function loss in people with or at risk for coronary disease. *Circulation* 2005;**112**(2):171–8.
92. Tonelli M, Moye L, Sacks FM, et al. Effect of pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease. *J Am Soc Nephrol* 2003;**14**(6):1605–13.
93. Tonelli M, Moye L, Sacks FM, et al. Pravastatin for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency. *Ann Intern Med* 2003;**138**(2):98–104.
94. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**(9784): 2181–92.
95. Shroff R, Aitkenhead H, Costa N, et al. Normal 25-hydroxyvitamin D levels are associated with less proteinuria and attenuate renal failure progression in children with CKD. *J Am Soc Nephrol* 2016;**27**(1):314–22.
96. Kist-van Holthe tot Echten JE, Nauta J, Hop WC, et al. Protein restriction in chronic renal failure. *Arch Dis Child* 1993;**68**(3):371–5.
97. Wingen AM, Fabian-Bach C, Schaefer F, Mehls O. Randomised multicentre study of a low-protein diet on the progression of chronic renal failure in children. European Study Group of Nutritional Treatment of Chronic Renal Failure in Childhood. *Lancet* 1997;**349**(9059):1117–23.
98. Kavey RE, Allada V, Daniels SR, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 2006;**114**(24):2710–38.
99. Parekh RS, Carroll CE, Wolfe RA, Port FK. Cardiovascular mortality in children and young adults with end-stage kidney disease. *J Pediatr* 2002;**141**(2):191–7.
100. Wilson AC, Schneider MF, Cox C, et al. Prevalence and correlates of multiple cardiovascular risk factors in children with chronic kidney disease. *Clin J Am Soc Nephrol* 2011;**6**(12):2759–65.
101. Matteucci MC, Wuhl E, Picca S, et al. Left ventricular geometry in children with mild to moderate chronic renal insufficiency. *J Am Soc Nephrol* 2006;**17**(1):218–26.
102. Mitsnefes M, Flynn J, Cohn S, et al. Masked hypertension associates with left ventricular hypertrophy in children with CKD. *J Am Soc Nephrol* 2010;**21**(1):137–44.
103. Mitsnefes MM, Kimball TR, Witt SA, Glascock BJ, Khoury PR, Daniels SR. Left ventricular mass and systolic performance in pediatric patients with chronic renal failure. *Circulation* 2003;**107**(6): 864–8.
104. Cho H, Choi HJ, Kang HG, et al. Influence of the method of definition on the prevalence of left-ventricular hypertrophy in children with chronic kidney disease: data from the Know-Ped CKD study. *Kidney Blood Press Res* 2017;**42**(3):406–15.
105. Litwin M, Wuhl E, Jourdan C, et al. Altered morphologic properties of large arteries in children with chronic renal failure and after renal transplantation. *J Am Soc Nephrol* 2005;**16**(5):1494–500.
106. Schaefer F, Doyon A, Azukaitis K, et al. Cardiovascular phenotypes in children with CKD: the 4C study. *Clin J Am Soc Nephrol* 2017;**12**(1):19–28.
107. Brady TM, Townsend K, Schneider MF, et al. Cystatin C and cardiac measures in children and adolescents with CKD. *Am J Kidney Dis* 2017;**69**(2):247–56.
108. Mackie FE, Rosenberg AR, Harmer JA, Kainer G, Celermajer DS. HMG CoA reductase inhibition and endothelial function in children with chronic kidney disease (CKD)–a pilot study. *Acta Paediatr* 2010;**99**(3):457–9.
109. Al-Uzri A, Matheson M, Gipson DS, et al. The impact of short stature on health-related quality of life in children with chronic kidney disease. *J Pediatr* 2013;**163**(3):736–41. e731.
110. Furth SL, Hwang W, Yang C, Neu AM, Fivush BA, Powe NR. Growth failure, risk of hospitalization and death for children with end-stage renal disease. *Pediatr Nephrol* 2002;**17**(6):450–5.
111. Wong CS, Gipson DS, Gillen DL, et al. Anthropometric measures and risk of death in children with end-stage renal disease. *Am J Kidney Dis* 2000;**36**(4):811–9.
112. Abraham AG, Mak RH, Mitsnefes M, et al. Protein energy wasting in children with chronic kidney disease. *Pediatr Nephrol* 2014; **29**(7):1231–8.
113. Rees L, Jones H. Nutritional management and growth in children with chronic kidney disease. *Pediatr Nephrol* 2013;**28**(4):527–36.
114. Rees L, Mak RH. Nutrition and growth in children with chronic kidney disease. *Nat Rev Nephrol* 2011;**7**(11):615–23.
115. Silverstein DM. Inflammation in chronic kidney disease: role in the progression of renal and cardiovascular disease. *Pediatr Nephrol* 2009;**24**(8):1445–52.
116. Sylvestre LC, Fonseca KP, Stinghen AE, Pereira AM, Meneses RP, Pecoits-Filho R. The malnutrition and inflammation axis in pediatric patients with chronic kidney disease. *Pediatr Nephrol* 2007; **22**(6):864–73.
117. Greenbaum LA, Munoz A, Schneider MF, et al. The association between abnormal birth history and growth in children with CKD. *Clin J Am Soc Nephrol* 2011;**6**(1):14–21.
118. Rees L, Rigden SP, Ward GM. Chronic renal failure and growth. *Arch Dis Child* 1989;**64**(4):573–7.
119. Strife CF, Quinlan M, Mears K, Davey ML, Clardy C. Improved growth of three uremic children by nocturnal nasogastric feedings. *Am J Dis Child* 1986;**140**(5):438–43.
120. Foster BJ, McCauley L, Mak RH. Nutrition in infants and very young children with chronic kidney disease. *Pediatr Nephrol* 2012;**27**(9):1427–39.
121. National Kidney Foundation Disease Outcomes Quality Initiative. KDOQI clinical practice guideline for nutrition in children with CKD: 2008 update. Executive summary. *Am J Kidney Dis* 2009;**53**:S11–104.
122. Rees L, Brandt ML. Tube feeding in children with chronic kidney disease: technical and practical issues. *Pediatr Nephrol* 2010;**25**(4): 699–704.
123. Mencarelli F, Kiepe D, Leozappa G, Stringini G, Cappa M, Emma F. Growth hormone treatment started in the first year of life in infants with chronic renal failure. *Pediatr Nephrol* 2009; **24**(5):1039–46.
124. Santos F, Moreno ML, Neto A, et al. Improvement in growth after 1 year of growth hormone therapy in well-nourished infants with growth retardation secondary to chronic renal failure: results of a multicenter, controlled, randomized, open clinical trial. *Clin J Am Soc Nephrol* 2010;**5**(7):1190–7.
125. Hobbs DJ, Bunchman TE, Weismantel DP, et al. Megestrol acetate improves weight gain in pediatric patients with chronic kidney disease. *J Ren Nutr* 2010;**20**(6):408–13.

126. Fine RN, Kohaut EC, Brown D, Perlman AJ. Growth after recombinant human growth hormone treatment in children with chronic renal failure: report of a multicenter randomized double-blind placebo-controlled study. Genentech Cooperative Study Group. *J Pediatr* 1994;**124**(3):374–82.
127. Hodson EM, Willis NS, Craig JC. Growth hormone for children with chronic kidney disease. *Cochrane Database Syst Rev* 2012;**2**: CD003264.
128. Andre JL, Bourquard R, Guillemin F, Krier MJ, Briancon S. Final height in children with chronic renal failure who have not received growth hormone. *Pediatr Nephrol* 2003;**18**(7):685–91.
129. Schaefer F, Seidel C, Binding A, et al. Pubertal growth in chronic renal failure. *Pediatr Res* 1990;**28**(1):5–10.
130. Zivicnjak M, Franke D, Filler G, et al. Growth impairment shows an age-dependent pattern in boys with chronic kidney disease. *Pediatr Nephrol* 2007;**22**(3):420–9.
131. Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO chronic kidney disease-mineral and bone disorder (CKD-MBD) guideline update: what's changed and why it matters. *Kidney Int* 2017;**92**(1):26–36.
132. Rees L, Shroff R. The demise of calcium-based phosphate binders-is this appropriate for children? *Pediatr Nephrol* 2015;**30**(12):2061–71.
133. Shroff R, Wan M, Gullett A, et al. Ergocalciferol supplementation in children with CKD delays the onset of secondary hyperparathyroidism: a randomized trial. *Clin J Am Soc Nephrol* 2012;**7**(2):216–23.
134. Tsampalieros A, Kalkwarf HJ, Wetzsteon RJ, et al. Changes in bone structure and the muscle-bone unit in children with chronic kidney disease. *Kidney Int* 2013;**83**(3):495–502.
135. Polinsky MS, Kaiser BA, Stover JB, Frankenfield M, Baluarte HJ. Neurologic development of children with severe chronic renal failure from infancy. *Pediatr Nephrol* 1987;**1**(2):157–65.
136. Rotundo A, Nevins TE, Lipton M, Lockman LA, Mauer SM, Michael AF. Progressive encephalopathy in children with chronic renal insufficiency in infancy. *Kidney Int* 1982;**21**(3):486–91.
137. Ruebner RL, Laney N, Kim JY, et al. Neurocognitive dysfunction in children, adolescents, and young adults with CKD. *Am J Kidney Dis* 2016;**67**(4):567–75.
138. Madden SJ, Ledermann SE, Guerrero-Blanco M, Bruce M, Trompeter RS. Cognitive and psychosocial outcome of infants dialysed in infancy. *Child Care Health Dev* 2003;**29**(1):55–61.
139. Hooper SR, Gerson AC, Butler RW, et al. Neurocognitive functioning of children and adolescents with mild-to-moderate chronic kidney disease. *Clin J Am Soc Nephrol* 2011;**6**(8):1824–30.
140. Groothoff JW. Long-term outcomes of children with end-stage renal disease. *Pediatr Nephrol* 2005;**20**(7):849–53.
141. Groothoff JW, Grootenhuis MA, Offringa M, Stronks K, Hutten GJ, Heymans HS. Social consequences in adult life of end-stage renal disease in childhood. *J Pediatr* 2005;**146**(4):512–7.
142. Gerson AC, Wentz A, Abraham AG, et al. Health-related quality of life of children with mild to moderate chronic kidney disease. *Pediatrics* 2010;**125**(2):e349–357.
143. Slickers J, Duquette P, Hooper S, Gipson D. Clinical predictors of neurocognitive deficits in children with chronic kidney disease. *Pediatr Nephrol* 2007;**22**(4):565–72.
144. Mendley SR, Matheson MB, Shinnar S, et al. Duration of chronic kidney disease reduces attention and executive function in pediatric patients. *Kidney Int* 2015;**87**(4):800–6.
145. Lande MB, Gerson AC, Hooper SR, et al. Casual blood pressure and neurocognitive function in children with chronic kidney disease: a report of the children with chronic kidney disease cohort study. *Clin J Am Soc Nephrol* 2011;**6**(8):1831–7.
146. Lande MB, Mendley SR, Matheson MB, et al. Association of blood pressure variability and neurocognition in children with chronic kidney disease. *Pediatr Nephrol* 2016;**31**(11):2137–44.
147. Foster BJ, Dahhou M, Zhang X, Platt RW, Hanley JA. Change in mortality risk over time in young kidney transplant recipients. *Am J Transplant* 2011;**11**(11):2432–42.
148. Gillen DL, Stehman-Breen CO, Smith JM, et al. Survival advantage of pediatric recipients of a first kidney transplant among children awaiting kidney transplantation. *Am J Transplant* 2008;**8**(12): 2600–6.
149. McDonald SP, Craig JC, Australian, New Zealand Paediatric Nephrology A. Long-term survival of children with end-stage renal disease. *N Engl J Med* 2004;**350**(26):2654–62.
150. Vats AN, Donaldson L, Fine RN, Chavers BM. Pretransplant dialysis status and outcome of renal transplantation in North American children: a NAPRTCS study. North American Pediatric Renal Transplant Cooperative Study. *Transplantation* 2000;**69**(7): 1414–9.
151. Areses Trapote R, Sanahuja Ibanez MJ, Navarro M, Investigadores Centros Participantes en el R, II. Epidemiology of chronic kidney disease in Spanish pediatric population. REPIR II Project. *Nefrologia* 2010;**30**(5):508–17.
152. Bhimma R, Adhikari M, Asharam K, Connolly C. The spectrum of chronic kidney disease (stages 2-5) in KwaZulu-Natal, South Africa. *Pediatr Nephrol* 2008;**23**(10):1841–6.
153. Huong NT, Long TD, Bouissou F, et al. Chronic kidney disease in children: the national paediatric hospital experience in Hanoi, Vietnam. *Nephrology* 2009;**14**(8):722–7.
154. Kim JJ, Booth CJ, Waller S, Rasmussen P, Reid CJ, Sinha MD. The demographic characteristics of children with chronic kidney disease stages 3-5 in South East England over a 5-year period. *Arch Dis Child* 2013;**98**(3):189–94.
155. Mong Hiep TT, Ismaili K, Collart F, et al. Clinical characteristics and outcomes of children with stage 3-5 chronic kidney disease. *Pediatr Nephrol* 2010;**25**(5):935–40.
156. Peco-Antic A, Bogdanovic R, Paripovic D, et al. Epidemiology of chronic kidney disease in children in Serbia. *Nephrol Dial Transplant* 2012;**27**(5):1978–84.

QUESTIONS AND ANSWERS

Question 1

A newborn male is referred to your clinic because of an abnormality of the kidneys noted on prenatal ultrasound. Review of the images suggests unilateral antenatal hydronephrosis. On physical examination the infant has normal growth parameters, a normal urinary stream and a normal physical examination. Which ONE of the following is the LEAST likely cause of the abnormality in this patient?

A. Transient dilatation of the collecting system
B. Ureteropelvic junction obstruction
C. VUR
D. PUV
E. ARPKD

Answer: E

Prenatal ultrasound can often identify many of the major causes of CKD in children, including CAKUT.[24] Abnormal prenatal ultrasounds should however be repeated postnatally, as transient dilatation of the collecting system can be seen which can completely resolve and abnormalities of the fetal kidneys (cysts, hydronephrosis, hyperechogenic, hypoplastic, or absent kidneys) must be confirmed.[26] Antenatal hydronephrosis, which is confirmed postnatally, can be due to UPJ, VUR, and PUV. In contrast, ARPKD does not usually present with evidence of hydronephrosis. Up to 50% of children with ARPKD are diagnosed prenatally.[31] The clinical criteria for the diagnosis of ARPKD include the presence of enlarged, echogenic kidneys by ultrasound, in the context of one or more additional findings (the absence of renal cysts in both parents, history of a previously affected sibling, parental consanguinity, clinical, laboratory, or pathologic features of hepatic fibrosis).[31,32]

Question 2

A 13-year-old boy with CKD secondary to PUV with VUR and hydronephrosis has an estimated GFR of 40 mL/min/1.73 m^2 by the CKiD formula.

Which ONE of the following should not be part of his clinical treatment plan?

A. Assessment of height, height velocity, and pubertal development
B. Immediate referral for kidney transplant
C. Maintenance of blood pressure below the 90th percentile for age, height, and gender
D. Monitoring S[Ca], S[P], PTH, and vitamin D levels
E. Monitoring hemoglobin levels

Answer: B

Growth failure, delayed puberty, hypertension, anemia, and disorders of bone and mineral metabolism are all common features of CKD in children. Assessing growth, hemoglobin levels, and bone health should be part of routine CKD care. The ESCAPE trial and subsequent KDIGO guidelines on the treatment of hypertension showed slower progression of kidney function decline in individuals with blood pressure lower than the 90th percentile for age, gender, and height, compared to those with BP greater than the 95th percentile and even slower rate of reaching the need for renal replacement therapy in those with BP below the 50th percentile, particularly in those with significant proteinuria.[88] Immediate referral for kidney transplantation in this young boy with CKD secondary to VUR is probably not indicated at this level of GFR, as rates of progression for individuals with nonglomerular causes of CKD are slow.[77] However, when this child enters puberty, he will likely be at risk for accelerated decline in kidney function.

Question 3

A prenatal ultrasound reveals a fetus with unilateral hydronephrosis and hyperechogenic kidney. What is the appropriate first step to evaluate these findings?

A. Postnatal renal ultrasound
B. Radionuclide scanning using technetium-99m−labeled DMSA
C. Voiding cystourethrography
D. Genetic testing for CAKUT
E. None of the above

Answer: A

Abnormal findings in the fetal kidneys (cysts, hydronephrosis, hyperechogenic, hypoplastic, or absent kidneys) must be confirmed postnatally, as hydronephrosis detected prenatally sometimes resolves spontaneously.[26] If the hydronephrosis persists postnatally, then further evaluation is warranted. PUV and VUR, which can both result in hydronephrosis, are diagnosed by voiding cystourethrography. Renal dysplasia is identified by radionuclide scanning using technetium-99m−labeled DMSA, which concentrates only in functional renal tissue.

Question 4

Which of the following statements is true about growth failure in children with CKD:

A. It is particularly problematic during infancy and puberty
B. Birthweight and gestational age play important roles

C. It is associated with increased morbidity and mortality
D. Anemia, renal osteodystrophy, and inflammation contribute to impaired growth
E. All of the above

Answer: E

Impaired growth is associated with impaired psychosocial maturation, decreased health-related quality of life, and increased morbidity and mortality.[109–111] The etiology of growth failure in children with CKD includes the etiology and treatment of the CKD, malnutrition, fluid and electrolyte disturbances, metabolic acidosis, anemia, renal osteodystrophy, and inflammation.[113–116] CKiD study findings indicate that birthweight and gestational age are also associated with growth in children with CKD.[117] Decreased growth is particularly problematic in infancy because about one-third of a child's postnatal growth occurs in the first 2 years. Puberty in children with CKD is often delayed and associated with an attenuated growth spurt.[128–130]

Question 5

A 9-year-old boy with PUV is seen for routine followup. He has an appendicovesicostomy due to inadequate bladder voiding. He has a history of recurrent urinary tract infections. His blood pressure is at the 90th percentile for age/gender/height. His urinalysis has 2+ proteinuria. His current estimated GFR using the bedside CKiD formula is 40 mL/min/1.73 m^2. His hemoglobin is 11.8 g/dL, S[Ca] is normal, and S[P] is elevated at 6.8. All of the following may help to slow progressive kidney disease in this patient EXCEPT:

A. Targeting blood pressure to the 50th percentile for age/gender/height
B. Maintenance of a regular bladder catheterization schedule
C. Institution of a low-protein diet
D. Initiation of therapy with an ACEI
E. Institution of a low phosphorus diet and use of phosphate binders

Answer: C

One of the most important modifiable risk factors of CKD progression is hypertension. The ESCAPE trial demonstrated that intensified blood pressure control (<50th percentile) slowed progressive kidney disease in children.[88] CAKUT is the leading cause of CKD in children, with PUV being one of the most common anomalies in males. In patients with obstructive uropathy and bladder dysfunction, maintenance of a regular voiding schedule is key in preventing urinary stasis, which can predispose to urinary tract infections. Repeated infections may contribute to decline in kidney function. ACEIs and ARBs are important in slowing CKD progression, as they improve blood pressure control and have antiproteinuria effects and antifibrotic effects.[85] Additional factors that may slow CKD progression in children include correction of anemia, dyslipidemia, and calcium–phosphate balance. Reduced protein intake has not been shown to slow CKD progression in children,[96,97] and protein restriction may affect nutrition and growth. Children with CKD should be given the age-appropriate recommended daily allowance for protein intake.

Question 6

A 13-year-old prepubertal girl was recently diagnosed with FSGS. She currently has an estimated GFR of 65 mL/min/1.73 m^2 and 1 gram of urinary protein excretion per day. Her blood pressure is at the 85th percentile for age/gender/height on a small dose of an ACEI. She wants to know about her risk for needing dialysis or a transplant. Which of the following is correct?

A. Her rate of decline in kidney function is expected to be slower than that of a child with a congenital anomaly of the kidney
B. When she reaches ESRD, HD will be the modality of choice
C. FSGS is a rare cause of ESRD in children
D. Lowering her blood pressure further may help to slow progressive kidney disease
E. Her kidney function may improve when she reaches menarche

Answer: D

Children with glomerular disease such as FSGS have a more rapid decline in GFR than children with nonglomerular disease such as CAKUT. In the CKiD prospective multicenter cohort of children with CKD, children with glomerular disease had a median decline in GFR of −4.3 mL/min/1.73 m^2 per year compared to children with nonglomerular disease whose median decline in GFR was only −1.5 mL/min/1.73 m^2 per year.[77] The rate of CKD progression in children is also affected by periods of rapid growth, as evidenced by a steeper decline in kidney function in puberty.[78] In the US, FSGS is the most common glomerular cause of CKD. Although it is likely that this girl will progress to ESRD, preemptive transplantation would be the preferred modality of renal replacement therapy as dialysis (in particular HD) is associated with significant morbidity and mortality. Targeting blood pressure to the 50th percentile for age/gender/height was associated with a decrease in progression of CKD in children in the ESCAPE trial.[88] This patient may benefit from an increased dose of ACE inhibition to improve blood pressure and decrease proteinuria.

CHAPTER

76

Reflux Nephropathy

Tej K. Mattoo[a], *Marva Moxey-Mims*[b]

[a]Children's Hospital of Michigan, Wayne State University School of Medicine, Detroit, MI, United States; [b]Children's National Health System, The George Washington University School of Medicine, Washington, DC, United States

Abstract

Vesicoureteral reflux (VUR) is the most common congenital urological abnormality in children and is most often diagnosed after an episode of urinary tract infection (UTI). Reflux nephropathy is the renal scarring associated with VUR. VUR may be congenital, a result of abnormal renal development leading to focal renal dysplasia, or acquired, from pyelonephritis-induced renal injury. High-grade VUR increases the risk of recurrent UTIs and renal scarring and the associated subsequent morbidity, although the exact mechanism for renal scarring following UTI is not known. The complications of renal scarring are more common in adults. Complications include proteinuria, hypertension, preeclampsia, and end-stage renal disease. There is no conclusive evidence to support a routine use of antimicrobial prophylaxis in the prevention of renal scarring in all children with VUR. Prophylaxis should be used "selectively" in high-risk patients such as those with a high-grade VUR, recurrent UTI, presence of bladder–bowel dysfunction, or coexisting renal scarring.

INTRODUCTION

Vesicoureteral reflux (VUR) is the commonest congenital urological abnormality in children. It is most often diagnosed after an episode of urinary tract infection (UTI), although an increasing number of patients with VUR are diagnosed during follow-up for antenatally diagnosed renal abnormalities, particularly hydronephrosis. The gold standard for diagnosing VUR is a voiding cystourethrogram (VCUG). In the past, the standard of care for a child with a UTI included a routine VCUG to determine the presence and grade of VUR.[1,2] However, currently VCUG is done selectively in high-risk patients as reflected in guidelines published in the United Kingdom and the US.[1,3] According to the International Reflux Grading Scheme, VUR is categorized as grade I through V, mildest to most severe (Figure 76.1).

Reflux nephropathy (RN), previously called chronic pyelonephritis, is the renal scarring associated with VUR. RN may be congenital (also called primary), a result of abnormal renal development leading to focal renal dysplasia, or acquired, resulting from pyelonephritis-induced renal injury. The differentiation of congenital from acquired RN on the basis of a preceding UTI can be arbitrary because the possibility of a preexisting renal scar before UTI cannot always be ruled out. Acquired RN is more common in females, whereas congenital RN occurs mostly in males. Some other important differences between acquired and congenital RN are shown in Table 76.1. A review of some more recent prospective studies revealed that the number of patients with renal scars was higher in studies that included more male patients even though UTI is significantly more common in females, indicating the possibility of more patients with congenital scarring in studies with more males.[2] Renal scars also occur with acute pyelonephritis in the absence of VUR. The current gold standard for diagnosing renal scarring is dimercaptosuccinic acid scintigraphy (^{99m}Tc-DMSA). Imaging does not differentiate between congenital and acquired RN.

INCIDENCE AND PREVALENCE

Primary VUR, which is the most common congenital anomaly of the urinary tract, has a prevalence of about 1% in newborns. It is found in 30%–40% of children with UTI. The genetic predisposition for primary VUR is well known as demonstrated in identical twins (80%), siblings of index cases (27%), and children of a parent with VUR (36%). VUR can occur with some chromosomal anomalies or due to mutations in developmental genes such as PAX2, EYE1,

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00076-0

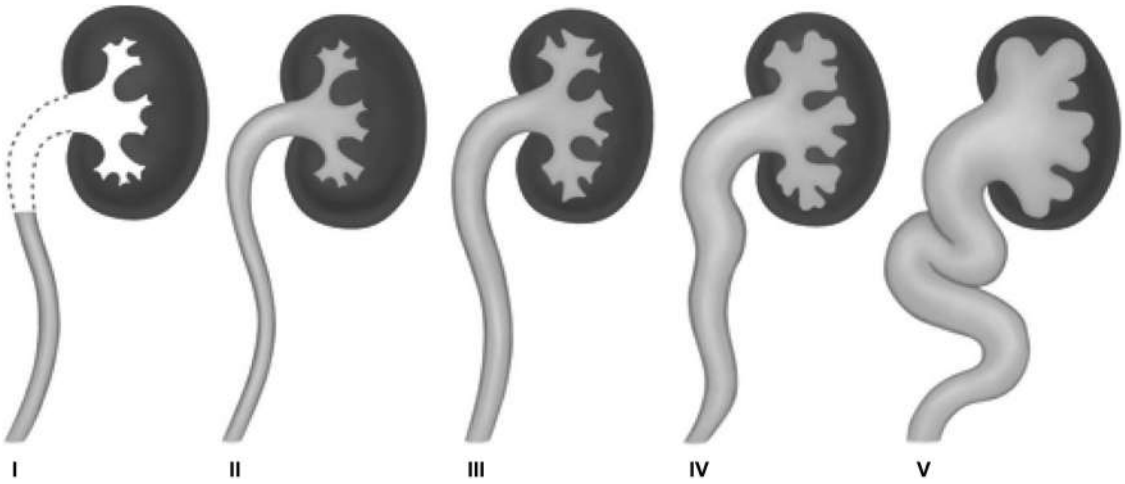


FIGURE 76.1 International Reflux Study grading scheme. Grade I—reflux into nondilated ureter. Grade II—reflux into the renal pelvis and calyces without dilatation. Grade III—mild/moderate dilatation of ureter and pelvicalyceal system. Grade IV—dilation of the renal pelvis and calyces with moderate ureteral tortuosity, blunting of fornices. Grade V—gross dilatation of the ureter, pelvis, and calyces; ureteral tortuosity; loss of papillary impressions.

TABLE 76.1 Congenital Versus Acquired Reflux Nephropathy (RN) in Children

	Acquired RN	Congenital RN
Time of occurrence	Postnatal	Prenatal
UTI before diagnosis	Common	Uncommon
Age distribution	All pediatric age groups	Mostly in younger children
Gender distribution	Predominantly females	Predominantly males
Grade of VUR	Mostly low grade	Mostly high grade
Dysplastic features on renal histopathology	No	Yes

UTI, urinary tract infection; *VUR*, vesicoureteral reflux.

and WT-1,[4,5] which are associated with infection and scarring. Secondary VUR may occur in children with posterior uretheral valves. Some secondary forms of VUR in adults occur due to bladder outlet obstruction as seen in men with enlarged prostates, and neurogenic bladder due to spina bifida—meningomyelocele, spinal cord injury, or multiple sclerosis. Primary VUR is seen predominantly in Caucasians, although the reason is unclear. 81% of the 607 patients randomized in the Randomized Intervention in Children with VUR (RIVUR) study were Caucasians.[4]

The risk of renal scarring after acute pyelonephritis is 5%–10%.[5,6] A systematic review of 33 studies that included DMSA renal scans in children with UTI revealed that 57% (95% confidence interval [CI]: 50–64) had changes consistent with acute pyelonephritis and 15% (95% CI: 11–18) had evidence of renal scarring on the follow-up DMSA scan.[7] In children with VUR and UTI, the incidence of renal scarring is higher at 30%–56%.[8–10] A systematic review of 23 studies that included a total of 2106 children with renal scarring after pyelonephritis revealed some regional variations between Australia (26.5%), Asia (49%), Europe (39.4%), the Middle East (34.3%), and the US (48.5%). The prevalence of renal scarring in healthy populations is not known. In a study in healthy children and adolescents who were evaluated for newly diagnosed hypertension, DMSA renal scans revealed renal scarring in 33 (21%) of 159 patients.[11] In a study in adults with hypertension, radionuclide VCUG revealed VUR in 19.1% (30/157) of the patients. 7 of the 30 (23%) had bilateral VUR, which was graded as severe. The patients were not evaluated for renal scarring.[12] Renal scars that occur in the absence of UTI (congenital RN) are seen in 30–60% of children with VUR diagnosed mostly during follow-up for antenatal hydronephrosis.[13–15]

RISK FACTORS FOR REFLUX NEPHROPATHY

Risk factors for renal scarring include patient age, severity of VUR, frequency of UTI, promptness of antibiotic treatment for pyelonephritis, coexisting bladder–bowel dysfunction (BBD), and genetic susceptibility. A meta-analysis of studies that included a total of 1280 patients aged 0–18 years with first UTI revealed that a temperature of at least 39° C, an etiologic organism other than *Escherichia coli*, an abnormal ultrasonographic finding, polymorphonuclear cell count of greater than 60%, C-reactive protein level of greater than 40 mg/L, and presence of VUR were all associated with the development of renal scars ($p \leq 0.01$ for all).[16]

Children with VUR are at a higher risk of having acute pyelonephritis (relative risk: 1.5 [95% CI: 1.1–1.9]) and renal scarring (relative risk: 2.6 [95% CI: 1.7–3.9]) compared with those without VUR. Those with VUR grades III or higher are more likely to develop scarring than children with lower VUR grades (RR: 2.1 [95% CI: 1.4–3.2]). The risk of renal scarring involving more than 25% of the renal parenchyma is significantly higher in patients with grade III–IV VUR (40%) compared with those with grade I–II VUR (14%) or no VUR (6%).[7] In the RIVUR study, the proportion of new scars due to UTI in kidneys with grade IV VUR was significantly higher than in those without VUR (odds ratio (OR), 24,2; 95% CI, 6.4–91.2).[3] Patients with VUR may have cortical abnormalities even in the absence of a UTI. Such abnormalities are more common in high-grade VUR. A meta-analysis of the published data revealed that renal abnormalities (per 100 renal units) occurred with a mean of 6.2% in those with grades I–III VUR and 47.9% in those with grades IV and V VUR. The abnormalities occurred in 2%–63% (mean 21.8%) of patients with VUR and 26%–42% (mean 32.3%) of the renal units.[17] VUR-related renal scarring is more common in patients with UTI. The OR of renal scarring with acute pyelonephritis in the presence of VUR is 2.8 for patients and 3.7 for renal units compared with those without VUR.[18]

The risk of renal scarring increases with BBD. The presence of BBD increases the risk of febrile UTI in children on antimicrobial prophylaxis for VUR to 44% compared with 13% in those without BBD. BBD delays VUR resolution at 24 months (31% with BBD and 61% without BBD). The frequency of postoperative UTI is greater in children with BBD (22% compared with 5% without BBD). Combined data from longitudinal studies (RIVUR and Careful Urinary Tract Infection Evaluation (CUTIE)) revealed that among toilet-trained children who are not on antimicrobial prophylaxis, those with both BBD and VUR are at higher risk (51%) of developing recurrent UTIs than children with isolated VUR (20%) or children with isolated BBD (35%).[19] In another study from the same cohorts, BBD was a risk factor for renal scarring (OR, 6.44; 95 CI, 2.89–14.38).[20]

Delay in the treatment of febrile UTI increases the risk of renal injury.[21] A multivariate analysis of 158 children with febrile UTI showed therapeutic delay of greater than 48 hours was associated with significantly increased risk of acute lesions on renal scan. However, the Italian Renal Infection Study Trials reported that a delay of the antibiotic treatment of acute pyelonephritis from <1 to ≥ 5 days after the onset of fever was not associated with any significant increase in the risk of scarring. The risk of scarring remained relatively constant at $30.7 \pm 7\%$ over the range of days of delayed antibiotic initiation. Clinical and laboratory indices of inflammation were comparable in all groups, as was the incidence of VUR. In another study, early and appropriate treatment of UTI, especially during the first 24 hours after the onset of symptoms, diminished the likelihood of renal involvement during the acute phase of the infection but did not prevent scar formation.[10] Analysis of the data from the RIVUR and CUTIE patient cohorts revealed that the median duration of fever before antimicrobial therapy in children with and without scarring was 72 and 48 hours, respectively ($p = 0.003$). A delay of 48 hours or more increased the risk of scarring by about 47%.[20]

Younger age has long been believed to be a risk factor for renal scarring due to UTI.[22] However, scarring occurs in adult kidneys as well, as seen in adult transplanted kidneys. Additionally, adult pig kidneys with VUR and UTI scar as quickly as those of piglets with the same comorbidities. Recent studies have reported that age may not be a risk factor for renal scarring and the risk in older children is the same[23–25] or even higher[26] compared with younger children. In the RIVUR study, children with renal scarring were significantly older compared with those with no scarring (median age 26 months vs. 11 months; $p = 0.01$).[3]

Recurrent UTI is a risk factor for renal scarring. In the RIVUR study, significantly more renal scarring was noted in children with a second UTI before enrollment compared with those with a single febrile UTI (OR 2.85; 95% CI, 1.38–5.92).[3]

Some studies suggest the involvement of vasomotor and inflammatory genes in the development of renal scarring after UTI. A meta-analysis of cumulative studies showed association with the angiotensin-converting enzyme insertion/deletion polymorphism [ACE I/D; recessive model for D allele; OR 1.73, 95% CI 1.09–2.74, $p = 0.02$] or transforming growth factor-beta 1 c.-509 T > C polymorphism (dominant model for T allele; OR 2.24, 95% CI 1.34–3.76, $p = 0.002$).[27,28]

COMPLICATIONS OF RENAL SCARRING

The complications of renal scarring are well known, but poorly defined because of their insidious onset, slow progression, and a lack of well-designed prospective studies in children and in adults. Hypertension and proteinuria are the most common reported complications. Other complications include focal segmental glomerulosclerosis (FSGS), urinary concentration defects, hyperkalemia, and acidosis, chronic kidney disease (CKD), and end-stage renal disease (ESRD).

Hypertension

Hypertension occurs in 17–30% of pediatric patients and 34–38% of adult patients with renal scarring.[29,30] In adults, confounding factors such as increasing frequency of primary hypertension and renal scarring due to other renal pathologies make interpretation difficult. According to a survival analysis, it was estimated that 50% of patients with unilateral and bilateral renal damage would have sustained hypertension at about 30 and 22 years of age, respectively. In a follow-up lasting 15 years in pediatric patients with renal scarring, about 13% of patients at age 20–31 years were hypertensive. In a 5-year prospective study of patients with long-standing RN, there was no correlation between blood pressure (BP) and plasma renin activity, plasma creatinine concentration, or degree of scarring.[31]

Some studies have reported no increase in BP after many years of follow-up. In a study of 146 subjects with VUR diagnosed at a mean age of 5 years, no hypertension was seen after a mean follow-up of about 10 years. The cohort included 34.3% patients with renal scarring. In another study of 53 patients with renal scarring following childhood UTI, there was no significant difference in ambulatory BP measurements 16–26 years later, compared with 47 matched subjects without scarring. Mean systolic or diastolic BP above +2 SD was found in 5/53 (9%) and 3/47 (6%) in the scarring and nonscarring group, respectively.[32]

Proteinuria

Overt proteinuria, which has been reported in 21% of adult patients with RN, is rare in pediatric patients. Proteinuria results from glomerular and/or tubulointerstitial damage caused by immunologic injury, macromolecular trapping, and mesangial dysfunction, hypertension, and glomerular hyperfiltration.[33] Microalbuminuria, which indicates glomerular damage at a very early stage and precedes the development of overt proteinuria, progressive renal damage, and renal failure, has been reported in 51% of pediatric patients (mean age 9.8 ± 4.2 years) with renal scarring.[34] Patients with RN also have increased urinary excretion of low molecular weight proteins (LMWPs) such as beta 2-microglobulin, retinol-binding protein, alfa 1-microglobin, and N-acetyl-β-D-glucosaminidase (NAG).[35,36] Microalbuminuria occurs around the same time or soon after the appearance of LMWP in urine. Urinary albumin excretion increases with the severity of renal scarring.[36–38]

FSGS is known to occur in patients with RN. The pathogenesis of FSGS in patients with RN is not clear. The development of FSGS has been attributed to glomerular hyperfiltration, deposition of antigen–antibody complexes, failure of the mesangium to clear macromolecules, and glomerular injury due to circulating immune complexes. FSGS is progressive and can occur in nonscarred parts of the kidney or in the normal contralateral kidney in patients with unilateral RN.[39]

CKD

Renal scarring is responsible for 5%–10% of pediatric and adult cases of ESRD.[40,41] According to the 2008 North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) report, RN is the fourth most common cause of CKD in 8.4% of the children and is present in 5.2% of transplanted patients and 3.5% of dialysis patients. In the CKiD study following a cohort of 586 children aged 1–16 years, with an estimated glomerular filtration rate of 30–90 mL/min/1.73 m^2, RN was the underlying cause of CKD in 87 (14.8%) patients, constituting 19% of the patients with a nonglomerular etiology of CKD.[42]

RN in Adult Patients

The complications of renal scarring are more common in adults, who may present with recurrent UTI, proteinuria, hypertension, increased S[Cr], and diminution in glomerular filtration rate. Adult males with RN generally present with hypertension, proteinuria, and renal failure (Table 76.2). Females present mostly with UTI

TABLE 76.2 Reflux Nephropathy in Adults

	Males	Females
UTI	Uncommon	Frequent
Plasma creatinine	Higher	Normal
End-stage renal failure	More common	Less common
VUR	High-grade/bilateral	Low-grade/unilateral
Proteinuria	Frequent/severe	Infrequent/less severe
Hypertension	More common	Less common

UTI, urinary tract infection; *VUR*, vesicoureteral reflux.

and pregnancy-related complications. Males have poorer outcomes compared with females. This difference has previously been attributed to a delayed diagnosis in males because of an insidious onset of proteinuria and renal failure compared with an earlier diagnosis in females due to recurrent UTI and pregnancy-related complications.[43] However, in view of the knowledge gained in pediatric patients, it is possible that gender differences in the clinical outcome in adults may be more a result of males having mostly congenital RN compared with acquired RN in females.[44]

In a study of 293 adults with RN (mean age at presentation 31 ± 13.4 years), females outnumbered males by a ratio of 5:1. The most common presenting complaints for both genders were UTI (65%), hypertension (20%), and proteinuria (6%). However, UTI as a presenting complaint was significantly more common in females compared with males (72% vs. 31%). In contrast, proteinuria was significantly more common in males (20% vs. 4%). Hypertension was also more common in males than females (29% vs. 18%). VUR was present in 65% of females and 75% of males. Of the 147 patients who were followed for a mean period of 6.9 ± 3.6 years, 21 (14%) developed ESRD after a mean follow-up of 7.0 ± 3.1 years.[40]

Potential complications during pregnancy in women with RN include UTI, hypertension, proteinuria, edema, deterioration in renal function, hematuria, preterm delivery, development of preeclampsia, and fetal loss.[45–47] The degree of renal function at conception seems to be associated with the outcome during pregnancy. A review of literature on the outcome of pregnancy in women with a history of VUR revealed that VUR increases the risk of UTI from 6% to 22%, which increases to 42% when associated with renal scarring. The incidence of hypertension and preeclampsia was significantly higher in women with VUR and renal scarring compared with patients with VUR without scarring.[47]

PREVENTION OF REFLUX NEPHROPATHY

Antimicrobial Prophylaxis

Many randomized studies, including the RIVUR trial, have evaluated the role of antimicrobial prophylaxis in the prevention of recurrent UTI and renal scarring in children with and without VUR.[48–52] The RIVUR study was a randomized, placebo-controlled trial that evaluated the role of antimicrobial prophylaxis in the prevention of UTI and renal scarring in 607 children less than 6 years old with grade I to IV VUR diagnosed after UTI.[53] In the other studies, patients were also randomized to antimicrobial prophylaxis or placebo/surveillance only. One of the studies used endoscopy treatment as the third intervention. Three studies included patients with UTI and VUR. The others included patients with UTI with or without VUR. Altogether, 2042 patients (74% females) were randomized (Table 76.3). A total of 1430 patients had DMSA renal scans to evaluate renal scarring (Table 76.3). None of the six studies showed any difference in the rate of scarring in patients who received prophylaxis/endoscopy compared with patients who did not. A meta-analysis of these studies (including those who underwent Deflux® procedure in a Swedish study) revealed renal scarring in 29% of cases with prophylaxis and endoscopy (Swedish trial) compared with 25% in those who received no intervention or placebo (RR 1.10 [95% CI: 0.98–1.22; p = NS]). Very few new scars were reported during the follow-up period.[44] Another recent meta-analysis of eight prospective studies revealed that the continuous antibiotic prophylaxis significantly reduced the risk of recurrent febrile or symptomatic UTI (pooled OR=0.63, 95% CI=0.42–0.96) in children with VUR but not renal scarring.[54]

TABLE 76.3 Renal Scarring in Recent Randomized Studies in Patients with UTI with or without VUR

Authors and Year of Study	Number of Patients with DMSA Renal Scan	Renal Scarring on DMSA		Relative Risk (95% CI)
		Prophylaxis/Endoscopy*	No Prophylaxis	
Garin et al., 2005	218	7/100 (7%)	6/118 (5%)	1.37 (0.47–3.96)
Pennesi et al., 2008	100	22/50 (44%)	18/50 (36%)	1.22 (0.75–1.98)
Montini et al., 2009	295	50/187 (27%)	33/108 (30.5%)	0.87 (0.60–1.26)
Craig et al., 2009	154	35/71 (49%)	38/83 (46%)	1.07 (0.77–1.50)
*Swedish Reflux Trial, 2010	201	82/133 (62%)*	45/68 (66%)	0.93 (0.75–1.15)
RIVUR Study	462	27/227 (12%)	24/235 (10%)	1.08 (0.78–1.40)
COMBINED	1430	223/768 (29%)	164/662 (25%)	1.10 (0.99–1.22)

UTI, urinary tract infection; *VUR*, vesicoureteral reflux.
* *Includes 40/68 patients on prophylaxis and 42/65 patients who underwent endoscopy.*

Reanalysis of the RIVUR data by using a risk classification system to identify children who are more likely to benefit from antibiotic prophylaxis revealed that high-risk children with VUR benefit even more with prophylaxis. The number needed to treat to prevent UTI recurrence was 5 compared with 18 in low-risk children. The study supported a risk-based approach for management of VUR.[55]

Based on the results of these studies, none of which were designed or powered to evaluate the development of scarring, there is no conclusive evidence to support routine use of antimicrobial prophylaxis for the prevention of renal scarring in children with VUR. Prophylaxis should be used "selectively" in high-risk patients such as those with high-grade VUR, recurrent UTI, presence of BBD, or coexisting renal scarring.[56,57]

Surgical Intervention

Surgical correction of VUR has not been shown to be superior to antimicrobial prophylaxis in the prevention of recurrence of UTI or renal scarring by the International Reflux Study,[58–60] the Birmingham Study, or more recently the Swedish Reflux Trial.[61,62] However, surgical intervention has the advantage that patients do not require follow-up VCUGs to the extent needed in patients on antimicrobial prophylaxis. Surgical treatment is generally recommended for patients with high-grade VUR, breakthrough febrile UTIs while on prophylaxis, allergies to antimicrobials, poor adherence, worsening of scars, and sometimes because of parental preference.[63] Currently, endoscopic treatment of reflux involving subureteral or intraureteral injection of dextranomer hyaluronidase (Deflux®) is offered as first-line surgical treatment in most cases. The success rate (reflux resolution measured by voiding cystography) for the endoscopic procedure is 83% compared with 98.1% for open surgical reimplantation.[18]

Other Management

Appropriate management of BBD is necessary to prevent recurrence of UTI, help resolution of VUR, and possibly prevent further renal injury. Management of BBD includes the treatment of constipation, training in frequent and complete voiding, biofeedback, and/or use of anticholinergic medications or alpha blockers, and continuous intermittent catheterization in extreme cases. Although there are no evidence-based guidelines for the management of increased BP, microalbuminuria/proteinuria, or other complications related to RN, the use of an ACEI or an ARB is recommended. In patients with a poorly functioning kidney due to unilateral RN, removal of the affected kidney may be considered, keeping in mind that the nephrectomy may not cure the hypertension.

SUMMARY

The longstanding dogma about pediatric VUR has been that UTIs are preventable with the use of prophylatic antibiotics, and reduction in the number of UTIs would lead to a reduction of renal scarring, thus preserving renal function. Therefore, the current management of VUR focuses on the prevention of UTI, with "selective" antimicrobial prophylaxis in high-risk patients and curative surgery limited primarily to children that fail conservative measures. Progress has been made in the understanding of the risk factors for RN after UTI. Appropriately designed studies are needed to evaluate the role of any intervention, including antimicrobial prophylaxis, in the prevention of renal scarring with UTI with or without VUR. Better understanding of genetic susceptibility for renal scarring after UTI could greatly enhance the management of VUR and help maximize the preservation of renal function.

References

1. Subcommittee on Urinary Tract Infection SCoQI, Management, Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics* 2011;**128**(3):595–610.
2. Mattoo TK, Chesney RW, Greenfield SP, et al. Renal scarring in the randomized intervention for children with vesicoureteral reflux (RIVUR) trial. *Clin J Am Soc Nephrol* 2016;**11**(1):54–61.
3. National Institute for Health and Clinical Excellence(NICE). *Urinary tract infection in children*. 2007.
4. Hoberman A, Greenfield SP, Mattoo TK, et al. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med* 2014;**370**(25):2367–76.
5. Winberg J, Andersen HJ, Bergstrom T, Jacobsson B, Larson H, Lincoln K. Epidemiology of symptomatic urinary tract infection in childhood. *Acta Paediatr Suppl* 1974;(252):1–20.
6. Pylkkanen J, Vilska J, Koskimies O. The value of level diagnosis of childhood urinary tract infection in predicting renal injury. *Acta Paediatr Scand* 1981;**70**(6):879–83.
7. Shaikh N, Ewing AL, Bhatnagar S, Hoberman A. Risk of renal scarring in children with a first urinary tract infection: a systematic review. *Pediatrics* 2010;**126**(6):1084–91.
8. Faust WC, Diaz M, Pohl HG. Incidence of post-pyelonephritic renal scarring: a meta-analysis of the dimercapto-succinic acid literature. *J Urol* 2009;**181**(1):290–7. discussion 7–8.
9. Rushton HG. The evaluation of acute pyelonephritis and renal scarring with technetium 99m-dimercaptosuccinic acid renal scintigraphy: evolving concepts and future directions. *Pediatr Nephrol* 1997;**11**(1):108–20.
10. Doganis D, Siafas K, Mavrikou M, et al. Does early treatment of urinary tract infection prevent renal damage? *Pediatrics* 2007;**120**(4): e922–8.

11. Ahmed M, Eggleston D, Kapur G, Jain A, Valentini RP, Mattoo TK. Dimercaptosuccinic acid (DMSA) renal scan in the evaluation of hypertension in children. *Pediatr Nephrol* 2008;**23**(3):435–8.
12. Barai S, Bandopadhayaya GP, Bhowmik D, et al. Prevalence of vesicoureteral reflux in patients with incidentally diagnosed adult hypertension. *Urology* 2004;**63**(6):1045–8. discussion 8–9.
13. Yeung CK, Godley ML, Dhillon HK, Gordon I, Duffy PG, Ransley PG. The characteristics of primary vesico-ureteric reflux in male and female infants with pre-natal hydronephrosis. *Br J Urol* 1997;**80**(2):319–27.
14. Ismaili K, Hall M, Piepsz A, et al. Primary vesicoureteral reflux detected in neonates with a history of fetal renal pelvis dilatation: a prospective clinical and imaging study. *J Pediatr* 2006;**148**(2): 222–7.
15. Sweeney B, Cascio S, Velayudham M, Puri P. Reflux nephropathy in infancy: a comparison of infants presenting with and without urinary tract infection. *J Urol* 2001;**166**(2):648–50.
16. Shaikh N, Craig JC, Rovers MM, et al. Identification of children and adolescents at risk for renal scarring after a first urinary tract infection: a meta-analysis with individual patient data. *JAMA Pediatr* 2014;**168**(10):893–900.
17. Skoog SJ, Peters CA, Arant BS, et al. Pediatric vesicoureteral reflux guidelines panel summary report: clinical practice guidelines for screening siblings of children with vesicoureteral reflux and neonates/infants with prenatal hydronephrosis. *J Urol* 2010;**184**(3): 1145–51.
18. Peters CA, Skoog SJ, Arant BS, et al. Summary of the AUA guideline on management of primary vesicoureteral reflux in children. *J Urol* 2010;**184**(3):1134–44.
19. Shaikh N, Hoberman A, Keren R, et al. Recurrent urinary tract infections in children with bladder and bowel dysfunction. *Pediatrics* 2016;**137**(1):1–7.
20. Shaikh N, Mattoo TK, Keren R, et al. Early antibiotic treatment for pediatric febrile urinary tract infection and renal scarring. *JAMA Pediatr* 2016;**170**(9):848–54.
21. Smellie JM, Poulton A, Prescod NP. Retrospective study of children with renal scarring associated with reflux and urinary infection. *BMJ* 1994;**308**(6938):1193–6.
22. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. *Pediatrics* 1999; **103**(4 Pt 1):843–52.
23. Ataei N, Madani A, Habibi R, Khorasani M. Evaluation of acute pyelonephritis with DMSA scans in children presenting after the age of 5 years. *Pediatr Nephrol* 2005;**20**(10):1439–44.
24. Lin KY, Chiu NT, Chen MJ, et al. Acute pyelonephritis and sequelae of renal scar in pediatric first febrile urinary tract infection. *Pediatr Nephrol* 2003;**18**(4):362–5.
25. Benador D, Benador N, Slosman D, Mermillod B, Girardin E. Are younger children at highest risk of renal sequelae after pyelonephritis? *Lancet* 1997;**349**(9044):17–9.
26. Pecile P, Miorin E, Romanello C, et al. Age-related renal parenchymal lesions in children with first febrile urinary tract infections. *Pediatrics* 2009;**124**(1):23–9.
27. Zaffanello M, Tardivo S, Cataldi L, Fanos V, Biban P, Malerba G. Genetic susceptibility to renal scar formation after urinary tract infection: a systematic review and meta-analysis of candidate gene polymorphisms. *Pediatr Nephrol* 2011;**26**(7):1017–29.
28. Cordell HJ, Darlay R, Charoen P, et al. Whole-genome linkage and association scan in primary, nonsyndromic vesicoureteric reflux. *J Am Soc Nephrol* 2010;**21**(1):113–23.
29. Zhang Y, Bailey RR. A long term follow up of adults with reflux nephropathy. *N Z Med J* 1995;**108**(998):142–4.
30. Kohler J, Tencer J, Thysell H, Forsberg L. Vesicoureteral reflux diagnosed in adulthood. Incidence of urinary tract infections, hypertension, proteinuria, back pain and renal calculi. *Nephrol Dial Transplant* 1997;**12**(12):2580–7.
31. Savage JM, Koh CT, Shah V, Barratt TM, Dillon MJ. Five year prospective study of plasma renin activity and blood pressure in patients with longstanding reflux nephropathy. *Arch Dis Child* 1987; **62**(7):678–82.
32. Wennerstrom M, Hansson S, Jodal U, Sixt R, Stokland E. Renal function 16 to 26 years after the first urinary tract infection in childhood. *Arch Pediatr Adolesc Med* 2000;**154**(4):339–45.
33. Cotran RS. Nephrology Forum. Glomerulosclerosis in reflux nephropathy. *Kidney Int* 1982;**21**(3):528–34.
34. Karlen J, Linne T, Wikstad I, Aperia A. Incidence of microalbuminuria in children with pyelonephritic scarring. *Pediatr Nephrol* 1996;**10**(6):705–8.
35. Miyakita H, Puri P. Urinary levels of N-acetyl-beta-D-glucosaminidase: a simple marker for predicting tubular damage in higher grades of vesicoureteric reflux. *Eur Urol* 1994;**25**(2):135–7.
36. Goonasekera CD, Shah V, Dillon MJ. Tubular proteinuria in reflux nephropathy: post ureteric re-implantation. *Pediatr Nephrol* 1996; **10**(5):559–63.
37. Bell FG, Wilkin TJ, Atwell JD. Microproteinuria in children with vesicoureteric reflux. *Br J Urol* 1986;**58**(6):605–9.
38. Tomlinson PA, Smellie JM, Prescod N, Dalton RN, Chantler C. Differential excretion of urinary proteins in children with vesicoureteric reflux and reflux nephropathy. *Pediatr Nephrol* 1994;**8**(1):21–5.
39. Kincaid-Smith P. Glomerular lesions in atrophic pyelonephritis and reflux nephropathy. *Kidney Int Suppl* 1975;**4**:S81–3.
40. el-Khatib MT, Becker GJ, Kincaid-Smith PS. Reflux nephropathy and primary vesicoureteric reflux in adults. *Q J Med* 1990;**77**(284): 1241–53.
41. Becker GJ, Kincaid-Smith P. Reflux nephropathy: the glomerular lesion and progression of renal failure. *Pediatr Nephrol* 1993;**7**(4): 365–9.
42. Furth SL, Abraham AG, Jerry-Fluker J, et al. Metabolic abnormalities, cardiovascular disease risk factors, and GFR decline in children with chronic kidney disease. *Clin J Am Soc Nephrol* 2011; **6**(9):2132–40.
43. Williams DG. Reflux nephropathy. *Q J Med* 1990;**77**(284):1205–7.
44. Mattoo TK. Vesicoureteral reflux and reflux nephropathy. *Adv Chron Kidney Dis* 2011;**18**(5):348–54.
45. el-Khatib M, Packham DK, Becker GJ, Kincaid-Smith P. Pregnancy-related complications in women with reflux nephropathy. *Clin Nephrol* 1994;**41**(1):50–5.
46. Jungers P, Houillier P, Chauveau D, et al. Pregnancy in women with reflux nephropathy. *Kidney Int* 1996;**50**(2):593–9.
47. Hollowell JG. Outcome of pregnancy in women with a history of vesico-ureteric reflux. *BJU Int* 2008;**102**(7):780–4.
48. Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. *Pediatrics* 2006;**117**(3): 626–32.
49. Pennesi M, Travan L, Peratoner L, et al. Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. *Pediatrics* 2008;**121**(6):e1489–94.
50. Montini G, Rigon L, Zucchetta P, et al. Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. *Pediatrics* 2008;**122**(5):1064–71.
51. Craig JC, Simpson JM, Williams GJ, et al. Antibiotic prophylaxis and recurrent urinary tract infection in children. *N Engl J Med* 2009;**361**(18):1748–59.

52. Brandstrom P, Esbjorner E, Herthelius M, et al. The Swedish reflux trial in children: I. Study design and study population characteristics. *J Urol* 2010;**184**(1):274–9.
53. Hoberman A, Chesney RW, Investigators RT. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med* 2014;**371**(11):1072–3.
54. Wang HH, Gbadegesin RA, Foreman JW, et al. Efficacy of antibiotic prophylaxis in children with vesicoureteral reflux: systematic review and meta-analysis. *J Urol* 2015;**193**(3):963–9.
55. Wang ZT, Wehbi E, Alam Y, Khoury A. A reanalysis of the RIVUR trial using a risk classification system. *J Urol* 2018;**199**(6):1608–14.
56. Mattoo TK, Thomas R. Routine prophylaxis is not necessary to prevent renal scarring in children with urinary tract infection. *Evid Based Med* 2017;**22**(6):208.
57. Mattoo TK, Carpenter MA, Moxey-Mims M, Chesney RW, For The RTI. The RIVUR trial: a factual interpretation of our data. *Pediatr Nephrol* 2015;**30**(5):707–12.
58. Piepsz A, Tamminen-Mobius T, Reiners C, et al. Five-year study of medical or surgical treatment in children with severe vesicoureteral reflux dimercaptosuccinic acid findings. International Reflux Study Group in Europe. *Eur J Pediatr* 1998;**157**(9):753–8.
59. Olbing H, Hirche H, Koskimies O, et al. Renal growth in children with severe vesicoureteral reflux: 10-year prospective study of medical and surgical treatment: the International Reflux Study in Children (European branch). *Radiology* 2000;**216**(3):731–7.
60. Smellie JM, Tamminen-Mobius T, Olbing H, et al. Five-year study of medical or surgical treatment in children with severe reflux: radiological renal findings. The International Reflux Study in Children. *Pediatr Nephrol* 1992;**6**(3):223–30.
61. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children: five years' observation. Birmingham Reflux Study Group. *Br Med J* 1987;**295**(6592):237–41.
62. Brandstrom P, Esbjorner E, Herthelius M, Swerkersson S, Jodal U, Hansson S. The Swedish reflux trial in children: III. Urinary tract infection pattern. *J Urol* 2010;**184**(1):286–91.
63. Diamond DA, Mattoo TK. Endoscopic treatment of primary vesicoureteral reflux. *N Engl J Med* 2012;**366**(13):1218–26.

QUESTIONS AND ANSWERS

Question 1

A 15-year-old patient is seen in the nephrology clinic for hypertension. The patient has a past history of UTIs. Laboratory investigations reveal normal blood chemistry and urinalysis. The renal ultrasound examination shows a normal right kidney and a smaller left kidney. Renal scarring of the left kidney is suspected. Of the following, which one is most associated with renal scarring that occurs after UTI in children?

A. Male gender
B. African-American ethnicity
C. Renal dysplasia
D. VUR
E. Ureteropelvic junction (UPJ) obstruction

Answer: D

Renal scarring may occur after acute pyelonephritis with or without VUR, but the risk is higher in those with VUR.[18] Such renal scarring (RN) is more common in females. VUR and hence renal scarring associated with VUR and UTI is less common in non-Caucasians. Renal dysplasia is seen in patients with congenital RN. UPJ obstruction can predispose to UTI and thereby cause renal scarring, but this is less common in children compared with renal scarring associated with VUR and UTI.

Question 2

A 13-year-old girl presents with a history of recurrent UTI for the last year. She denied sexual activity. The parents believe that she had a couple of UTIs in early childhood. Of the following, which one would be the most helpful investigation?

A. VCUG
B. DMSA renal scan
C. CT scan
D. Renal ultrasound
E. Diuretic renal scan

Answer: B

Doing a DMSA renal scan goes with a "top-down" approach, in which instead of doing a VCUG to see if patient has VUR, a DMSA renal scan is done to see if the patient has any renal scarring. If the DMSA renal scan is normal, there is no need to do a VCUG. However, if the DMSA is positive, it might be worth considering a VCUG to see if she has VUR that needs to be managed appropriately. Renal ultrasound or a CT scan is not the investigation of choice for renal scarring. The latter is helpful in diagnosing renal stones, which is an important cause of UTI and scarring in adult patients. A diuretic renal scan is indicated in patients with hydronephrosis with suspected UPJ obstruction, but it is not indicated in this patient.

Question 3

An 8-year-old boy was seen recently in an Emergency Department because of abdominal trauma. A CT scan of the abdomen revealed scarring in the right kidney. He has a past history of VUR on the right that was treated surgically at the age of 2 years. The patient is suspected of having right RN. Which one is true of RN?

A. VUR is present when renal scarring is diagnosed
B. VUR may occur in the absence of a UTI
C. Adult males most often present with recurrent UTI
D. FSGS is seen in scarred renal tissue
E. In patients with VUR, surgical correction is better than antimicrobial prophylaxis in preventing recurrent UTI

Answer: B

VUR may have resolved by the time renal scarring is diagnosed. Absence of VUR does not rule out the possibility of RN. Renal scarring (evaluated by a DMSA renal scan) can be present in association with VUR with no history of UTI, which is called congenital RN. It is adult females with RN who most often present with recurrent UTI compared with male. FSGS occurs in nonscarred portions of the kidney and can even occur in the contralateral kidney. Multiple studies have demonstrated no difference between surgical correction and long-term antimicrobial prophylaxis in the prevention of recurrent UTI.[60,61]

Question 4

An infant is evaluated postnatally due to a history of antenatal hydronephrosis. He is found to have VUR and renal scarring. Which of the following is true of congenital RN?

A. Congenital RN results from abnormal renal development and focal renal dysplasia
B. Congenital RN requires a history of UTI
C. Congenital RN occurs more commonly in females
D. Congenital RN is also known as primary RN
E. Both A and D

Answer: E

RN may be congenital, a result of abnormal renal development resulting in focal renal dysplasia, or acquired, from pyelonephritis-induced renal injury. Congenital RN includes patients with antenatal hydronephrosis who on postnatal evaluation are found to have VUR and renal scarring with no history of UTI.

The differentiation of congenital and acquired RN on the basis of a preceding UTI can be arbitrary because the possibility of a preexisting renal scar before UTI cannot always be ruled out. Acquired RN is seen more often in females, whereas congenital RN occurs mostly in males.

Question 5

A 5-year-old child with VUR is found to have elevated S[Cr] and significant scarring on DMSA scan. Mechanisms underlying post-UTI renal scarring include which of the following?

A. Hemodynamic alterations
B. Focal ischemia
C. Inflammatory responses
D. Macromolecular trapping
E. All of the above

Answer: E

The mechanism for renal scarring following UTI is believed to result from a combination of factors that include focal ischemia, inflammatory response to released toxins, immunological mechanisms, macromolecular trapping, and mesangial dysfunction, vascular alterations, hypertension, and hemodynamic alterations.[33] Antioxidant-mediated renal tubular injury is attributed to the release of superoxides during tissue reperfusion.

Question 6

A woman with a history of VUR goes to the emergency room at 30 weeks gestation with symptoms consistent with a UTI. Potential complications for this pregnancy include which of the following?

A. Preterm delivery
B. Hypertension
C. Preeclampsia
D. Fetal loss
E. All of the above

Answer: E

The potential complications during pregnancy in women with RN include UTI, hypertension, proteinuria, edema, deterioration in renal function, hematuria, preterm delivery, preeclampsia, and fetal loss.[45–47] The incidence of hypertension and preeclampsia is significantly higher in women with VUR and renal scarring compared with those with VUR without scarring.[47]

CHAPTER

77

Chronic Kidney Disease in the Elderly—Who Has It? Who Does One Treat? and How are They to be Treated?

Samir S. Patel

Renal Section, Veterans Affairs Medical Center, Washington, DC and George Washington University Medical Center, Washington, DC, United States

Abstract

Age is a major risk factor for chronic kidney disease (CKD). The world population that is elderly is growing dramatically, making CKD and end-stage renal disease (ESRD) a significant public health concern worldwide. The aging kidney undergoes changes that lead to a decline in glomerular filtration rate (GFR) and possibly increased susceptibility to injury. The diagnosis of early CKD vs. normal aging in the elderly by GFR estimation equations is controversial, but level of albuminuria remains an important prognostic indicator. Advances in prediction of progressive CKD in the elderly will assist in the important task of advance care planning. Nephrologists will need to consider illness trajectory, comorbidities, frailty, and overall functional status in the management of the elderly patient with failing kidneys. For certain elderly individuals, conservative, or nondialytic, management for ESRD may be appropriate because extension of life is minimal and diminished quality of life is almost certain. Early and ongoing discussions of goals of care are critical to nephrologic care in the elderly. Palliative care is an important concept for nephrologists to understand and utilize in the care of all elderly patients with CKD regardless of treatment with renal replacement therapy or conservative care.

INTRODUCTION

The term "elderly" has traditionally been defined as greater than 60 for demographers, but is often defined as above 65 in many developed nations due to its association with retirement and pension benefits. With improvements in public health in the modern era, functional and chronological age has increasingly been dissociated and has resulted in an expanding elder population throughout the world. Concomitant chronic illnesses, including chronic kidney disease (CKD), have increased along with higher individual and societal costs. The overall burden of CKD in the older population has been increasingly recognized and was the topic of World Kidney Day 2014.

The high prevalence of CKD in the elderly has multiple causes including not only increased longevity and rising rates of risk factors such as obesity and diabetes mellitus but also greater recognition based on diagnostic criteria for CKD. Although there is clearly a need to address CKD in the aging population, advanced age often presents challenges in the management of CKD. Aging is often associated with complicating factors such as orthostatic hypotension, labile blood pressure, and decline in vision, hearing, cognition, and balance. In addition, reduced social support, limited financial resources, and polypharmacy add to the challenges involved in management of CKD in the elderly. The nephrology community has become increasingly aware of the special considerations for the care of the elderly with CKD including decisions regarding renal replacement therapy (RRT).

EPIDEMIOLOGY AND PUBLIC HEALTH IMPLICATIONS

The world population has been growing dramatically since the beginning of the 20th century. There exist 7.6 billion individuals in mid-2017, of whom 13% are greater than 60 years of age.[1] People are living longer, leading to a larger percentage of elderly worldwide.

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00077-2

Although the segment of the population defined as elderly has increased disproportionately in developed nations, life expectancy is projected to rise further in high-income areas of the world, as well as in low- and middle-income regions. Life expectancy exceeds 75 years in Europe, North American, and Oceania. Life expectancy is projected to rise from 71 years in 2010−2015 to 77 years in 2045−2050 for the entire world population.[1] The reported prevalence of CKD worldwide increases with age and is highest in the elderly population. An analysis of adults living in 32 countries, accounting for nearly one half of the world population, found a CKD (stages 1−5) prevalence of 10.4% in men and 11.8 % in women. Approximately 50% of those individuals were greater than 60 years of age.[2] However, there is considerable variation in estimates between countries and reported studies.

The wide range of reported CKD prevalence is likely a result of the number of S[Cr] measures taken, estimation equations used to determine glomerular filtration rate (GFR), incorporation of albuminuria in the diagnosis, and varying laboratory standards.[3] Estimates of CKD in the US, based on a large representative sample of the noninstitutionalized US population, found approximately 7% of the US population has a reduced GFR, defined as less than 60 mL/min/1.73 m^2, based on an estimated GFR (eGFR) using both S[Cr] and cystatin C.[4] Also in the US, the prevalence of CKD appears to have increased dramatically in the elderly, perhaps reaching over 45% of the 70 years or older population.[5] Most of these individuals are categorized in the CKD stage 3a group (eGFR between 45 and 60 mL/min/1.73 m^2).

Regardless of the exact prevalence of CKD, the health consequences of CKD are substantial. The Global Burden of Disease study (2013) estimated 956,000 deaths worldwide in 2013 were attributable to CKD.[2] Most of the elderly with CKD die before reaching end-stage renal disease (ESRD) from cardiovascular disease (CVD).[6,7] The associated disease burden attributable to CKD is based on the related burden of hypertension and associated coronary, cerebral, and peripheral vascular disease. CKD has been tightly associated with CVD risk, and kidney disease accounts for the mortality risk in patients with diabetes mellitus.[8]

Costs for earlier stages of CKD are difficult to define due to inaccurate reporting and inability to attribute costs directly to CKD, because it is frequently associated with other costly comorbidities such as congestive heart failure and diabetes mellitus. The US Renal Data System reported that, in 2016, Medicare spending for beneficiaries with CKD exceeded 67 billion dollars for those aged 65 and older.[9] CKD is considered a cost multiplier, because individuals with recognized CKD represent 13% of the point prevalent aged Medicare population, yet account for 25% of total expenditures.

The incidence of ESRD in the elderly and the cost of treatment have major public health implications throughout the world. In the US, the highest incidence rate for ESRD is in those aged 75 and greater. The estimated cost of the ESRD program in the US for Medicare was 35 billion dollars in 2016, representing approximately 7% of the entire Medicare budget.[9] The tremendous economic and health burden of ESRD and its treatment in the elderly population underscores the need to slow progression of CKD and prevent ESRD.

KIDNEY SENESCENCE

The biologic aging of the kidneys from maturity to death, or kidney senescence, involves both structural changes involving all compartments of the kidney (renal blood vessels, glomeruli, tubules, and interstitium) and physiologic changes in renal blood flow, GFR, filtration fraction, and electrolyte and water handling. A number of theories of aging exist, broadly described as a natural process influenced by both genetic and environmental factors. Genetic and environmental factors likely combine in any individual aging kidney to different levels, explaining the variability seen in human studies.[10] Factors associated with progressive loss of renal function are listed in Table 77.1. Greater knowledge of the biology of aging will be needed to develop strategies to limit age-related decline in renal function. However, cellular senescence *in vivo* and the link to whole organ senescence as seen clinically remain to be elucidated.[11]

TABLE 77.1 Factors Associated With Renal Aging

ENVIRONMENTAL
Hypertension
Smoking
Dyslipidemia
Obesity
Male gender
Atherosclerotic disease
GENETIC
Epigenetic changes (DNA methylation, acetylation, microRNAs)
Replicative termination (telomere shortening)
Oxidative stress
Klotho signaling

Oxidative stress (a result of increased free radical generation and decreased antioxidant capacity) and inflammation both increase with aging and are likely agents of age-related renal decline. Increased circulating inflammatory cytokines are seen in CKD and aging, even before a measurable decrease in GFR.[12] Oxidative stress is hypothesized to be a critical factor in age-related chronic inflammation, leading to cell senescence and DNA damage.[13] Chronic inflammation leads to fibrosis because inflammatory factors stimulate proliferation of fibroblasts. The proinflammatory cytokines TNF-α and interleukin-1 induce apoptosis, particularly when oxidative stress is at high levels.

Inflammation may lead to cell senescence, and senescent cells release high amounts of inflammatory factors leading to the development of a vicious cycle. One other important component of the aging process is advanced glycation end products (AGEs), which can generate reactive oxygen species (ROS). On the other hand, ROS enhances glycation, leading to another vicious cycle. AGEs induce proinflammatory genes and activate NF-κB and mitogen-activated protein kinase in various cell types *in vitro*. Ultimately, inflammatory cytokines, AGEs, and oxidative stress may be the mediators that impair repair and regeneration of the kidneys.[10]

THE AGING KIDNEY

Early studies showed renal mass *in vivo* declined from approximately 400 to 300 g with age, but not until individuals were very old. In addition, renal blood flow (per unit of kidney mass) was found to decline slowly after the fourth decade with reduced blood flow to the cortex relative to the medulla.[14] New insights into the structural changes in the kidney have been gained from imaging studies of the general population and also of kidney donors. One study of 1852 adults using magnetic resonance imaging to measure kidney volume found total kidney volume decreased by about 16 cm^3 per decade. Most of the decline was seen in those over 60 years old.[15] Another study of 1334 living kidney donors by computed tomography scan found volume only declined after age 50, and then at a rate of 22 cm^3 per decade. Furthermore, the investigators found cortical volume decreases with age, but medullary volume increases to maintain relatively stable kidney volume until after age 50 years.[16]

Hemodynamic changes including decreased afferent arteriolar resistance and decreased ultrafiltration coefficient, corresponding to reduced filtration surface, have been found in animal models of aging. Studies performed in healthy human kidney donors seem to confirm these animal studies.[17] Changes in the renin–angiotensin–aldosterone system, particularly reduced circulating levels of renin and aldosterone, are seen with aging.[18] The finding of decreased afferent arteriolar resistance with an overall enhanced sensitivity to vasoconstriction at the efferent arteriole may predispose to the development of glomerular hypertension, contributing to renal decline.[19] There may be a normal and also pathologic decline in nitric oxide (NO) with aging as a result of oxidative stress, reduced L-arginine, and increased asymmetric dimethylarginine. The reduced NO is thought to be responsible for the reduced vasodilatory capacity or increased sensitivity to vasoconstriction in the kidneys of elderly people.[20] Endothelin regulation is impaired in the aging kidney, leading to heightened vasoconstriction.[21] The balance of vasodilation and vasoconstrictive responsiveness may be related to susceptibility to acute kidney injury (AKI) in the elderly.[22,23]

Histologic changes in the kidney are difficult to attribute specifically to aging. The findings of an increased proportion of globally sclerotic glomeruli (glomerulosclerosis), increased arteriosclerosis (fibrointimal hyperplasia), medial hypertrophy, arteriolar hyalinosis, and tubular atrophy with surrounding areas of interstitial fibrosis, designated often as arterionephrosclerosis of aging, may be the result of injuries from environmental factors.[24] Traditional tissue pathology is not clearly helpful because healthy kidney donors have vascular changes and glomerulosclerosis. Increased global glomerulosclerosis is often cited as indicative of renal senescence, but as much as 10% of glomeruli may be globally sclerosed in people up to age 40.[25]

Most individuals demonstrate a decline in GFR over time. GFR remains normal until the fourth decade when it gradually declines in a linear fashion, as seen in the landmark Baltimore Longitudinal Study. This was confirmed subsequently in 254 subjects, who had a mean decrease in creatinine clearance of 0.75 mL/min/year.[26] Of note, approximately one-third of the subjects had no absolute decrease in renal function, and a small group of patients had an increase in creatinine clearance with age.[27] A natural decline in renal structure and function appears inevitable once an individual is elderly, but it does not culminate in the development of ESRD. The individuals that progress to substantial decrements in renal function and ESRD must have other contributing factors.

DIAGNOSIS OF CKD IN THE ELDERLY

As with other age groups, screening for renal disease in the elderly may be done by a combination of measurement of GFR using serum markers such as S[Cr] and a urinary protein (preferably albumin) measurement in a spot sample, as recommended by the KDIGO

guidelines.[28] Urinary abnormalities (primarily proteinuria), imaging, or histologic evidence of renal damage or disease qualifies as CKD if present for longer than 3 months. Once CKD is diagnosed, evaluation for associated systemic disease and determination of the anatomic location of the kidney lesion (e.g. vascular, glomerular, tubular, and interstitial) is advocated by the KDIGO guidelines. Estimation equations for GFR using S[Cr] along with age, gender, and ethnicity have been commonly used for both clinical practice and epidemiological studies.

Accurate GFR estimation is needed for diagnostic and epidemiological purposes but has been problematic in the elderly population. Initially, the MDRD estimation equation underestimated GFR in patients with near normal GFR and in the elderly. This was partially addressed by use of the CKD-EPI equation and use of a standardized laboratory measurement technique to measure S[Cr], although some sources of variation remain.[29] The CKD-EPI equation was found to be superior to the MDRD equation for patients 65 or older and with a GFR greater than 60 mL/min/1.73 m^2.[30]

Despite a general tendency toward declining renal function with age, S[Cr] often does not change as patients age due to decreased muscle mass, reduced creatinine generation, and/or reduced protein intake in the diet of elderly patients. Therefore, estimation equations using cystatin C may be more accurate in the elderly, because cystatin C is not affected by muscle mass, particularly for those with GFR 60 mL/min/1.73 m^2 or above. Cystatin C-based estimation equations were better than S[Cr]-based equations for predicting both cardiovascular and kidney outcomes in the elderly without CKD.[31]

The distinction between age-related decline in GFR and significant CKD in an elderly person may be difficult. Although renal changes associated with aging in basic science studies using animal models demonstrate proteinuria, urinary protein excretion greater than 300 mg/g creatinine (overt proteinuria), should not be considered a consequence of normal aging in humans.[32] This proposition is primarily buttressed by the fact that proteinuria is an independent risk factor for progression to ESRD. Both eGFR and proteinuria are predictive of ESRD in the elderly.[33] Indeed, proteinuria is more predictive and reliable for progression of CKD and development of ESRD than eGFR. The KDIGO guidelines incorporated proteinuria, specifically, albuminuria, into its staging. The combination of using eGFR assessed by S[Cr] and cystatin C, as well as consideration of albuminuria, may be the best strategy to diagnose CKD in the elderly.[34–36]

The accurate diagnosis of CKD in the elderly remains a challenge in epidemiological studies. As mentioned earlier, the elderly population has varying muscle loss and changes in protein intake that may affect serum creatinine concentration. Aging women reach the arbitrary threshold of an eGFR of less than 60 mL/min/1.73 m^2 sooner than men. In a comprehensive review of the subject, Glassock et al. noted that prevalence estimates of CKD vary widely throughout the world despite good calibration of S[Cr] measurement by the IDMS (isotope dilution mass spectrometry) reference method.[3] Age, estimation equation used, biomarkers used (e.g. cystatin C, albuminuria), and number of S[Cr] measures (one at initiation of study vs. follow-up measures) all add to the variance. Furthermore, calibration of cystatin C remains an issue. Age-based cutoffs for GFR in the definition of CKD have been proposed based on studies that indicate an overdiagnosis of CKD (vs. age-related decline in GFR) using S[Cr]-based GFR estimation equations. However, it remains controversial if this will help achieve the goal of accurate diagnosis and prognosis.

PROGRESSIVE CKD TO ESRD IN THE ELDERLY

The development of ESRD is of great concern on both the individual and societal level. Although the incidence rate has slowed in the US, the prevalence of ESRD continues to grow. The average age at initiation of dialysis is greater than 60 years of age, and the greatest rise in incidence rates has been in the very old.[9] Unfortunately, mortality remains very high, particularly in the first year of dialysis. Many elderly patients initiate hemodialysis (HD) after prolonged hospitalization and with central venous catheters.[37] In the US, worsening functional decline or death in the year after initiation of dialysis occurs in the majority of elderly nursing home residents.[38] Although alive on RRT, elderly patients suffer from high rates of depression, decreased quality of life, pain, and sleep disturbances.

To better serve elderly individuals with CKD, better methods to determine risk for ESRD would be of tremendous value in healthcare decision-making. As in younger patients, the baseline eGFR and proteinuria predict progressive loss of renal function. Prediction equations have been developed for risk of ESRD, most notably the Kidney Failure Risk equation by Tangri and colleagues.[39] Rate of progression, as estimated by changes in eGFR over time, has been advanced as an additional parameter to further refine prediction. Tangri and colleagues later developed a dynamic predictive model for progression of CKD and found that eGFR changes improved prediction vs. prediction based on one baseline value of eGFR.[40]

In the elderly patient with advanced CKD, rate of decline tends to be slower than in younger patients. A number of studies indicate risk for ESRD declines vs. the competing risk for death with advancing age until

the eGFR is less than 15 mL/min/1.73 m^2, or with elevated proteinuria.[6] Drawz and colleagues developed a model to predict one year risk for ESRD in 1866 elderly (65 years or older) US Veterans with eGFR less than 30 mL/min/1.73 m^2.[41] Risk factors for ESRD in the final model were age, congestive heart failure, systolic blood pressure, eGFR, potassium, and albumin. The researchers found that the Tangri model also had good predictive ability on their validation cohort, with a concordance index of 0.78. Clinicians should use prediction equations to help determine timing of clinical follow-up and whether discussion about RRT is prudent.

RENAL REPLACEMENT THERAPY VERSUS CONSERVATIVE MANAGEMENT

Although life may be prolonged with RRT, it does not necessarily improve quality of life, because treatment with dialysis for elderly patients is associated with more time spent in healthcare settings, decreased satisfaction with life, and increased risk of dying in the hospital rather than at home.[42–44] For elderly CKD stage 5 patients with poor prognostic factors, such as ischemic heart disease, peripheral vascular disease, and dementia, a time-limited trial of dialysis may be offered with a commitment to review goals of care after the patient has stabilized on RRT (e.g. 4 weeks). Based on the patient progress in terms of goals of care, dialysis may be stopped or continued. Shared decision-making must be part of the process of making a decision for RRT vs. conservative care.

There is a growing literature of observational studies that indicate RRT does not prolong survival in those aged >80 years, and with poor baseline health as assessed by comorbidities such as congestive heart failure or poor functional status.[45–49] Given the poor survival and quality of life of many elderly CKD patients beginning RRT, conservative care, or nondialytic management of such patients, has become a valid fourth option for management of incident ESRD along with HD, peritoneal dialysis, and transplantation. Detailed guidelines on withholding and withdrawal of dialysis are available to assist clinicians regarding shared decision-making.[50]

To aid the clinician, prognostic tools have been developed to determine mortality risk for individuals who are initiated on RRT. A risk calculator for six-month mortality after initiation of dialysis was developed from data on nearly 2200 individuals 65 years or older in Canada. AKI was excluded, and the 19 point scale uses commonly available clinical data: age 80 years or older (two points), GFR of 10–14.9 mL/min/1.73 m^2 (one point) or ≥15 mL/min/1.73 m^2 (three points), atrial fibrillation (two points), lymphoma (five points), congestive heart failure (two points), hospitalization in the prior 6 months (two points), and metastatic cancer (three points). Although estimating prognosis for any single individual is difficult, prediction equations may help inform decisions about dialysis or conservative management that fit with the patient's values and goals of care.[51]

IMPACT OF FRAILTY

In addition to estimating prognosis with chronological age and comorbid conditions, the geriatric syndrome of frailty may be useful in estimating outcomes for elderly CKD patients considering RRT. The term frailty can be considered to encompass age-related decline and increased vulnerability to adverse health outcomes. Frailty may herald other geriatric syndromes such as falls, fractures, delirium, and incontinence.[52,53] Although no gold standard exists to determine frailty, it is usually measured in terms of physical parameters and described as the frailty phenotype. The most common measure for the frailty phenotype was identified by Linda Fried and colleagues. It is based on five parameters (weight loss, muscle weakness, fatigue or exhaustion, low physical activity, and gait speed) in participants of the Cardiovascular Health Study (CHS). The frailty phenotype (if three of the five criteria are present) was associated with increased risk of falls, hospitalization, and death in CHS.[54]

A systematic review of 32 studies of frailty and CKD found that 72% of studies determined frailty by the phenotype outlined by Fried.[55] Several studies found an increasing prevalence of frailty with worsening CKD, although the prevalence of frailty depends on the measure and the population studied. Of note, a decline in muscle mass seen with frail elders may affect S[Cr] and therefore eGFR and CKD diagnosis. Studies using cystatin C showed a tighter association between GFR decline and frailty. Frailty predicts adverse outcomes in both the CKD and ESRD populations.[56,57] Bao et al. showed that frailty was associated with a higher eGFR at dialysis initiation, perhaps in part explaining the observed association of mortality with higher eGFR at the start of dialysis.[58] The finding of frailty in elderly patients with advancing CKD should lead to earlier discussions of prognosis and discussions regarding conservative care once ESRD develops.

ILLNESS TRAJECTORY AND ADVANCE CARE PLANNING

In making treatment decisions for elderly patients with CKD, clinicians must consider the illness trajectory to help decision-making for conservative care vs. RRT. An estimation of rate of renal loss would help determine if, and approximately when, ESRD will develop. This may be estimated from age, baseline GFR, level of proteinuria, and rate of decline in GFR. CKD illness trajectory may not be a linear decline from year to year, but rather characterized by events causing an abrupt drop in GFR from AKI with incomplete recovery of renal function.[59] In addition, acute changes in functional status may also occur with supervening illness (such as a myocardial infarction, prolonged hospitalization, or amputation). The high rates of initiation of RRT with a central venous catheter and after intensive medical care in the Medicare population[37] may be due to unexpected deterioration of renal function in elderly patients with stable but advanced CKD.

The decision to start or withhold RRT begins with a discussion about prognosis between the patient and physician. This information can be used to assist in shared decision-making regarding management of ESRD. Advance care planning (ACP) includes a discussion in which the patient's values, preferences, and goals are identified which will be used to inform future healthcare decision-making. ACP is appropriate for all patients with CKD and should be done early in the disease course when the patient has healthcare decision-making capacity and is not suffering from the effects of uremia or acute illness.[50] The goal of ACP is to ensure the patient's wishes (fulfilling the right to autonomy) and the communication of those wishes to family, significant others, healthcare proxies, and healthcare providers. It is important to note that patients and families expect physicians to introduce the topic and to facilitate such discussions among families.[60,61] Furthermore, nephrologists need to address and readdress goals of care throughout the course of progressive CKD in an elderly patient because the illness trajectory can be unpredictable.

Advance directives (ADs) are legal documents that allow patients to record their wishes for future healthcare, including end-of-life (EOL) care. AD may result from ACP but are not necessarily the goal of the process. Although associated with decreased healthcare costs, decreased in-hospital deaths, and increased use of hospice, ADs are often not completed.[62,63] In the ESRD population, AD completion rates are lower than in other chronic illnesses.[63] A detailed evaluation of the contents of AD among 808 patients treated with chronic HD (mean age of 68.6 years old; men = 61.2%) found that 49% had ADs, of which 10.6% mentioned dialysis and only 3% specifically addressed dialysis management at EOL.[64] Small studies in the dialysis population indicate completion of AD may improve surrogate bereavement and increase hospice utilization.[65,66] At the minimum, the designation of a healthcare surrogate or proxy and do-not-resuscitate preferences should be documented as AD in accordance with guidelines.[50]

ISSUES FOR ELDERLY PATIENTS CHOOSING RENAL REPLACEMENT THERAPY

Modality and Timing of Initiation

Elderly patients who choose to include RRT in their care for ESRD should be offered all forms of RRT, including in-center HD, Home HD, peritoneal dialysis (PD), and transplantation based on similar criteria for younger individuals with ESRD. No modality has been proven to be superior to the other in the elderly population, although transplantation, as with the younger population, is still the preferred treatment in suitable candidates and based on life expectancy.[67] In general, candidates for RRT make a selection based on personal preferences that are usually influenced by lifestyle and social circumstances.

Early initiation of RRT has not been supported by observational trial data and one large randomized trial.[68,69] Observational studies show that many are initiated with an eGFR between 10 and 15 mL/min/1.73 m^2, but this is associated with worsened survival. This finding may be due to overestimation of GFR in individuals with muscle wasting, frailty, or reduced functional status (including amputations). Recent guidelines support starting RRT when eGFR is less than 10 and closer to 6 mL/min/1.73 m^2.[70] However, in the elderly population, symptoms have frequently been cited as a reason for starting dialysis rather than decline in eGFR below a cutoff level.[71] In the elderly, poor nutrition, reduced ability to perform activities of daily living, and nonspecific gastrointestinal symptoms are commonly cited reasons for dialysis initiation over traditional indications (e.g refractory hyperkalemia, fluid overload, uremic pericaridits, or neuropathy). However, functional decline and nutritional deficiency have both been shown to worsen despite initiation of dialysis. The option to delay initiation until definitive indications present may be valid in the elderly patient and should be included in shared decision-making.[72,73]

Hemodialysis Access

Initiation of HD with an arteriovenous fistula (AVF) is associated with better outcomes and lower costs; however, successful creation and development of a fistula is a challenge in elderly individuals. The reduced risk of infection conferred by an AVF over an arteriovenous graft (AVG) is attenuated considerably by advanced age and limited life expectancy, making AVG a viable initial access for HD.[74] Early discussions about RRT can not only allow additional time for AVF creation but can also lead to a significant number of AVF that are never used, leading to an unfavorable balance in harm to benefit. Based on modeling of data on US Veterans, O'Hare and colleagues found only one in five AVF would be unnecessary for those over 85 years old if guidelines are followed.[75] Decision-making regarding AVF creation has to be individualized to account for likelihood of development of ESRD and perhaps rate of progression.[76] For some elderly patients, despite their risks, central venous catheters may be an appropriate permanent access if it fits with their goals of care.

Peritoneal Dialysis

Few elderly patients are started on PD in the US.[9] Concerns over ability to perform the procedure in elderly patients with the frailty phenotype or cognitive decline may dissuade the treating nephrologist from recommending this modality. Observational studies regarding survival are mixed, but it is generally accepted that PD is a viable option for the elderly.[77,78] Advantages of PD over HD that may be appealing for the elderly patient with goals of care that emphasize quality of life include reduced time away from home, reduced transportation requirements, avoidance of HD-associated discomfort such as muscle cramping, needle cannulation, and posttreatment fatigue.[79] Additional training by the PD nurse and center, as well as support at home by caregivers to assist in the procedure, may overcome barriers to PD in the elderly patient with ESRD.[80] Reported experiences on assisted PD in the elderly population from Europe support this as a reasonable alternative to in-center HD.[81]

Kidney Transplantation

Kidney transplantation remains the modality of choice for RRT even in the elderly population. Wolfe and colleagues reported a 61% reduction in long-term risk of death and increase in life span by 4 years for older dialysis patients (ages 60–74) who received a cadaveric transplant over those that remained on the wait list.[82] In a similar study of wait-listed individuals on dialysis and over the age of 70 years, Rao and colleagues found a 56% lower mortality in cadaveric transplant recipients, including a 47% reduction in mortality for diabetic patients.[83] Age is not a contraindication to transplantation but transplantation occurs less frequently in the elderly then in other age groups. Many elderly patients on dialysis die on the transplant wait list. The kidney allocation system was changed in January 2015 to prioritize longevity matching. This is likely to increase waiting times for the elderly population.[84] Schold and colleagues demonstrated that it may be advantageous for elderly individuals treated with dialysis to receive an expanded criteria donor over waiting for a standard deceased donor kidney. Similar survival rates were obtained with the benefit of reduced time on dialysis.[85,86]

PALLIATIVE AND END OF LIFE CARE FOR ESRD

The burden of disease is high for the elderly with ESRD, with high mortality rates, particularly in the first several months after initiation of HD. Dialysis patients over the age of 65 years have substantially higher mortality compared with Medicare populations with cancer, diabetes, or CVD at a rate of 164 per 1000 patient years in 2016.[9] Morbidity and mortality in ESRD are largely due to extensive CVD and increased risk of infection. Additional morbidity from uremia, as well as dialysis treatment and its complications, may be found in elders with ESRD on RRT. Although not well characterized, it appears that patients on dialysis suffer from numerous symptoms. Davison and colleagues found an average of 7.5 symptoms per patient on HD, with 4.5 characterized as moderate or severe.[87] Using the Dialysis Symptom Index, Weisbord and colleagues found a median of 9.0 symptoms among dialysis patients, with the majority reporting dry skin, fatigue, itching, and musculoskeletal pain.[88]

A palliative approach to care of the elderly patient with ESRD is reasonable in patients with low potential for rehabilitation and high risk of death in one year. A predictive tool validated for elderly dialysis patients that incorporates age, serum albumin concentration (S[Alb]), dementia, and peripheral vascular disease along with a "surprise" question ("Would I be surprised if this patient died in the next 12 months?") could be used to prioritize palliative care for those that are at risk for early mortality.[89] Palliative care differs from the standard approach of disease-oriented care to one that prioritizes patient quality of life and relief of symptoms. The approach is molded by the patient's goals of care and preferences. Palliative care, by a proposed definition from the International Association for Hospice and Palliative Care, is "active holistic care of individuals across all ages with serious health-related suffering due to severe illness

TABLE 77.2 Key Aspects of Palliative Care

Includes prevention, early detection, comprehensive assessment, and management of physical symptoms, psychological distress, and social needs.
Provides support to help patients live as fully as possible until death by facilitating effective communication, helping them and their families determine goals of care.
Is applicable in conjunction with disease-modifying therapies whenever needed.
May positively influence the course of illness.
Intends neither to hasten nor postpone death, affirms life, and recognizes dying as a natural process.
Provides support to the family and caregivers during the patient's illness and in their own bereavement.
Is delivered recognizing and respecting the cultural values and beliefs of the patient and the family.
Is applicable throughout all healthcare settings (place of residence and institutions) and at all levels (primary to tertiary).
Can be provided by professionals with basic palliative care training.
Requires specialist palliative care with a multiprofessional team for referral of complex cases.

Adapted from Consensus based definition of palliative care. *International Association for Hospice and Palliative Care. www.hospicecare.com.*

and especially at the EOL. It aims to improve quality of life in all patients, their families, and caregivers." This definition includes key aspects which are listed in Table 77.2.

Standard care focuses on provision of RRT to achieve quality metrics such as urea clearance and phosphate levels. However, this may not coincide with the patient's priorities in the final year of life. Palliative care emphasizes relief of suffering by treatment of pain and other physical, psychological, and spiritual problems. It is important to communicate to patients and their families that palliative care is not equivalent to hospice care, but referral to hospice may be part of palliative care. Life prolonging therapies may still be continued with the palliative care approach, but there is no intention to prolong, or shorten, life with this approach.[90,91]

Palliative care can be part of conservative care (nondialytic care of ESRD) or can be provided with continued RRT. Conservative care, or comprehensive conservative care, for ESRD may be everything in standard care except initiation of RRT.[92] It often includes palliative care, particularly in the final months, weeks, or days of life. However, palliative care may also be part of the management plan for patients treated with RRT.[93] Incremental or reduced HD, assisted PD, liberalized diet, catheter as permanent access, and prudent reduction in pill burden are potential strategies in palliative care in elderly patients treated with dialysis.

TABLE 77.3 Clinical Practice Guidelines and Web Resources for Palliative and End-Of-Life Care in CKD/ESRD

Renal Physicians Association. *Shared decision-making in the appropriate initiation of and withdrawal from dialysis*. 2nd ed.; 2010—https://www.renalmd.org—(summary and toolkit available for download)
International Association of Hospice and Palliative Care. *Manual of palliative care*. 3rd ed.; 2013—https://hospicecare.com (full manual available for download)
Coalition for the Supportive Care of Kidney Patients. www.kidneysupportivecare.org
National Consensus Project for Quality Palliative Care. *Clinical practice guidelines for quality palliative care*. 4th ed. https://www.nationalcoalitionhpc.org/ncp (full guidelines available for download)

Palliative care involves determination of patient preferences and therefore emphasizes the need for early and ongoing discussions of patient's goals of care, or ACP. ACP is an integral part of palliative care and may include AD and Physician Orders for Life-Sustaining Treatment (POLST). Importantly, the palliative care approach is more likely to be beneficial to the patient and family when provided in a multidisciplinary setting that includes social workers, physical and occupational therapists, dietitians, clergy or the equivalent, nephrologists, primary care physicians, and specialists in palliative medicine. Studies have identified physician factors as barriers to ACP and EOL discussions, such as timing of discussions, reluctance to discuss death, and poor communication during EOL discussions.[94–96] Multiple resources exist to assist nephrologists in the palliative care of CKD and dialysis patients (Table 77.3).

Nephrologists and other healthcare providers may be reluctant to discuss EOL or withdrawal of dialysis due to concerns over depression. It has long been recognized that the burdens of CKD and ESRD, including RRT itself, are associated with high rates of depressive affect and depression.[97] Furthermore, suicide rates are higher in those with ESRD than the general population for those over 29 years of age, with age greater than 75 years as an additional risk factor.[98] The role of depression in withdrawal of dialysis remains unclear and requires further study. However, screening for depression in all patients with ESRD has been advocated and should be part of management of those considering withholding or withdrawal of dialysis.[99] It is reasonable to attempt treatment of depression before a final decision regarding withholding or withdrawal of dialysis is undertaken.

All patients who stop dialysis and many patients who choose not to begin dialysis should be offered hospice care to facilitate symptom management and bereavement care for families and loved ones. Discontinuation of dialysis before death has been the case in approximately 20% of all US dialysis patients and approximately 30%

or more for those aged 75 years or older.[9] Average survival after discontinuation of dialysis is reported to be between 7 and 10 days.[100] However, extended survival may occur if there is residual kidney function. Symptoms such as fatigue, dyspnea, and pain are fairly common among those with ESRD near the EOL. Symptoms may be addressed appropriately with involvement of palliative medicine specialists and avoidance of emergent initiation of RRT that may be incongruent with the patient's goals of care. In general, hospice care is available for individuals with a predicted survival of less than 6 months and may be provided on an inpatient or outpatient basis. In the US, dialysis patients who discontinue dialysis are eligible for hospice under Medicare. In cases in which the admitting diagnosis to hospice is a terminal condition outside of ESRD (e.g. metastatic cancer), dialysis may be continued under the ESRD Medicare benefit. Although hospice is underutilized by patients with ESRD in comparison with patients with terminal cancer, the rates may be rising with enhanced palliative care services over the past two decades.[101,102]

SUMMARY AND CONCLUSIONS

The prevalence of CKD in the elderly is rising worldwide with the potential for tremendous individual and societal burdens. Early diagnosis of disease or impairment in renal function along with improved prognostication regarding development of ESRD is critical in managing this challenge. Scientific discovery regarding the aging kidney may help to prevent age-related decline in renal reserve, renal function, and susceptibility to AKI. Determination of illness trajectory and mortality risk and establishing goals of care are essential considerations for the caring nephrologist. Management of failing kidneys in elderly patients requires ongoing discussions between the physician and the patient and family. Nephrologists should be skilled in facilitating shared decision-making. Nephrologists should be knowledgeable regarding the risks and benefits of dialysis in the elderly and, if appropriate, the implementation of conservative and/or palliative care in the treatment of elderly patients with renal failure.

References

1. United Nations DoEaSA. *Word population prospects: the 2017 revision, key findings and advance tables*. United Nations; 2017.
2. Mills KT, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, et al. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int* 2015;**88**(5):950–7.
3. Glassock RJ, Warnock DG, Delanaye P. The global burden of chronic kidney disease: estimates, variability and pitfalls. *Nat Rev Nephrol* 2017;**13**(2):104–14.
4. Grams ME, Juraschek SP, Selvin E, Foster MC, Inker LA, Eckfeldt JH, et al. Trends in the prevalence of reduced GFR in the United States: a comparison of creatinine- and cystatin C-based estimates. *Am J Kidney Dis* 2013;**62**(2):253–60.
5. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. *J Am Med Assoc* 2007;**298**(17):2038–47.
6. O'Hare AM, Choi AI, Bertenthal D, Bacchetti P, Garg AX, Kaufman JS, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol* 2007;**18**(10):2758–65.
7. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004;**164**(6):659–63.
8. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, et al. Kidney disease and increased mortality risk in type 2 diabetes. *J Am Soc Nephrol* 2013;**24**(2):302–8.
9. United States Renal Data System. *2018 USRDS annual data report: epidemiology of kidney disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018.
10. O'Sullivan ED, Hughes J, Ferenbach DA. Renal aging: causes and consequences. *J Am Soc Nephrol* 2017;**28**(2):407–20.
11. Melk A, Halloran PF. Cell senescence and its implications for nephrology. *J Am Soc Nephrol* 2001;**12**(2):385–93.
12. Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, et al. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation* 2003;**107**(1):87–92.
13. Vlassara H, Torreggiani M, Post JB, Zheng F, Uribarri J, Striker GE. Role of oxidants/inflammation in declining renal function in chronic kidney disease and normal aging. *Kidney Int Suppl* 2009;(114):S3–11.
14. Hollenberg NK, Adams DF, Solomon HS, Rashid A, Abrams HL, Merrill JP. Senescence and the renal vasculature in normal man. *Circ Res* 1974;**34**(3):309–16.
15. Roseman DA, Hwang SJ, Oyama-Manabe N, Chuang ML, O'Donnell CJ, Manning WJ, et al. Clinical associations of total kidney volume: the Framingham Heart Study. *Nephrol Dial Transplant* 2017;**32**(8):1344–50.
16. Wang X, Vrtiska TJ, Avula RT, Walters LR, Chakkera HA, Kremers WK, et al. Age, kidney function, and risk factors associate differently with cortical and medullary volumes of the kidney. *Kidney Int* 2014;**85**(3):677–85.
17. Hoang K, Tan JC, Derby G, Blouch KL, Masek M, Ma I, et al. Determinants of glomerular hypofiltration in aging humans. *Kidney Int* 2003;**64**(4):1417–24.
18. Duggan J, Kilfeather S, O'Brien E, O'Malley K, Nussberger J. Effects of aging and hypertension on plasma angiotensin II and platelet angiotensin II receptor density. *Am J Hypertens* 1992;**5**(10):687–93.
19. Fuiano G, Sund S, Mazza G, Rosa M, Caglioti A, Gallo G, et al. Renal hemodynamic response to maximal vasodilating stimulus in healthy older subjects. *Kidney Int* 2001;**59**(3):1052–8.
20. Kielstein JT, Bode-Boger SM, Frolich JC, Ritz E, Haller H, Fliser D. Asymmetric dimethylarginine, blood pressure, and renal perfusion in elderly subjects. *Circulation* 2003;**107**(14):1891–5.
21. Castellani S, Ungar A, Cantini C, La Cava G, Di Serio C, Altobelli A, et al. Excessive vasoconstriction after stress by the aging kidney: inadequate prostaglandin modulation of increased endothelin activity. *J Lab Clin Med* 1998;**132**(3):186–94.

22. Anderson S, Eldadah B, Halter JB, Hazzard WR, Himmelfarb J, Horne FM, et al. Acute kidney injury in older adults. *J Am Soc Nephrol* 2011;**22**(1):28–38.
23. Abdel-Rahman EM, Okusa MD. Effects of aging on renal function and regenerative capacity. *Nephron Clin Pract* 2014;**127**(1–4): 15–20.
24. Zhou XJ, Rakheja D, Yu X, Saxena R, Vaziri ND, Silva FG. The aging kidney. *Kidney Int* 2008;**74**(6):710–20.
25. Rule AD, Amer H, Cornell LD, Taler SJ, Cosio FG, Kremers WK, et al. The association between age and nephrosclerosis on renal biopsy among healthy adults. *Ann Intern Med* 2010;**152**(9):561–7.
26. Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J Clin Investig* 1950;**29**(5):496–507.
27. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc* 1985; **33**(4):278–85.
28. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:1–150.
29. Kwong YT, Stevens LA, Selvin E, Zhang YL, Greene T, Van Lente F, et al. Imprecision of urinary iothalamate clearance as a gold-standard measure of GFR decreases the diagnostic accuracy of kidney function estimating equations. *Am J Kidney Dis* 2010; **56**(1):39–49.
30. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro 3rd AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**(9):604–12.
31. Shlipak MG, Katz R, Sarnak MJ, Fried LF, Newman AB, Stehman-Breen C, et al. Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. *Ann Intern Med* 2006;**145**(4):237–46.
32. Verma V, Kant R, Sunnoqrot N, Gambert SR. Proteinuria in the elderly: evaluation and management. *Int Urol Nephrol* 2012; **44**(6):1745–51.
33. Hallan SI, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR. Combining GFR and albuminuria to classify CKD improves prediction of ESRD. *J Am Soc Nephrol* 2009;**20**(5):1069–77.
34. Zhang M, Cao X, Cai G, Wu D, Wei R, Yuan X, et al. Clinical evaluation of serum cystatin C and creatinine in patients with chronic kidney disease: a meta-analysis. *J Int Med Res* 2013;**41**(4):944–55.
35. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis* 2008;**51**(3):395–406.
36. Shlipak MG, Matsushita K, Arnlov J, Inker LA, Katz R, Polkinghorne KR, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med* 2013; **369**(10):932–43.
37. Wong SP, Kreuter W, O'Hare AM. Healthcare intensity at initiation of chronic dialysis among older adults. *J Am Soc Nephrol* 2014;**25**(1):143–9.
38. Kurella Tamura M, Covinsky KE, Chertow GM, Yaffe K, Landefeld CS, McCulloch CE. Functional status of elderly adults before and after initiation of dialysis. *N Engl J Med* 2009;**361**(16): 1539–47.
39. Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *J Am Med Assoc* 2016;**315**(2):164–74.
40. Tangri N, Inker LA, Hiebert B, Wong J, Naimark D, Kent D, et al. A dynamic predictive model for progression of CKD. *Am J Kidney Dis* 2017;**69**(4):514–20.
41. Drawz PE, Goswami P, Azem R, Babineau DC, Rahman M. A simple tool to predict end-stage renal disease within 1 year in elderly adults with advanced chronic kidney disease. *J Am Geriatr Soc* 2013;**61**(5):762–8.
42. Berger JR, Hedayati SS. Renal replacement therapy in the elderly population. *Clin J Am Soc Nephrol* 2012;**7**(6):1039–46.
43. Wongrakpanich S, Susantitaphong P, Isaranuwatchai S, Chenbhanich J, Eiam-Ong S, Jaber BL. Dialysis therapy and conservative management of advanced chronic kidney disease in the elderly: a systematic review. *Nephron* 2017;**137**(3):178–89.
44. Lovell N, Jones C, Baynes D, Dinning S, Vinen K, Murtagh FE. Understanding patterns and factors associated with place of death in patients with end-stage kidney disease: a retrospective cohort study. *Palliat Med* 2017;**31**(3):283–8.
45. Hussain JA, Mooney A, Russon L. Comparison of survival analysis and palliative care involvement in patients aged over 70 years choosing conservative management or renal replacement therapy in advanced chronic kidney disease. *Palliat Med* 2013;**27**(9): 829–39.
46. Murtagh FE, Marsh JE, Donohoe P, Ekbal NJ, Sheerin NS, Harris FE. Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. *Nephrol Dial Transplant* 2007;**22**(7):1955–62.
47. Chandna SM, Da Silva-Gane M, Marshall C, Warwicker P, Greenwood RN, Farrington K. Survival of elderly patients with stage 5 CKD: comparison of conservative management and renal replacement therapy. *Nephrol Dial Transplant* 2011; **26**(5):1608–14.
48. Verberne WR, Dijkers J, Kelder JC, Geers ABM, Jellema WT, Vincent HH, et al. Value-based evaluation of dialysis versus conservative care in older patients with advanced chronic kidney disease: a cohort study. *BMC Nephrol* 2018;**19**(1):205.
49. Reindl-Schwaighofer R, Kainz A, Kammer M, Dumfarth A, Oberbauer R. Survival analysis of conservative vs. dialysis treatment of elderly patients with CKD stage 5. *PLoS One* 2017;**12**(7): e0181345.
50. *Shared decision-making in the appropriate initiation of and withdrawal from dialysis: clinical practice guideline*. 2nd ed. Rockville, MD: Renal Physicians Association; 2010.
51. Wick JP, Turin TC, Faris PD, MacRae JM, Weaver RG, Tonelli M, et al. A clinical risk prediction tool for 6-month mortality after dialysis initiation among older adults. *Am J Kidney Dis* 2017; **69**(5):568–75.
52. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci* 2004;**59**(3):255–63.
53. Hamerman D. Toward an understanding of frailty. *Ann Intern Med* 1999;**130**(11):945–50.
54. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;**56**(3):M146–56.
55. Chowdhury R, Peel NM, Krosch M, Hubbard RE. Frailty and chronic kidney disease: a systematic review. *Arch Gerontol Geriatr* 2017;**68**:135–42.
56. Roshanravan B, Khatri M, Robinson-Cohen C, Levin G, Patel KV, de Boer IH, et al. A prospective study of frailty in nephrology-referred patients with CKD. *Am J Kidney Dis* 2012;**60**(6):912–21.

57. Dalrymple LS, Katz R, Rifkin DE, Siscovick D, Newman AB, Fried LF, et al. Kidney function and prevalent and incident frailty. *Clin J Am Soc Nephrol* 2013;**8**(12):2091−9.
58. Bao Y, Dalrymple L, Chertow GM, Kaysen GA, Johansen KL. Frailty, dialysis initiation, and mortality in end-stage renal disease. *Arch Intern Med* 2012;**172**(14):1071−7.
59. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med* 2014;**371**(1):58−66.
60. Singer PA, Martin DK, Kelner M. Quality end-of-life care: patients' perspectives. *J Am Med Assoc* 1999;**281**(2):163−8.
61. Steinhauser KE, Christakis NA, Clipp EC, McNeilly M, McIntyre L, Tulsky JA. Factors considered important at the end of life by patients, family, physicians, and other care providers. *J Am Med Assoc* 2000;**284**(19):2476−82.
62. Nicholas LH, Langa KM, Iwashyna TJ, Weir DR. Regional variation in the association between advance directives and end-of-life Medicare expenditures. *J Am Med Assoc* 2011;**306**(13):1447−53.
63. Holley JL. Advance care planning in CKD/ESRD: an evolving process. *Clin J Am Soc Nephrol* 2012;**7**(6):1033−8.
64. Feely MA, Hildebrandt D, Edakkanambeth Varayil J, Mueller PS. Prevalence and contents of advance directives of patients with ESRD receiving dialysis. *Clin J Am Soc Nephrol* 2016;**11**(12):2204−9.
65. Kirchhoff KT, Hammes BJ, Kehl KA, Briggs LA, Brown RL. Effect of a disease-specific advance care planning intervention on end-of-life care. *J Am Geriatr Soc* 2012;**60**(5):946−50.
66. Song MK, Ward SE, Fine JP, Hanson LC, Lin FC, Hladik GA, et al. Advance care planning and end-of-life decision making in dialysis: a randomized controlled trial targeting patients and their surrogates. *Am J Kidney Dis* 2015;**66**(5):813−22.
67. Segall L, Nistor I, Van Biesen W, Brown EA, Heaf JG, Lindley E, et al. Dialysis modality choice in elderly patients with end-stage renal disease: a narrative review of the available evidence. *Nephrol Dial Transplant* 2017;**32**(1):41−9.
68. Cooper BA, Branley P, Bulfone L, Collins JF, Craig JC, Fraenkel MB, et al. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med* 2010;**363**(7):609−19.
69. Rosansky S, Glassock RJ, Clark WF. Early start of dialysis: a critical review. *Clin J Am Soc Nephrol* 2011;**6**(5):1222−8.
70. Nesrallah GE, Mustafa RA, Clark WF, Bass A, Barnieh L, Hemmelgarn BR, et al. Canadian Society of Nephrology 2014 clinical practice guideline for timing the initiation of chronic dialysis. *CMAJ* 2014;**186**(2):112−7.
71. Rosansky SJ, Cancarini G, Clark WF, Eggers P, Germaine M, Glassock R, et al. Dialysis initiation: what's the rush? *Semin Dial* 2013;**26**(6):650−7.
72. Rosansky SJ, Schell J, Shega J, Scherer J, Jacobs L, Couchoud C, et al. Treatment decisions for older adults with advanced chronic kidney disease. *BMC Nephrol* 2017;**18**(1):200.
73. Treit K, Lam D, O'Hare AM. Timing of dialysis initiation in the geriatric population: toward a patient-centered approach. *Semin Dial* 2013;**26**(6):682−9.
74. Tamura MK, Tan JC, O'Hare AM. Optimizing renal replacement therapy in older adults: a framework for making individualized decisions. *Kidney Int* 2012;**82**(3):261−9.
75. O'Hare AM, Bertenthal D, Walter LC, Garg AX, Covinsky K, Kaufman JS, et al. When to refer patients with chronic kidney disease for vascular access surgery: should age be a consideration? *Kidney Int* 2007;**71**(6):555−61.
76. Shechter SM, Skandari MR, Zalunardo N. Timing of arteriovenous fistula creation in patients with CKD: a decision analysis. *Am J Kidney Dis* 2014;**63**(1):95−103.
77. Weinhandl ED, Foley RN, Gilbertson DT, Arneson TJ, Snyder JJ, Collins AJ. Propensity-matched mortality comparison of incident hemodialysis and peritoneal dialysis patients. *J Am Soc Nephrol* 2010;**21**(3):499−506.
78. Mehrotra R, Chiu YW, Kalantar-Zadeh K, Bargman J, Vonesh E. Similar outcomes with hemodialysis and peritoneal dialysis in patients with end-stage renal disease. *Arch Intern Med* 2011;**171**(2):110−8.
79. Meeus F, Brown EA. Caring for older patients on peritoneal dialysis at end of life. *Perit Dial Int* 2015;**35**(6):667−70.
80. Brown EA, Finkelstein FO, Iyasere OU, Kliger AS. Peritoneal or hemodialysis for the frail elderly patient, the choice of 2 evils? *Kidney Int* 2017;**91**(2):294−303.
81. Iyasere OU, Brown EA, Johansson L, Huson L, Smee J, Maxwell AP, et al. Quality of life and physical function in older patients on dialysis: a comparison of assisted peritoneal dialysis with hemodialysis. *Clin J Am Soc Nephrol* 2016;**11**(3):423−30.
82. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999;**341**(23):1725−30.
83. Rao PS, Merion RM, Ashby VB, Port FK, Wolfe RA, Kayler LK. Renal transplantation in elderly patients older than 70 years of age: results from the Scientific Registry of Transplant Recipients. *Transplantation* 2007;**83**(8):1069−74.
84. Israni AK, Salkowski N, Gustafson S, Snyder JJ, Friedewald JJ, Formica RN, et al. New national allocation policy for deceased donor kidneys in the United States and possible effect on patient outcomes. *J Am Soc Nephrol* 2014;**25**(8):1842−8.
85. Schold J, Srinivas TR, Sehgal AR, Meier-Kriesche HU. Half of kidney transplant candidates who are older than 60 years now placed on the waiting list will die before receiving a deceased-donor transplant. *Clin J Am Soc Nephrol* 2009;**4**(7):1239−45.
86. Schold JD, Meier-Kriesche HU. Which renal transplant candidates should accept marginal kidneys in exchange for a shorter waiting time on dialysis? *Clin J Am Soc Nephrol* 2006;**1**(3):532−8.
87. Davison SN, Jhangri GS. Impact of pain and symptom burden on the health-related quality of life of hemodialysis patients. *J Pain Symptom Manag* 2010;**39**(3):477−85.
88. Weisbord SD, Fried LF, Arnold RM, Fine MJ, Levenson DJ, Peterson RA, et al. Prevalence, severity, and importance of physical and emotional symptoms in chronic hemodialysis patients. *J Am Soc Nephrol* 2005;**16**(8):2487−94.
89. Moss AH, Ganjoo J, Sharma S, Gansor J, Senft S, Weaner B, et al. Utility of the "surprise" question to identify dialysis patients with high mortality. *Clin J Am Soc Nephrol* 2008;**3**(5):1379−84.
90. Grubbs V, Moss AH, Cohen LM, Fischer MJ, Germain MJ, Jassal SV, et al. A palliative approach to dialysis care: a patient-centered transition to the end of life. *Clin J Am Soc Nephrol* 2014;**9**(12):2203−9.
91. Combs SA, Davison SN. Palliative and end-of-life care issues in chronic kidney disease. *Curr Opin Support Palliat Care* 2015;**9**(1):14−9.
92. Murtagh FE, Burns A, Moranne O, Morton RL, Naicker S. Supportive care: comprehensive conservative care in end-stage kidney disease. *Clin J Am Soc Nephrol* 2016;**11**(10):1909−14.
93. Kurella Tamura M, Meier DE. Five policies to promote palliative care for patients with ESRD. *Clin J Am Soc Nephrol* 2013;**8**(10):1783−90.
94. Lazenby S, Edwards A, Samuriwo R, Riley S, Murray MA, Carson-Stevens A. End-of-life care decisions for haemodialysis

patients - 'We only tend to have that discussion with them when they start deteriorating'. *Health Expect* 2017;**20**(2):260–73.
95. Ladin K, Buttafarro K, Hahn E, Koch-Weser S, Weiner DE. "End-of-Life care? I'm not going to worry about that yet." Health literacy gaps and end-of-life planning among elderly dialysis patients. *Gerontologist* 2018;**58**(2):290–9.
96. Fung E, Slesnick N, Kurella Tamura M, Schiller B. A survey of views and practice patterns of dialysis medical directors toward end-of-life decision making for patients with end-stage renal disease. *Palliat Med* 2016;**30**(7):653–60.
97. Kimmel PL, Weihs K, Peterson RA. Survival in hemodialysis patients: the role of depression. *J Am Soc Nephrol* 1993;**4**(1):12–27.
98. Kurella M, Kimmel PL, Young BS, Chertow GM. Suicide in the United States end-stage renal disease program. *J Am Soc Nephrol* 2005;**16**(3):774–81.
99. Cohen SD, Norris L, Acquaviva K, Peterson RA, Kimmel PL. Screening, diagnosis, and treatment of depression in patients with end-stage renal disease. *Clin J Am Soc Nephrol* 2007;**2**(6):1332–42.
100. O'Connor NR, Dougherty M, Harris PS, Casarett DJ. Survival after dialysis discontinuation and hospice enrollment for ESRD. *Clin J Am Soc Nephrol* 2013;**8**(12):2117–22.
101. Chen JC, Thorsteinsdottir B, Vaughan LE, Feely MA, Albright RC, Onuigbo M, et al. End of life, withdrawal, and palliative care utilization among patients receiving maintenance hemodialysis therapy. *Clin J Am Soc Nephrol* 2018;**13**(8):1172–9.
102. Schmidt RJ, Weaner BB, Long D. The power of advance care planning in promoting hospice and out-of-hospital death in a dialysis unit. *J Palliat Med* 2015;**18**(1):62–6.

QUESTIONS AND ANSWERS

Question 1

A number of functional changes have been attributed to the aging kidney. Which of the following is **false**?

A. GFR declines in most individuals at an average rate of approximately 0.8 mL/min/year
B. Renal blood flow declines with age, with greater reduction in cortical compared with medullary blood flow
C. Although glomerular size may increase, renal mass may decline with age, primarily in the very elderly population
D. Increased afferent arteriolar resistance and decreased Kf (ultrafiltration coefficient) are common features
E. There is a general reduction in vasodilatory capacity and/or increased sensitivity to vasoconstriction.

Answer: D

Afferent arteriolar resistance decreases with age. Both animal and human studies support such findings.[19] This is distinct from the general reduction in vasodilatory capacity or increased sensitivity to vasoconstriction in the kidney, thought to be mediated by reduced NO in older individuals. Of note, Answer **A** is true because GFR declines with age in most but not all individuals. The Baltimore Longitudinal study demonstrated that approximately one-third of the patients did not show a decline in renal function.

Question 2

A 65-year-old man with a history of well-controlled hypertension for 10 years and osteoarthritis presents with concern for renal disease based on a recent serum chemistry panel performed at his primary care provider's office as part of a routine annual examination. He is on a low dose of diltiazem alone for blood pressure control. His blood pressure is 130/70 mm Hg, heart rate is 65 bpm. His examination is unremarkable. His urinalysis is normal.

In consideration of diagnosing renal disease in this elderly patient, which of the following is **false**?

A. S[Cr] rises gradually with age greater than 60 in most individuals, making the estimation equations for GFR less accurate than a traditional 24-hour urine collection for creatinine clearance
B. The MDRD estimation equation underestimates GFR in elderly patients
C. The CKD-EPI estimation equation was found to be superior to the MDRD equation in patients greater than 65 years of age and with GFR greater than 60 mL/min/1.73 m^2
D. Cystatin C-based estimation equations for GFR are better than both creatinine-based equations (MDRD and CKD-EPI) for prediction of both cardiovascular and kidney outcomes in the elderly without CKD
E. Proteinuria is associated with the development of ESRD in patients greater than 65 years of age

Answer: A

The S[Cr] tends to remain unchanged with increasing age, despite reduction in GFR. This has been attributed to decreasing muscle mass, decreased creatinine generation, and reduced protein in the diet. The MDRD equation does underestimate GFR, particularly in those with GFR greater than 60 mL/min. Cystatin C is not affected by muscle mass, making it a more promising marker for the elderly, particularly with GFR greater than 60 mL/min/1.73 m^2. Despite evidence that glomerular basement membrane permeability may increase with age, proteinuria remains predictive of renal disease and failure in the elderly.

Question 3

The patient in Question 2 is seen by another physician who recommends a renal biopsy to determine the presence of disease. Which of the following is **true**?

A. Thickening of the glomerular basement membrane and increased mesangial matrix expansion are consistent and specific findings of age-related changes in renal tissue
B. As much as 10% global glomerulosclerosis can be seen in healthy individuals before the age of 40
C. Medial hypertrophy, arteriolar hyalinosis, and increased arteriosclerosis (fibrointimal hyperplasia) are all specific for hypertensive kidney disease and not associated with aging alone
D. Glomerular changes are associated with increased peritubular capillary density
E. The degree of interstitial fibrosis seen on biopsy directly corresponds to the degree of kidney senescence

Answer: B

Histologic renal changes are difficult to attribute specifically to aging.[24] The finding of an increased proportion of globally sclerotic glomeruli (glomerulosclerosis) may be the result of injuries from environmental factors, but is also seen in healthy kidney donors. Answers **A** and **E** are incorrect because the changes are proposed markers but inconsistent and nonspecific findings. Answer **C** is incorrect because vascular changes can be seen in healthy kidney donors as well. Answer **D** is incorrect because glomerular changes are associated with decreased rather than increased peritubular capillary density, probably the

result of reduced vascular endothelial growth factor from oxidative stress.

Question 4

An 83-year-old man with hypertension has slowly progressive CKD with a recent eGFR of 15 mL/min/1.73 m^2 and albuminuria of 200 mg/g creatinine. He has steadily lost weight over the past 3 years, without a discernible cause. He has mild dementia and now lives in an assisted living facility. His only complaint is fatigue. Blood pressure is 140/65 mm Hg and weight is 50 kg. He is a thin male who ambulates slowly and has some difficulty sitting and getting up from the chair. In consideration of his severe renal insufficiency and RRT, which would be the most appropriate to advise the patient and his family?

A. Early start of RRT (before when eGFR is greater than 10 and closer to 15 mL/min/1.73 m^2) is associated with overall improvement in health outcomes
B. RRT would likely improve his functional status
C. RRT is unlikely to significantly prolong life and is associated with reduced quality of life in elderly patients with disabilities
D. HD is associated with superior outcomes vs. PD in the elderly
E. An AVF should be created now

Answer: C

Multiple observational studies in elderly patients show little to no prolongation in survival for those who initiate dialysis after the age of 80 years with significant comorbidities. This patient has weight loss, fatigue, and low physical activity and likely meets the criteria for the frailty phenotype. Frailty has been shown to be a risk factor for mortality in dialysis patients. Poor functional status, age, low S[Alb], and comorbid conditions including dementia, peripheral vascular disease, and heart disease are all risk factors for mortality in patients with ESRD. RRT has not improved functional status for elderly patients residing in extended care facilities. Early initiation of RRT has not been shown to improve outcomes in a large randomized trial and has even been associated with worse outcomes in the elderly. Dialysis modality does not appear to affect survival in elderly patients. Creation of AVF automatically at stage 4 or 5 CKD may not be appropriate in the very elderly because a large percentage may go unused depending on illness trajectory.

Question 5

A 69-year-old with atrial fibrillation, CHF, COPD, liver cirrhosis, and Parkinson's disease develops AKI during a hospital admission for a fall and urinary tract infection. He has baseline CKD stage 3b with low grade albuminuria (less than 100 mg/g creatinine). In the six months before admission, he developed worsening diuretic-resistant fluid overload. On presentation to the hospital, he is encephalopathic and has nonoliguric AKI. HD is initiated for massive fluid overload and possible uremic encephalopathy. After initiation of HD with a central venous catheter and treatment for urinary tract infection, his mental status improves. Over the next 12 weeks, attempts to discontinue HD fail due to continued massive fluid overload that is diuretic-resistant and his intolerance to high rates of fluid removal at dialysis. He remains bed-bound and totally dependent for all activities of daily living. What would be the next appropriate step for his physician?

A. Discussion of quality of life and goals of care
B. Vascular surgery consultation for arteriovenous access for HD
C. Referral to hospice with continued dialysis
D. Palliative care consultation
E. Ask patient to complete ADs

Answer: A

The patient probably has severe cardiorenal syndrome with multiple other comorbidities. His 1-year mortality is very high and can be estimated with various tools such as the Charlson Comorbidity Score and a predictive tool for survival in dialysis patients as described in Ref. 89. He is now unlikely to recover renal function or even be discharged from a chronic healthcare facility. At this transition from CKD to probable ESRD, it is appropriate to perform ACP. The other choices may be appropriate, but only after clarification of the patient's wishes after discussion of prognosis and goals of care. Once this is established, ADs such as designation of a healthcare surrogate do not resuscitate orders, and completion of a living will or POLST (physician orders for life-sustaining treatment) may occur. A palliative care consultation certainly is reasonable even if dialysis is to be continued, but this would be after discussions with the patient and ACP. Referral to hospice is premature at this point and cannot be guaranteed to include dialysis. Depending on this patient's prognosis and wishes, an arteriovenous access may be advised but it seems unlikely to be of benefit in his case.

CHAPTER

78

Pain and Chronic Kidney Disease

Scott D. Cohen[a], *Sara N. Davison*[b], *Paul L. Kimmel*[a]

[a]Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States; [b]Department of Medicine, University of Alberta, Edmonton, AB, Canada

Abstract

Several studies evaluate the deleterious impact of pain in patients with chronic kidney disease (CKD). The prevalence of pain has been estimated at approximately 50%–70% in patients with advanced CKD. The causes of pain in CKD patients are often unrelated to the kidney disease and can be categorized as neuropathic (pain due to nerve damage) or nociceptive (pain due to tissue damage) in nature. There are a variety of validated screening tools available to determine the location, degree, and quality of a patient's pain, and any exacerbating or alleviating factors. These tools include, but are not limited to, the McGill Pain Questionnaire, Edmonton Symptom Assessment System-revised:Renal and the Brief Pain Inventory. A thorough evaluation should be undertaken to determine the underlying etiology of a patient's acute or chronic pain syndrome. Management of pain can be divided into nonpharmacologic and pharmacologic options. Nonpharmacologic alternatives should be considered before prescribing chronic pain medications. Pharmacologic treatment should follow specific guidelines with careful selection of appropriate analgesics and dose reduction for reduced estimated glomerular filtration rate, as most commonly used pain medications and their metabolites are renally cleared with a higher risk for adverse events in CKD. Opioids should only be used for severe pain refractory to other measures, including nonopioid and adjuvant analgesics. Greater provider awareness and a multidisciplinary approach including assessment and management of concurrent psychosocial issues are likely required to adequately address pain in CKD patients.

INTRODUCTION

Perception of pain is an often overlooked yet prevalent condition in patients with chronic kidney disease (CKD).[1,2] Perception of pain in patients with advanced CKD is associated with decreased quality of life (QOL), increased depressive affect, and increased perception of illness burden.[3–8] Psychosocial parameters including perception of decreased QOL and increased depressive affect have been associated with worse clinical outcomes, including increased mortality, higher rates of hospitalizations, and decreased compliance with prescriptions in patients with CKD or end-stage renal disease (ESRD).[6–10] Perceived pain severity is a potentially modifiable risk factor for poor clinical outcomes in CKD patients who often have multiple comorbid conditions. This chapter reviews the literature on the epidemiology of pain in patients with CKD worldwide, options for the screening for and diagnosis of pain, and the various management approaches to ameliorate the perception of pain in patients with CKD.

EPIDEMIOLOGY

The high prevalence of chronic pain is well documented in patients with ESRD treated with dialysis.[10–14] It is estimated that approximately 30–50% of patients with ESRD have chronic pain. Many of these patients are prescribed opioids, which have many adverse effects.[10–14] Based on 2010 US Renal Data System data,[15] approximately two-thirds of all dialysis patients were prescribed opioids. Opioid prescriptions in dialysis patients are associated with adverse effects including increased mortality, hospitalizations, and dialysis discontinuation.[15,16]

In the general population, prescription opioid overdoses continue to increase across the US, leading the US Department of Health and Human Services to declare a public health emergency in 2017.[17] In 2016, more than 42,000 deaths were attributed to opioid overdoses, and 40% of these were attributed to prescription opioids.[17] Given the magnitude of the problem and the adverse health impacts, there is an urgent need to address proper management approaches for pain in patients with CKD.

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00078-4

There are few data on the prevalence of pain in predialysis CKD patients. Cohen et al.[6] studied 92 predialysis CKD patients and found 69% of the cohort reported pain. There was no difference between patients' pain intensity scores across CKD stages. There was also no difference between CKD patients' perception of pain when compared with pain ratings of a control group of 61 general medical patients without CKD. In contrast, another study of 130 CKD patients reported a prevalence of 72.9% for acute and chronic pain[1]. This compared with a pain prevalence of only 9% for 100 control non-CKD ambulatory medicine patients. The majority of CKD patients reported musculoskeletal pain. Pain intensity and duration were higher in patients with CKD stages 3–5 compared with earlier stages of CKD. Data from SPRINT show no difference in pain between hypertensive patients with and without CKD.[18] The disparate results likely reflect the heterogeneity of the CKD population and differences in study design.

Grams et al.[19] recently evaluated the prevalence of opioid, gabapentinoids, and nonsteroidal antiinflammatory drug (NSAID) use among patients with CKD in the Geisinger and John Hopkins health systems. Patients with CKD stages 4 and 5 were significantly more likely to receive an opioid prescription compared with patients with earlier stages of CKD. Gabapentinoid prescriptions were also more commonly prescribed in those with advanced stages of CKD but were prescribed at significantly lower rates compared with opioids.

The incidence of symptoms, including pain, in earlier stages of CKD, also appears high. Twenty five symptoms were assessed in a cohort of 1118 patients with stage 1–5 CKD.[20] The most prevalent symptom in stages 1–3 were bone and joint pain, which was reported by 86% of patients. Muscle cramps were also reported commonly in 71% of patients. There was a slight trend toward increasing incidence of pain with stage of disease such that 97% of dialysis patients in this cohort reported bone and joint pain and 92% reported muscle cramps.

There are a variety of potential causes for pain in CKD patients.[7] Many causes of pain are not unique to CKD but are due to comorbidities such as osteoarthritis, inflammatory arthritis, peripheral neuropathy, peripheral vascular disease, and traumatic injuries. Pain can result from the underlying kidney disease, such as with polycystic kidney disease (PKD). PKD has its own unique pain syndromes, often related to the enlarging cysts or cyst rupture. Pain may also be due to complications of poor kidney function such as secondary or tertiary hyperparathyroidism, particularly in advanced CKD stages. Patients often have more than one cause of pain.

SCREENING FOR AND DIAGNOSIS OF PAIN IN CKD

A variety of tools have been validated to screen for pain in CKD patients. The McGill Pain Questionnaire,[10,21] first developed in 1975, remains one of the foremost tools used to assess pain. The questionnaire asks participants to describe the quality and intensity of their pain. The scale is rated from 0 to 78, with higher scores reflecting worse degrees of pain.

The Brief Pain Inventory[22] has been used to assess the location, type, and intensity of pain in patients with chronic medical illnesses including CKD. The questionnaire also evaluates the impact of pain on parameters such as general activity, mood, walking ability, work, relationships, sleep, and enjoyment of life. The standard instrument characterizes pain based on a 32-question survey, while the short form has been condensed to nine questions.

The Edmonton Symptom Assessment System-revised:Renal (ESAS-r:R)[23–25] can be used to screen for pain and psychosocial parameters. The ESAS-r:R consists of visual analog scales with a 0–10 likert scale representing "no" to "worst possible" for pain, tiredness, drowsiness, nausea, lack of appetite, shortness of breath, depression, anxiety, well-being, sleep, itch, and restless legs. Total scores range between 0 and 130, with higher scores indicating greater symptom burden. Similar global symptom assessment tools with evidence of validity for use in CKD patients include the renal version of the Palliative (or Patient) Outcome Scale, symptom module (POSs renal)[26] and the Dialysis Symptom Index.[27] All three of these patient-completed symptom screening tools can be downloaded from websites.

If a patient screens positive for pain, further evaluation by a pain history is required. This includes documenting location, type of pain, alleviating or exacerbating factors, effect on physical and psychosocial functioning, and associated symptoms. All these variables affect treatment strategies. It is important to differentiate between acute, chronic, and episodic pain as the management differs (Table 78.1).

The patient's experience of chronic pain is affected by psychosocial factors as well as pathology that originally caused the pain. These psychosocial factors typically need to be addressed to manage pain adequately. A further psychosocial assessment may be warranted to better determine any underlying aggravating factors.[7] In a study of 92 patients with CKD, pain intensity and frequency were associated with multiple psychosocial variables including depressive affect, perception of social support, and satisfaction with life.[6] These results

TABLE 78.1 Types and Categories of Pain

TYPES OF PAIN	
Acute pain	Occurs following tissue damage and activation of nociceptors at the site of injury, such as after surgery. Acute pain can occur over long periods with repeated injury. This is termed recurrent pain and tends to be episodic with periods without pain.
Chronic pain	Initiated by tissue injury but perpetuated by peripheral and central nervous system changes leading to continuation of pain in the absence of the original injury/pain stimulus. Chronic pain is not defined by duration but rather by the absence of persistent nociceptor damage. Chronic pain is typically present for long periods of time and is often out of proportion to the extent of the originating injury.
Episodic, incident, paroxysmal, and breakthrough pain	Pain that breaks through, i.e. occurs despite regular analgesic medication.
CATEGORIES OF PAIN	
Nociceptive	Pain due to tissue damage. Pain may be described as sharp or dull. Nociceptive pain typically responds well to traditional analgesics.
Neuropathic	Pain due to nerve damage. Pain is characteristically described as burning, painful, cold, or like electric shocks. Neuropathic pain may be associated with tingling, feeling pins and needles, numbness, and itching. It may also be associated with episodes of spontaneous pain, hyperalgesia, and allodynia. Neuropathic pain is typically poorly responsive to opioids and generally requires the use of adjuvant analgesics such as anticonvulsants and antidepressants.

highlight the importance of integrating a psychosocial evaluation into the management of patients' pain syndromes.

For the purpose of treatment, it is also helpful to categorize pain into nociceptive, neuropathic, or mixed nociceptive and neuropathic pain. Patients and their significant others should be educated on the nature of the pain, potential causes of pain, and on the proposed management plan. Complete relief of pain is not always possible, and it is important that patients and their families as well as their physicians have realistic expectations.

MANAGEMENT OF PAIN IN CKD PATIENTS

Management of chronic pain should first focus on nonpharmacologic options.[7,28] These include topical therapies such as heating pads or ice to reduce local inflammation.[7,28–31] Physical therapy programs often form an essential component of pain management. Other nonpharmacologic therapies include transcutaneous electrical stimulation (TENS) and ultrasound technology.[28] Arthritis and other musculoskeletal causes of pain are felt to be the most responsive to TENS.[28,32] Lifestyle modifications including diet and exercise and mind-body interventions such as cognitive behavioral therapy have been shown to be effective.[33,34] Surgical options and referral to a pain subspecialist may be appropriate in certain circumstances, depending on the underlying etiology of a patient's pain. For example, patients with inflammatory arthritis may require evaluation by a rheumatologist and patients with traumatic injuries may need orthopedic evaluation. PKD patients may require laparoscopic cyst decortications (unroofing and collapse of cysts) and marsupialization if pain is related to cyst growth.[35]

The World Health Organization (WHO) advocates a stepwise approach to pain management that was demonstrated to be useful and efficacious in cancer patients and is now adopted for use in nonmalignant pain (Figure 78.1). Preliminary data suggest this approach may be used effectively for patients with ESRD and CKD.[36,37] Caution with prescription opioids is strongly advised given the multitude of adverse health outcomes associated with this medication class. When prescribing analgesics, five principles should be followed (Table 78.2).

The choice of analgesic in stage 4 or 5 CKD is challenging because of the pharmacokinetic and pharmacodynamic consequences associated with severe diminution in glomerular filtration rate. Drug metabolism is altered significantly, and the risk of toxicity from accumulation of renally excreted drugs and their metabolites is high. In view of the potential for toxicity, short-acting rather than long-acting preparations should be used until stable pain relief has been achieved. There are a variety of analgesic options for the management of pain in CKD patients (Table 78.3). Dose adjustments are usually necessary in patients with advanced CKD.

WHO Ladder Step 1

Acetaminophen is the first-line step 1 analgesic for most CKD patients. The dose of acetaminophen does not need to be adjusted for kidney function. Recent evidence suggests that lifetime cumulative doses of

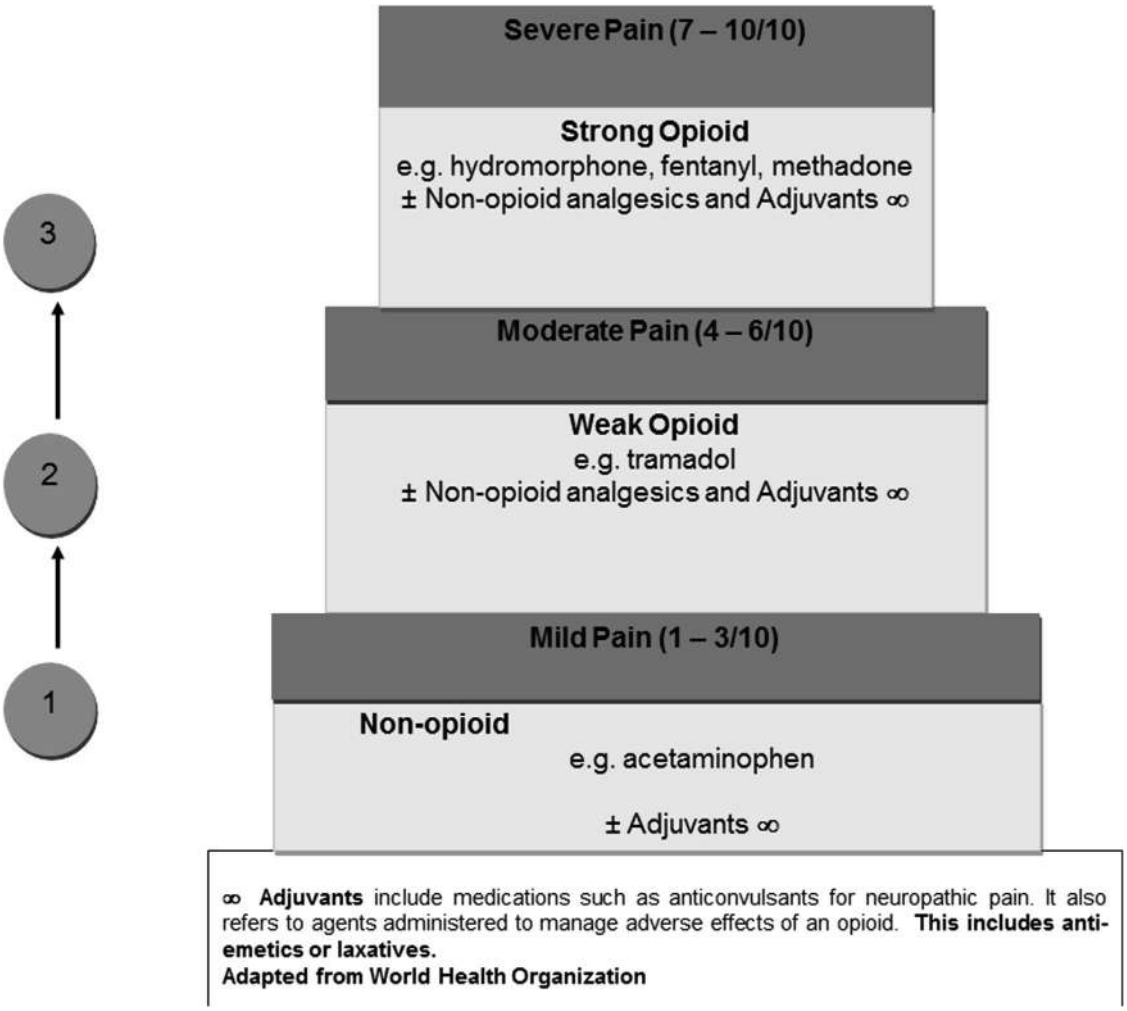


FIGURE 78.1 World Health Organization 3 Step Analgesic Ladder, ∞ Adjuvants include medications such as anticonvulsants for neuropathic pain. It also refers to agents administered to manage adverse effects of an opioid. This includes antiemetics or laxatives. *Adapted from World Health Organization.*

acetaminophen do not have an adverse effect on CKD progression. Despite its widely accepted use in CKD patients, acetaminophen may have nephrotoxic potential. Fored et al.[38] found an increased risk for CKD in those patients who used acetaminophen either alone or in combination with aspirin. Patients on combination acetaminophen and aspirin therapy had 2.2 higher odds for development of CKD. Perneger et al.[39] also found an increased risk of ESRD among patients who took increasing cumulative doses of acetaminophen over time. Other studies have not confirmed these findings. When patients with CKD have been prescribed therapeutic doses of acetaminophen, there is no evidence to support a risk for development of worsening renal function.[40] However, patients with chronic alcoholism and malnutrition may be at increased risk for hepatotoxicity.[41–43] To avoid toxicity, it is recommended to not exceed 3 g/day of acetaminophen. In high-risk patients, such as malnourished or alcoholic patients, ingestion should be limited to 2.6 g/day.[44]

The renal hemodynamic effects of NSAIDs are related to inhibition of renal prostaglandin synthesis, thereby causing renal afferent arteriolar vasoconstriction and hemodynamically mediated acute kidney injury (AKI).[45] Kidney injury in the setting of NSAIDs may result from acute interstitial nephritis, which rarely can be associated with minimal change disease. Other complications associated with NSAID use include hyperkalemia, edema, hypertension, and papillary necrosis.[7,28,45–47] Even in dialysis-dependent patients with no residual kidney function, NSAIDs are associated with an increased risk of gastrointestinal bleeding, and studies have suggested that there might be an increased risk of myocardial infarction.[48] For these reasons, chronic NSAID use, including NSAIDs with supposedly less potential for AKI, such as sulindac and

TABLE 78.2 Principles of Pain Management

By mouth	Use the oral or transdermal route whenever possible.
By the clock	Where pain is continuous, analgesics should be given regularly. Additional breakthrough medication should be available on an "as needed" (PRN) basis.
By the ladder	Initial analgesia should be started at the lowest appropriate WHO analgesic ladder level based on severity of pain. The drug should be used to its full-tolerated dose before titrating up to the next level on the ladder. Adjuvant drugs can be added to all three steps of the ladder. There are no safe step 2 analgesics for patients with advanced CKD. Step 1 analgesics can be added to step 3 drugs.
For the individual	There is no standard dose of strong opioids. The "right dose" is that which relieves pain without causing unacceptable side effects. Sensitivity to adverse effects varies between patients and must be monitored closely.
Attention to detail	Pain changes over time, thus there is a need for ongoing reassessment.

salsalate,[26,47–49] should be avoided in patients with advanced CKD. Low-dose aspirin for cardioprotection can be used safely in CKD patients.[50]

WHO Ladder Step 2

There are no weak opioids considered safe for use in patients with advanced CKD. For example, tramadol, a weak synthetic opioid related to codeine, is extensively metabolized in the liver. Both the parent drug and the main active metabolite O-desmethyltramadol (M1) are renally cleared. There is an unpredictable risk of serious overdosing or underdosing after administration of standard doses.[51] In addition, patients with advanced CKD are at an increased risk for seizures and respiratory depression with increased levels of M1.[52–54] There is no evidence that weak opioids are less risky than strong opioids if the strong opioid is used at its lowest effective dose.[55] There is also no evidence that at equivalent analgesic efficacy, weak opioids carry a lower risk of addiction than low-dose strong opioids. A recent study of 140,899 hemodialysis patients in the US showed the risk for altered mental status, falls, and fractures were greater with codeine rather than with strong opioids.[2,51]

TABLE 78.3 Analgesic Options for Chronic Pain Management in CKD Patients

Pain Category	Recommend	Recommend with Caution and Adjust Dose for Renal Function	Avoid
WHO STEP I (MILD PAIN)			
Acetaminophen	X		
NSAIDs			X
WHO STEP II (MODERATE PAIN)			
Tramadol			X
Codeine			X
Hydrocodone			X
WHO STEP III (SEVERE PAIN)			
Morphine sulfate			X
Hydromorphone		X	
Methadone		X	
Fentanyl		X	
Oxycodone		X	
ADJUVANTS			
Gabapentin		X	
Duloxetine		X	
Pregabalin		X	
Tricyclic antidepressants		X	

Adjuvant Therapy

Adjuvant drugs are those that have a primary indication other than pain but are analgesic in some situations. Adjuvant therapy is the first pharmacological step for people with a neuropathic component to their pain. Anticonvulsants and tricyclic antidepressants (TCAs) are the two classes of drugs for which there is the most evidence of efficacy in neuropathic pain. In patients with normal kidney function, TCAs are considered first-line treatment options for the treatment of neuropathic pain. However, due to the increased potential for anticholinergic and cardiac adverse events in CKD patients, this class of medications is considered second-line in patients with CKD.

Anticonvulsants are considered first line for the pharmacologic treatment of chronic neuropathic pain in patients with advanced CKD. There is no evidence that they are effective for acute pain. Gabapentin, an analog of the neurotransmitter gamma-aminobutyric acid, is increasingly being used for the management of chronic neuropathic pain and fibromyalgia.[56] The drug undergoes renal clearance and elimination is reduced markedly in patients with advanced CKD.[57,58] Therefore, patients are at increased risk for adverse effects such as neurotoxicity and AKI.[57,58] Caution must be used and appropriate dose reduction applied. A recent study in ESRD patients demonstrated an association between prescription of gabapentin and adverse events such as falls.[59] In patients with an estimated glomerular filtration rate (eGFR) between 15 and 30 mL/min/1.73 m^2, the suggested maximum daily dose is 600 mg, and for patients with an eGFR <15 mL/min/1.73 m^2, the suggested maximum daily dose is 300 mg. Neuropathic pain often tends to be worse at night. Because of a delayed onset of action, the drug should be taken two to three hours before going to bed.

Pregabalin is another anticonvulsant that can be used to treat refractory neuropathic pain. There have been case reports of neurotoxicity when using pregabalin in CKD patients.[60,61] Pregabalin has also been associated with peripheral edema. A recent study in ESRD patients found an association between pregabalin use and increased risk for falls and altered mental status.[59]

Dose reduction is required based on GFR. The maximum recommended dose for eGFR 30–60 mL/min/1.73 m^2 is 150 mg twice per day. For eGFR 15–30 mL/min/1.73 m^2, the maximum recommended dose is 150 mg once per day, and for eGFR <15 mL/min/1.73 m^2, the maximum daily dose is 75 mg daily. Carbamazepine appears as effective as both gabapentin and pregabalin. Although carbamazepine may have more adverse effects, it requires no dose adjustment in CKD.

Duloxetine, a selective norepinephrine and serotonin reuptake inhibitor, is increasingly being used for the treatment of neuropathic pain in a variety of clinical scenarios including diabetic and chemotherapy-associated neuropathy, fibromyalgia, and chronic musculoskeletal pain in the general population.[62–64] Serotonin and norepinephrine play an essential role in mediating chronic pain signals. Similar to gabapentin and pregabalin, duloxetine and its metabolites are renally cleared.[65] There is very limited experience with its use in patients with advanced CKD. Duloxetine is not recommended in patients with eGFR less than 30 mL/min/1.73 m^2. For patients with lower stages of CKD, duloxetine may be started at a reduced dose of 30 mg daily with cautious upward titration based on the patient's tolerance and symptoms.

Lidocaine patches are another option for the management of neuropathic pain, because they have less systemic absorption. This topical analgesic is particularly effective for the treatment of postherpetic neuralgia.[66,67] Caution is advised in patients with severe renal impairment who use lidocaine patches due to concern for toxicity.

WHO Ladder Step 3

Strong opioids should only be reserved for severe pain that is refractory to other measures. Opioids should be prescribed in close consultation with the patient and with the patient's primary care provider. In the setting of CKD, opioids carry an increased risk for adverse events including hypotension, depression of the central nervous and respiratory systems, seizures, and myoclonus.[68–70] As with other medications, appropriate dose reduction should be applied when prescribing to patients with advanced CKD.

Morphine undergoes hepatic metabolism and its metabolites are renally cleared.[71] Therefore, CKD patients are at higher risk for morphine toxicity. Morphine should be avoided in patients with advanced CKD stages.[71] Methadone, hydromorphone, fentanyl, and buprenorphine may have more favorable pharmacokinetic characteristics (Table 78.3).[72–74] Hydromorphone has a shorter half-life, lower volume of distribution, and lower molecular weight compared with morphine.[71] Hydromorphone may also cause less nausea, pruritus, and sedation compared with morphine.[71] Methadone may be preferable to other opioids in the setting of CKD, because its metabolites undergo both gastrointestinal and renal clearance.[72] There is believed to be increased gastrointestinal clearance of methadone in CKD patients.[72] The metabolites of fentanyl are reportedly "inactive" and less toxic. The drug can be given topically *via* a transdermal

patch.[74] Compared with morphine, fentanyl may cause less constipation, hemodynamic instability, and histamine release.[71] Fentanyl undergoes predominately hepatic metabolism, with only 5–10% of it undergoing renal clearance. Caution must be exercised with prescription of fentanyl because of its potential for abuse and its therapeutic/toxic ratio.

Strong opioids should be considered a last resort option due to risk of addiction and adverse effects. A complete history and physical examination should be performed before prescribing to determine the underlying cause of the patient's pain, and to ascertain if the patient may be at increased risk for adverse events. A thorough social history should be documented to determine if patients have a previous history of drug-seeking behaviors, which places them at a higher risk for addiction. Once opioids are prescribed, close medical follow-up and monitoring is indicated to screen for signs of aberrant use or addiction such as inappropriate or escalating doses.

CONCLUSION

Pain is prevalent in CKD patients and can be associated with psychosocial variables including poorer QOL and increased depressive affect. There are a variety of screening tools available to determine the severity and impact of a patient's pain. Management of pain in CKD patients should follow specific guidelines and appropriate dose reduction for reduced eGFR. Many of the commonly used pain medications and their metabolites are renally cleared, with a higher risk for adverse events in CKD. Nonpharmacologic alternatives should be considered before prescribing chronic pain medications for CKD patients. Patients' psychosocial needs should be addressed, as treatment of depression and anxiety may be associated with decreased perception of pain. In the midst of the opioid epidemic and increasing data regarding the multiple deleterious health consequences of prescription of opioids, additional studies are urgently needed to determine the optimal management approach for the treatment of pain in patients with CKD. With more provider awareness and using multidisciplinary approaches, the pain epidemic in CKD patients may be more effectively managed.

References

1. Pham PC, Dewar K, Hashmi S, et al. Pain prevalence in patients with chronic kidney disease. *Clin Nephrol* 2010;**73**:294–9.
2. Raj R, Ahuja KD, Frandsen M, Jose M. Symptoms and their recognition in adult haemodialysis patients: interactions with quality of life. *Nephrology* 2017;**22**(3):228–33.
3. Skevington SM. Investigating the relationship between pain and discomfort and quality of life, using the WHO-QOL. *Pain* 1998; **76**:395–406.
4. Perlman RL, Finkelstein FO, Liu L, et al. Quality of life in chronic kidney disease (CKD): a cross-sectional analysis in the Renal Research Institute-CKD study. *Am J Kidney Dis* 2005;**45**:658–66.
5. Unruh M, Weisbord SD, Kimmel PL. Health-related quality of life in nephrology research and clinical practice. *Semin Dial* 2005;**18**: 82–90.
6. Cohen SD, Patel SS, Khetpal P, Peterson RA, Kimmel PL. Pain, sleep disturbance, and quality of life in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2007;**2**:919–25.
7. Davison SN. Chronic kidney disease: psychosocial impact of chronic pain. *Geriatrics* 2007;**62**:17–23.
8. Davison SN, Jhangri GS. The impact of pain and symptom burden on the health-related quality of life of hemodialysis patients. *J Pain Symptom Manag* 2010;**39**(3):477–85.
9. Mapes DL, Lopes AA, Satayathum S, et al. Health-related quality of life as a predictor of mortality and hospitalization. The dialysis outcomes and practice patterns study (DOPPS). *Kidney Int* 2003;**64**: 339–49.
10. Patel SS, Kimmel PL. Quality of life in patients with chronic kidney disease: focus on end-stage renal disease treated with hemodialysis. *Semin Nephrol* 2005;**26**:68–79.
11. Davison SN. Chronic pain in end-stage renal disease. *Adv Chron Kidney Dis* 2005;**12**:326–34.
12. Harris TJ, Nazir R, Khetpal P, et al. Pain, sleep disturbance, and survival in hemodialysis patients. *Nephrol Dial Transplant* 2012;**27**: 758–65.
13. Almutary H, Bonner A, Douglas C. Symptom burden in chronic kidney disease: a review of recent literature. *J Ren Care* 2013; **39**(3):140–50.
14. Almutary H, Bonner A, Douglas C. Which patients with chronic kidney disease have the greatest symptom burden? A comparative study of advanced CKD stage and dialysis modality. *J Ren Care* 2016;**42**(2):73–82.
15. Kimmel PL, Fwu CW, Abbott KC, et al. Opioid prescription, morbidity, and mortality in United States Dialysis Patients. *J Am Soc Nephrol* 2017;**28**:3658–70.
16. Ishida JH, McCulloch CE, Steinman MA, Grimes BA, Johansen KL. Opioid analgesics and adverse outcomes among hemodialysis patients. *Clin J Am Soc Nephrol* 2018;**13**:746–53.
17. https://www.hhs.gov/opioids/about-the-epidemic/index.html.
18. The Sprint Research Group. Randomized trial of intensive versus standard blood pressure control. *N Engl J Med* 2015;**373**:2103–16.
19. Novick TK, Surapaneni A, Shin JI, et al. Prevalence of opioid, gabapentinoid and NSAID use in patients with CKD. *Clin J Am Soc Nephrol* 2018;**13**(12):1886–8.
20. Senanayake S, Gunawardena N, Palihawadana P, Bandara P, Haniffa R, Karunarathna R, et al. Symptom burden in chronic kidney disease; a population based cross sectional study. *BMC Nephrol* 2017;**18**:228.
21. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975;**1**:277–99.
22. Cleeland C. Research in cancer pain. What we know and what we need to know. *Cancer* 1991;**67**(3 Suppl.):823–7.
23. Davison SN, Jhangri GS, Johnson JA. Cross sectional validity of a modified Edmonton Symptom Assessment System (ESAS) in dialysis patients: a simple assessment of symptom burden. *Kidney Int* 2006;**69**:1621–5.
24. Davison SN, Jhangri G, Johnson J. Longitudinal validation of a modified Edmonton symptom assessment system (ESAS) in hemodialysis patients. *Nephrol Dial Transplant* 2006;**21**:3189–95.
25. Edmonton Zone Palliative Care Program and Northern Alberta Renal Program. Available from: http://www.palliative.org/tools.html.

26. Murphy EL, Murtagh FE, Carey I, Sheerin NS. Understanding symptoms in patients with advanced chronic kidney disease managed without dialysis: use of a short patient-completed assessment tool. *Nephron Clin Pract* 2009;**111**(1):c74–80.
27. Weisbord SD, Fried LF, Arnold RM, Rotondi AJ, Fine MJ, Levenson DJ, et al. Development of a symptom assessment instrument for chronic hemodialysis patients: the Dialysis Symptom Index. *J Pain Symptom Manag* 2004;**27**(3):226–40.
28. Pham PT, Toscano E, Pham PT, et al. Pain management in patients with chronic kidney disease. *Nephrol Dial Transplant* 2009;**2**:111–8.
29. Ciolek JJ. Cryotherapy. Review of physiological effects and clinical application. *Clevel Clin Q* 1985;**52**:193–201.
30. Collins NC. Is ice right? Does cryotherapy improve outcome for acute soft tissue injury? *Emerg Med J* 2008;**25**:65–8.
31. Adams ML, Arminio GJ. Non-pharmacologic pain management intervention. *Clin Podiatr Med Surg* 2008;**25**:409–29.
32. Johnson M, Martinson M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: a meta-analysis of randomized controlled trials. *Pain* 2006;**130**:157–65.
33. National Center for Complementary and Alternative Medicine. http://nccam.nih.gov.
34. Gilpin HR, Keyes A, Stahl DR, Greig R, McCracken LM. Predictors of treatment outcome in contextual cognitive and behavioural therapies for chronic pain: a systematic review. *J Pain* 2017;**18**(10): 1153–64.
35. Bajwa ZH, Gupta S, Warfield CA, et al. Pain management in polycystic kidney disease. *Kidney Int* 2001;**60**:1631–44.
36. Barakzoy AS, Moss AH. Efficacy of the World Health Organization analgesic ladder to treat pain in end-stage renal disease. *J Am Soc Nephrol* 2006;**17**:3198–203.
37. Launay-Vacher V, Karie S, Fau JB, Izzedine H, Deray G. Treatment of pain in patients with renal insufficiency: the World Health Organization three-step ladder adapted. *J Pain* 2006;**6**:137–48.
38. Fored CM, Ejerblad E, Lindblad P, et al. Acetaminophen, aspirin, and chronic renal failure. *N Engl J Med* 2001;**345**:1801–8.
39. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1994;**331**:1675–9.
40. Evans M, Fored CM, Bellocco R, et al. Acetaminophen, aspirin and progression of advanced chronic kidney disease. *Nephrol Dial Transplant* 2009;**24**:1908–18.
41. Mazer M, Perrone J. Acetaminophen-induced nephrotoxicity: pathophysiology, clinical manifestations, and management. *J Med Toxicol* 2008;**4**:2–6.
42. Khandkar MA, Parmar DV, Das M, Katyare SS. Is activation of lysosomal enzymes responsible for paracetamol-induced hepatotoxicity and nephrotoxicity? *J Pharm Pharmacol* 1996;**48**:437–40.
43. Eguia L, Materson BJ. Acetaminophen-related acute renal failure without fulminant liver failure. *Pharmacotherapy* 1997;**17**:363–70.
44. Chandok N, Watt KD. Pain management in the cirrhotic patient: the clinical challenge. *Mayo Clin Proc* 2010;**85**:451–8.
45. Whelton A, Hamilton CW. Nonsteroidal anti-inflammatory drugs: effects on kidney function. *J Clin Pharmacol* 1991;**31**:588–98.
46. Clive DM, Stoff JS. Renal syndromes associated with nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1984;**310**:563–72.
47. Patrono C, Dunn MJ. The clinical significance of inhibition of renal prostaglandin synthesis. *Kidney Int* 1987;**32**:1–12.
48. Chen YF, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, et al. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib, and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. *Health Technol Assess* 2008;**12**:278.
49. Laffi G, Daskalopoulos G, Kronborg I, et al. Effects of sulindac and ibuprofen in patients with cirrhosis and ascites: an explanation for the renal-sparing effect of sulindac. *Gastroenterology* 1986;**90**:182–7.
50. McCullough PA, Sandberg KR, Borzak S, et al. Benefits of aspirin and beta-blockade after myocardial infarction in patients with chronic kidney disease. *Am Heart J* 2002;**144**:226–32.
51. Davison SN. Clinical pharmacology considerations in pain management in patients with advanced kidney failure. *Clin J Am Soc Nephrol* 2019;**14**(6):917–31.
52. Lee CR, McTavish D, Sorkin EM. Tramadol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs* 1993;**46**:313–40.
53. Raffa RB, Friderichs E, Reimann W, et al. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharmacol Exp Ther* 1992;**260**:275–85.
54. Gardner JS, Blough D, Drinkard CR, et al. Tramadol and seizures: a surveillance study in a managed care population. *Pharmacotherapy* 2000;**20**:1423–31.
55. "Weak" opioid analgesics. Codeine, dihydrocodeine and tramadol: no less risky than morphine. *Prescrire Int* 2016;**25**(168):45–50.
56. Moore RA, Wiffen PJ, Derry S, McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2011;**3**:CD007938.
57. Torregrosa-de Juan E, Olague-Diaz P, Royo-Maicas P, et al. Acute renal failure due to gabapentin: a case report and literature. *Nefrologia* 2012;**32**:130–1.
58. Bassilios N, Launay-Vacher V, Khoury N, et al. Gabapentin neurotoxicity in a chronic hemodialysis patient. *Nephrol Dial Transplant* 2001;**16**:2112–3.
59. Ishida JH, McCulloch CE, Steinman MA, et al. Gabapentin and pregabalin use and association with adverse outcomes among hemodialysis patients. *J Am Soc Nephrol* 2018;**29**:1970–8.
60. Randinitis EJ, Posvar EL, Alvey CW, et al. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. *J Clin Pharmacol* 2003;**43**:277–83.
61. Healy DG, Ingle GT, Brown P. Pregabalin- and gabapentin-associated myoclonus in patient with chronic renal failure. *Mov Disord* 2009;**24**:2028–9.
62. Boyle J, Eriksson ME, Gribble L, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomonographic sleep, daytime functioning, and quality of life. *Diabetes Care* 2012;**35**:2451–8.
63. Pergolizzi Jr JV, Raffa RB, Taylor Jr R, et al. A review of duloxetine 60 mg once-daily dosing for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain due to chronic osteoarthritis pain and low back pain. *Pain Pract* 2013;**13**:239–52.
64. Takenaka M, Iida H, Matsumoto S, et al. Successful treatment by adding duloxetine to pregabalin for peripheral neuropathy induced by paclitaxel. *Am J Hosp Palliat Care* 2013;**30**:734–6.
65. Lobo ED, Heathman M, Kuan HY, et al. Effects of varying degrees of renal impairment on the pharmacokinetics of duloxetine: analysis of a single-dose phase I study and pooled steady-state data from phase II/III trials. *Clin Pharmacokinet* 2010;**49**:311–21.
66. Argoff CE. New analgesics for neuropathic pain: the lidocaine patch. *Clin J Pain* 2000;**16**:S62–6.
67. Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain* 1999;**80**:533–8.

68. Murtagh FEM, Chai MO, Donohoe P, et al. The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. *J Pain Palliat Care Pharmacother* 2007; **21**:5–16.
69. Kurella M, Bennett WM, Chertow GM. Analgesia in patients with ESRD: a review of available evidence. *Am J Kidney Dis* 2003;**42**: 217–28.
70. Saboory E, Derchansky M, Ismaili M, et al. Mechanisms of morphine enhancement of spontaneous seizure activity. *Anesth Analog* 2007;**105**:1729–35.
71. Nayak-Rao S. Achieving effective pain relief in patients with chronic kidney disease: a review of analgesics in renal failure. *J Nephrol* 2011;**24**:35–40.
72. Kreek MJ, Schecter AJ, Gutjahr CL, et al. Methadone use in patients with chronic renal disease. *Drug Alcohol Depend* 1980;**5**:197–205.
73. Davies G, Kingswood C, Street M. Pharmacokinetics of opioids in renal dysfunction. *Clin Pharmacol Kinet* 1996;**31**:410–22.
74. Labroo RB, Paine MF, Thummel KE, et al. Fentanyl metabolism by human hepatic and intestinal cytochrome P450 3A4: implications for interindividual variability in disposition, efficacy, and drug interactions. *Drug Metab Dispos* 1997;**25**:1072–80.
75. Zhang X, Donnan PT, Bell S, Guthrie B. Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: systematic review and meta-analysis. *BMC Nephrol* 2017;**18**: 256.

QUESTIONS AND ANSWERS

Question 1

A 64-year-old man with stage 4 CKD, baseline eGFR 25 mL/min, presents to his nephrologist reporting lower back pain for the past week. He reports lifting heavy objects before the onset of pain.

Which of the following statements is correct?

A. Pain prevalence consistently decreases as CKD stages advance
B. The back pain is likely secondary to nephrolithiasis
C. Pain is a common symptom reported in CKD patients
D. You should immediately refer the patient to a pain specialist

Answer: C

Pain is prevalent in patients with CKD. Studies have estimated the prevalence of reported pain to be up to 70% in patients with CKD. The prevalence of pain did not change across the different CKD stages in one study; however, in another study pain was perceived as more intense in those with advanced stages of CKD. Immediate referral to a pain specialist is not appropriate until other measures are tried in close consultation with the patient's primary care provider.[1,6]

Question 2

The patient has tried acetaminophen and heating pads with no relief and requests "something stronger" for pain.

Which of the following analgesic medications would be most appropriate to treat this patient's chronic pain?

A. Amitriptyline
B. Morphine Sulfate
C. Ibuprofen
D. Tramadol
E. None of the above

Answer: E

Based on current recommendations, the analgesics listed should be avoided in CKD patients and none of the above is the correct answer.[52–54]

Question 3

The patient returns 2 weeks later reporting shooting pains radiating down the back of his right leg down to his foot. You recommend physical therapy and that he consult with his primary care physician for additional options. Which of the following medications would you recommend to the primary care physician as the best adjuvant to help with this patient's pain?

A. Gabapentin
B. Ibuprofen
C. Morphine sulfate
D. Amitriptyline

Answer: A

This patient has sciatic neuropathic pain which is best managed with an adjuvant analgesic such as the anticonvulsant gabapentin. The other medications listed are contraindicated in patients with advanced CKD. Recent studies in ESRD patients suggest more data are needed regarding results of treatment with gabapentin in patients with CKD.[56,59]

Question 4

A 58-year-old woman with breast cancer metastatic to the bone and stage 4 CKD, GFR 20 mL/min, reports severe diffuse bone pain. She requests stronger analgesics. She currently takes acetaminophen with no relief of her symptoms. You discuss the case with the patient's primary care physician to develop an optimal therapeutic plan. Which of the following medications would you recommend as the next best option for this patient?

A. Fentanyl patch
B. Amitriptyline
C. Ibuprofen
D. Morphine sulfate

Answer: A

This patient has severe bone pain from metastatic disease which often requires the strongest analgesic options. Fentanyl patch is the best choice of the options listed. Fentanyl undergoes primarily hepatic clearance; however, clearance of the drug is reduced in patients with several renal failure, therefore a reduced dose should be considered. The other medications should be avoided in patients with advanced CKD.[73,74]

Question 5

A 64-year-old woman with a history of type 2 diabetes mellitus for 25 years and stage 4 CKD, GFR 25 mL/min, reports painful burning in both feet for the past month. She requests analgesic relief. Which of the following medications may be most effective in relieving her symptoms?

A. Morphine sulfate
B. Duloxetine
C. Ibuprofen
D. Acetaminophen

Answer: B

This patient has neuropathic pain, which is best managed with an adjuvant such as duloxetine. Other

appropriate options might include gabapentin or pregabalin which are not listed as answer choices. These medications, in light of recent data in the ESRD population, need study in the CKD population. The other medications listed are either not appropriate for patients with CKD or not shown to be effective for neuropathic pain.[59,62–64]

Question 6

A 53-year-old woman with stage 3a CKD, GFR 50 mL/min presents to the hospital with AKI. Her admission S[Cr] is 6.7 mg/dL. She states she has had severe back pain for the past month and recently started taking over the counter pain medication. Over the past week, she developed gastroenteritis with poor oral intake. Which of the following medications most likely contributed to the AKI?

A. Duloxetine
B. Tramadol
C. Ibuprofen
D. Acetaminophen

Answer: C

This patient presented to the hospital with AKI in the setting of volume depletion. Ibuprofen is a cause of AKI, especially in the setting of volume depletion and preexisting CKD. The other answer choices listed are not associated with AKI.[45–47,75]

CHAPTER

79

The Perioperative Management of the Patient with Chronic Kidney Disease

Amrita D. Karambelkar[a], *Lakhmir S. Chawla*[b,c,d], *Laurence W. Busse*[e]

[a]Department of Internal Medicine, Emory University School of Medicine, GME Office of Graduate Medical Education, Atlanta, GA, United States; [b]Department of Anesthesiology and Critical Care Medicine, George Washington University Medical Center, Washington, DC, United States; [c]Division of Kidney Diseases and Hypertension, Department of Medicine, George Washington University, Washington, DC, United States; [d]University California of San Diego, San Diego, CA, United States; [e]Emory University, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Department of Medicine, Emory Johns Creek Hospital, Johns Creek, GA, United States

Abstract

Patients with chronic kidney disease (CKD) are at higher risk for mortality and adverse outcomes in the perioperative setting. Although surgical procedures in CKD patients are commonly performed, a paucity of research exists on the adequate evaluation and minimization of perioperative risk. Most data are tangential and explore the surgical risk of conditions that are associated with CKD, such as cardiovascular disease or anemia. Some strategies that have been adopted in the management of perioperative CKD patients include avoidance of nephrotoxic medications, analysis, and adjustment of electrolyte and glucose abnormalities, correction of anemia, and careful attention to types and amount of resuscitative fluids. Intraoperatively, the proper use of anesthetics, analgesics, and neuromuscular blocking agents, which exhibit altered pharmacodynamics and pharmacokinetics in CKD patients, can minimize unwanted side effects. Proper attention should be paid to postoperative planning and management, with specific attention paid to reinitiation of home medications, as well as adequate nutrition, mobilization, and discharge strategies.

INTRODUCTION

The perioperative management of the patient with chronic kidney disease (CKD) can be complex and challenging for the surgeon and the intensivist. Surgical risk is higher in CKD patients due in part to difficulties managing vascular access, electrolytes, volume status, and dosing adjustments for commonly used perioperative drugs. More importantly, cardiovascular comorbidities place CKD patients at a higher risk for perioperative mortality. In the preoperative period, proper patient selection, risk assessment, and strategies for risk abatement are vital for optimizing patient survival. Intraoperative management of blood pressure, electrolytes, fluids, and blood products warrants particular attention. Postoperative dosing of analgesia, reinitiation of home medications, and monitoring can minimize hospital length of stay (LOS) and adverse outcomes.

EPIDEMIOLOGY AND RISK ASSESSMENT

CKD is defined as long-term (≥3 months) structural or functional abnormality of the kidney associated with a decrease in glomerular filtration rate (GFR).[1] CKD is common in the US, with a prevalence in adults approaching 11% for stages 1 through 5. The prevalence for CKD stages 3 through 5, corresponding to a GFR of <60 mL/min/1.73 m^2, is 4.6%.[1] CKD is associated with higher rates of mortality, with hazard ratios of 1.03, 1.38, and 3.11 for estimated glomerular filtration rates (eGFRs) of 60, 45, and 15 mL/min/1.73 m^2, respectively.[2] Moreover, patients with CKD are at particular risk for development of acute kidney injury (AKI). A systematic review by Novis et al. of over ten thousand surgical patients found that increased serum creatinine (S[Cr]), increased BUN, and preoperative renal dysfunction were the three most common risk factors for the development of postoperative renal dysfunction.[3] AKI is also associated with increased risk of adverse outcomes. In a series of over

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00079-6

9000 hospitalized patients, AKI, as defined by an increase in S[Cr] of ≥0.5 mg/dL, was associated with a 6.5-fold increase in the odds of death, a 3.5-day increase of LOS, and $7500 in excess hospital costs.[4]

Surgical procedures are commonly performed in the US. According to the National Institutes of Health, 15 million people in the US each year undergo a surgical procedure.[5] Overall surgical perioperative mortality is estimated to be 1.85%, based on a large Dutch study of 3.7 million surgical procedures,[6] although mortality rates have recently been reported as high as 3.6%–4%.[7,8]

CKD is encountered commonly in the perioperative setting. As an example, an estimated 600,000 patients undergo coronary artery bypass grafting (CABG) each year in the US; of these, 10%–20% have a baseline S[Cr] of over 1.5 mg/dL.[9] Mortality rises considerably in these patients. In fact, in the perioperative setting, both CKD and AKI are associated with adverse outcomes. Postoperative AKI in the cardiac surgery population, for example, occurs in 1%–30% of patients, with a mortality of approximately 15%–30%.[10,11] A preoperative elevation of S[Cr] (and corresponding reduction in eGFR) was shown to be associated with mortality in a retrospective case-control study of 80 patients undergoing femoral neck fracture operative repair.[12] eGFR was further predictive of mortality in a retrospective analysis of almost 400 endovascular aortic aneurysm repair patients.[13] In a recent analysis by Jacob et al., patients with CKD who underwent cardiac surgery experienced a higher rate of renal replacement therapy and death than their counterparts without CKD (27.1% vs. 11.4%, $p < 0.001$).[14] A retrospective Veterans Administration database review of almost 4000 CABG patients showed that a S[Cr] level between 1.5 mg/dL and 3.0 mg/dL was associated with a more than doubled mortality rate (7% vs. 3%, $p < 0.001$).[9] Cooper et al. analyzed renal dysfunction and patient outcome during CABG using data from the Society of Thoracic Surgeons National Adult Cardiac Database over a three and a half year period. They concluded that preexisting renal dysfunction, as measured by GFR, carried a sixfold increase in operative mortality and a threefold increase in complications (including sepsis, stroke, LOS, and length of time on ventilator).[15] Longer-term outcomes in patients with severe renal dysfunction (defined as eGFR 15–45 mL/min/1.73 m^2) who underwent CABG were significantly worse than those with moderate renal dysfunction (eGFR 45–60 mL/min/1.73 m^2) or eGFR greater than 60 mL/min/1.73 m^2. The patients with severe dysfunction experienced more cardiovascular events or deaths (hazard ratio 1.36 with 95% confidence interval of 1.22–1.53).[16] Numerous other studies have demonstrated an increase in perioperative morbidity and mortality in the CKD population in other noncardiac surgical settings, including vascular, orthopedic procedures, and urologic oncological surgery.[12,13,17–19]

Lee's index of cardiac risk assessment in noncardiac surgery includes preoperative S[Cr] >2.0 mg/dL as one of the six independent predictors of adverse outcome.[20] Based on the aforementioned and other data, the American College of Cardiologists/American Heart Association (ACC/AHA) considers CKD to be a perioperative risk factor equal to ischemic heart disease and stroke.[21] Surgical risk accumulates with the presence of active cardiac conditions, limitations in the patient's underlying functional capacity, type of surgery, and underlying comorbidities, of which CKD is one. Figure 79.1 illustrates the 2007 ACC/AHA guidelines for perioperative risk stratification for noncardiac surgery.

PREOPERATIVE ASSESSMENT

Preoperative assessment is essential in understanding the nature of the patient's renal impairment, as well as the likelihood of adverse outcome. Figure 79.2 depicts some of the expected physiological and hormonal effects on the kidney in the operative setting, which can become dysregulated when kidney disease is present.

KDOQI guidelines suggest the following assessments as part of a comprehensive evaluation of all CKD patients.[1]

- Diagnosis of the type of kidney disease
- Comorbid conditions
- Severity of kidney disease
- Complications related to level of kidney function
- Risk for loss of kidney function
- Risk for cardiovascular disease

These factors are also of particular importance in the perioperative period, as an understanding of renal dysfunction can assist the surgeon and intensivist in managing essential tasks, such as minimizing metabolic and pharmacological sequelae, maintaining electrolyte homeostasis, managing acid–base levels, and mitigating fluid shifts. For example, a surgeon may avoid administering excess blood products or causing muscle trauma (both of which can increase S[K] levels) in patients with CKD who have an inability to regulate electrolytes.[22] Patients with CKD frequently have several comorbid conditions, including hypertension and diabetes, which are themselves associated with myocardial dysfunction, coronary artery disease, and peripheral vascular disease.[23] The presence of these conditions is associated with increased cardiovascular risk and may influence a surgeon's opinion on the necessity, timing, and duration of surgery. Additional factors, such as anemia, uremia, protein malnutrition, and bone disease

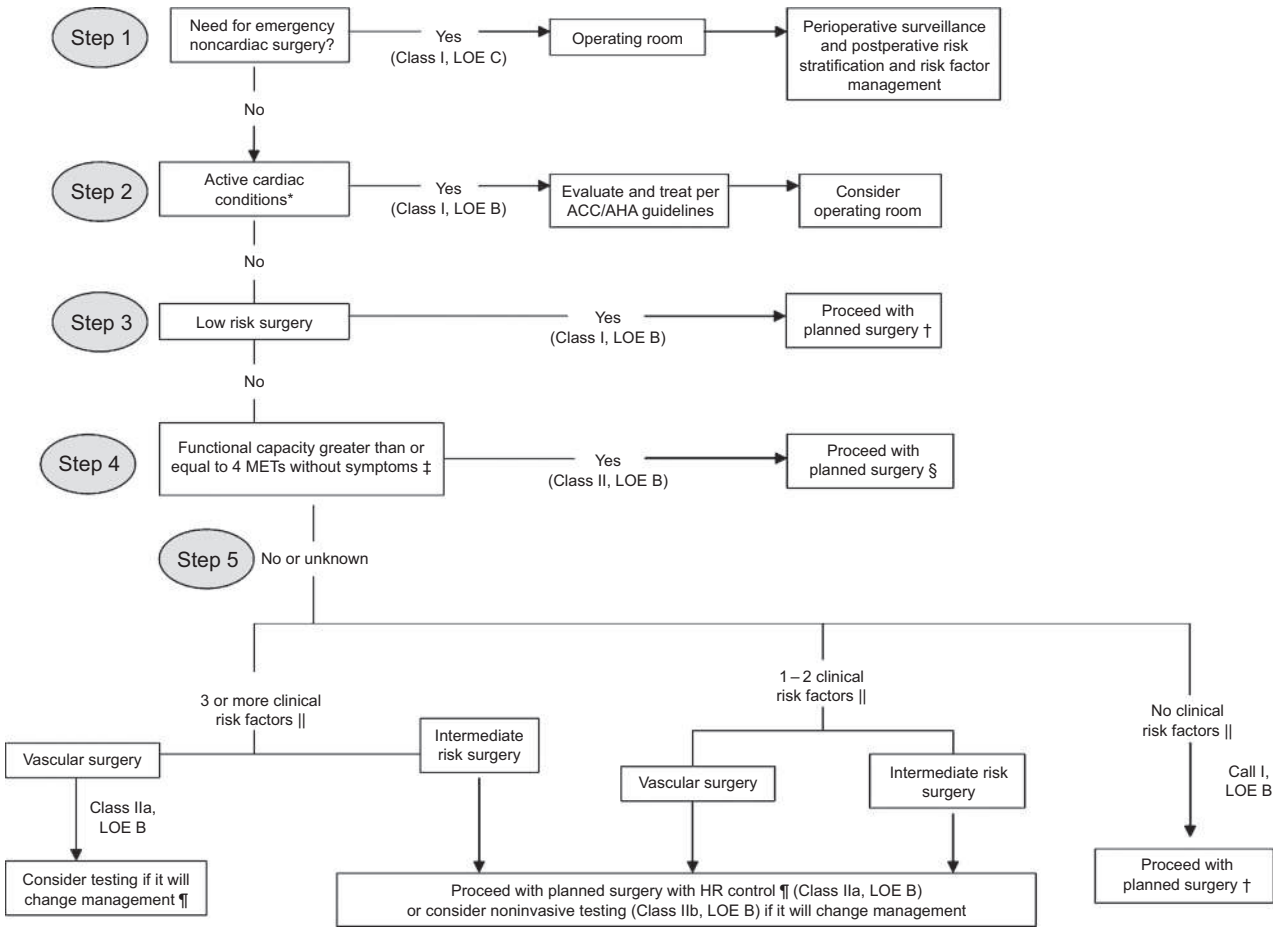


FIGURE 79.1 Stepwise algorithm for determining perioperative risk in noncardiac surgery. Active cardiac conditions include unstable coronary syndromes, decompensated heart failure, significant arrhythmia, or significant valvular conditions. Clinical risk factors include ischemic heart disease, compensated or prior heart failure, diabetes mellitus, renal insufficiency, or cerebrovascular disease. *Reproduced with permission from Fleisher et al. (2007).*[21]

(calcium−phosphorus metabolism), are also potential issues in CKD patients and can make it difficult in the operative setting to address blood loss, endocrine function, and wound healing. Infection can be more common in CKD patients due to a relatively immunocompromised state.[23] In addition, patients with CKD may develop neuropathy, which can affect postoperative pain management.[1] Moreover, because the magnitude of azotemia correlates with increasing levels of mortality, it behooves the surgeon and intensivist to understand the stage of CKD and the rate of decline in GFR, as well as to avoid interventions that may worsen kidney function (such as nephrotoxic medications or radiocontrast agents).

Medications in the Perioperative Period

Abnormalities in drug metabolism occur in patients with CKD related to alterations in volume of distribution and protein binding, changes in bioavailability, and prolongation of half-lives of both the drug and any metabolites.[24] Additionally, patients with CKD are more prone to adverse drug reactions, including neurological, psychiatric, integumentary, gastrointestinal, and cardiovascular events.[25] Accordingly, careful attention should be paid to the preoperative (i.e. home) medications that many CKD patients routinely take. Dose adjustment or discontinuation of certain agents may avoid unnecessary renal injury in the perioperative period. The American College of Physicians and the American Society of Internal Medicine have both published guidelines for prescribing drugs in the setting of diminished renal function.[24] Common drugs used in the CKD population are angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta blockers, calcium channel blockers, diuretics, antiarrhythmics, and analgesics.

Prior administration of ACEIs and ARBs is commonly associated with hypotension in the operating room, particularly on induction of anesthesia.[26,27] In a retrospective study of 267 patients on chronic ACEI or ARB therapy, those who took their home medication within

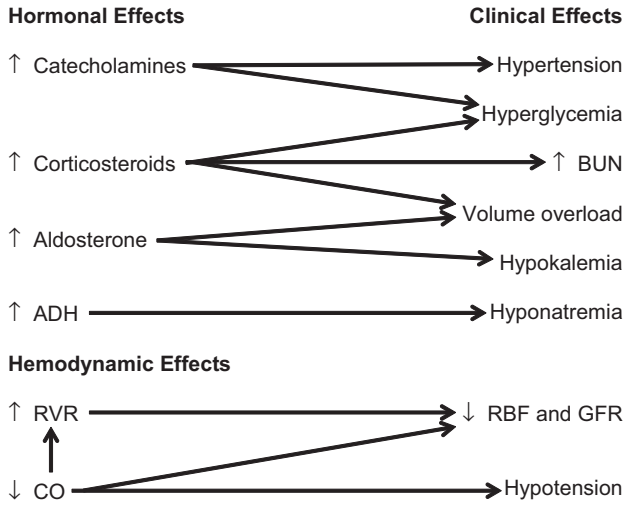


FIGURE 79.2 Physiologic and hormonal responses to surgery affecting the kidney. *ADH*, antidiuretic hormone; *BUN*, serum urea nitrogen; *CO*, cardiac output; *RVR*, renal vascular resistance.

10 hours of the onset of surgery were more likely to have moderate hypotension (systolic blood pressure ≤85 mm Hg) during the first 30 minutes after induction of anesthesia.[27] Currently, there is no consensus on management of preoperative ACEI/ARB administration. However, discontinuation of ACEI/ARB therapy and management of blood pressure with other short-acting and titratable agents may be prudent and should be considered in CKD patients before surgery.[28] The management of operative hypotension in the setting of preoperative ACEI or ARB use may be accomplished through conventional methods, such as fluid resuscitation and vasopressor therapy. Choice of vasopressor may have implications for kidney health and is addressed below, in addition to other novel therapies. On the other hand, ACEI/ARB therapy may provide the additional benefit of inhibiting the renin–angiotensin–aldosterone system (RAAS), which can affect the progression of renal disease.[29] Perioperative RAAS inactivation may be accomplished through the use of ACEI/ARB therapy, as well as alternative pathways. A randomized controlled trial studied the effects of human atrial natriuretic peptide (hANP) infusion intraoperatively and the ARB olmesartan in the immediate postoperative period in patients undergoing CABG. Those treated with hemodialysis and taking ACEI preoperatively were excluded. There was no significant difference in baseline variables including CKD stage, use of circulatory assist devices, or perioperative catecholamine use. Compared with placebo, the groups that received hANP alone and hANP in combination with ARB had lower 30-day mortality (6% for placebo vs. 0% for the other two groups) and lower need for dialysis (12% for placebo vs. 1.7% for hANP and 1.8% for hANP plus ARB).[30]

Beta blockers are safe in the perioperative period and have been shown in numerous studies to confer protection against perioperative myocardial ischemia, mostly due to avoidance of beta blocker withdrawal.[31] The ACC/AHA guidelines state that beta blockers should be continued in patients undergoing surgery who are receiving beta blockers to treat angina, symptomatic arrhythmia, or hypertension.[32] Data on other vasoactive drugs, such as calcium channel blockers, amiodarone, and alpha 2 blockers, are lacking.

Diuretics are also commonly used in CKD patients. In addition to altering volume status, diuretics can potentiate abnormalities in electrolyte levels.[33] For example hypokalemia (a common effect of most diuretics) has been shown in a prospective, observational, case-control study of over 2400 cardiac surgery patients to predict serious perioperative or intraoperative arrhythmia, postoperative atrial fibrillation/flutter, or the need for cardiopulmonary resuscitation.[34] Volume status can be difficult to manage perioperatively, as it is governed as much by free water as by total body sodium levels, serum and urine osmolality, and antidiuretic hormone levels.[35] Consensus opinion based in part on early observational studies is that diuretics be held before surgery.[31,36]

Other classes of drugs should be used judiciously, taking into consideration expected side effects, and how these may manifest in the perioperative period, especially with the possibility of worsening renal function. For example, the clinician should acknowledge the possibility of hypertension with the administration of erythropoietin, cyclosporine, and corticosteroids, or the lowering of the seizure threshold with certain antibiotics or meperidine.[23,37] Nephrotoxic agents, such as aminoglycosides and NSAIDs, should be avoided, as these are thought to contribute to the incidence of AKI.[38] Essential medications for other comorbid conditions, such as aspirin or clopidogrel for stents in the setting of coronary artery disease or peripheral vascular disease, should be evaluated on a case-by-case basis and continued if possible. The cardiac surgery literature suggests that aspirin may be continued, but that it is reasonable to hold clopidogrel 5–7 days before cardiac surgery.[39,40]

Perioperative Laboratory Evaluation/Tests

Routine preoperative laboratory evaluation is warranted, as a patient with CKD is at higher risk for anemia, electrolyte instability, coagulopathy, and abnormal levels of calcium, phosphate, and magnesium. These abnormalities have been associated with worse outcomes. Prompt attention to these abnormalities may mitigate perioperative risk.

eGFR

A basic metabolic panel and patient demographic data can be used to calculate the eGFR. eGFR can be determined using the widely accepted Modification of Diet in Renal Disease (MDRD) equation. Some clinicians still use the outdated Cockroft–Gault equation. This practice should be updated with MDRD or CKD-EPI equations. The results of this analysis can assist in medication adjustment, CKD staging, and identification of the presence of AKI. AKI is associated with adverse outcomes, and depending on etiology, its presence should be addressed perioperatively.

Some attempts have been made pharmacologically to address and correct a reduced eGFR. Dopamine and the dopaminergic analogue fenoldopam have been used in an attempt to prevent deterioration of renal function in CKD patients undergoing surgery. "Low" or "renal" dose dopamine infusion has been shown to increase urine output, but has not resulted in any renal protective effects and has, in fact, been associated with harmful side effects.[41–43] Dopamine is not recommended for the prevention or treatment of AKI in the critical care or perioperative setting. Fenoldopam, a pure dopamine type-1 agonist, has been studied in the prevention of AKI in high-risk surgery patients as well as in the critical care setting. A recent meta-analysis of 440 patients from six studies concluded that fenoldopam consistently and significantly reduced the incidence of AKI (odds ratio—0.41) but had no effect on the need for renal replacement therapy, survival, or LOS.[44] Other studies have found equivocal and inconsistent results.[45] Currently, fenoldopam is not recommended in the perioperative setting to prevent the development of AKI.[46] Other therapies aimed at mitigating kidney injury have been evaluated in various settings, including perioperatively.[47] The antioxidant alpha-lipoic acid (ALA) has been studied in renal ischemia-reperfusion injury, with adequate results.[48] Propofol, a common anesthetic, has proven to be superior to volatile anesthetics for renal protection in multiple studies.[49–51] Both ALA and propofol are known antioxidants, which may be beneficial in reducing the deleterious oxidative effects associated with AKI.

Glucose

Serum glucose should be routinely evaluated in the perioperative setting for hyperglycemia, especially in those CKD patients who have concomitant diabetes mellitus. Hyperglycemia (glucose values >200 mg/dL) has been found to be very common in the perioperative setting, occurring in 21%–41% of diabetic surgical patients, and is associated with perioperative morbidity and mortality in this population.[52,53] There are no data on perioperative outcomes of CKD patients with hyperglycemia. However, a cohort study found that chronic hyperglycemia (defined as HbA1c greater than or equal to 6.0%) was independently associated with AKI in patients undergoing CABG.[54] In addition, CKD was associated with worse outcomes in diabetic patients undergoing percutaneous coronary intervention in a retrospective analysis by Nikolsky et al.[55] Moreover, it has been shown that poor glucose control in diabetic CKD patients is associated with increased mortality.[56,57] Elevations in serum glucose can be corrected with parenteral insulin. Current guidelines recommend moderate glucose control, based on a preponderance of evidence.[58,59]

Minerals

Calcium and phosphate abnormalities in CKD patients have been associated with increased all-cause mortality, although studies evaluating mineral abnormalities in the perioperative setting are lacking.[60] Mechanisms of morbidity are thought to be related to vascular calcification, abnormalities in the microcirculation, decreased myocardial contractility, nutritional deficits, and respiratory insufficiency. Abnormalities in mineral metabolism in CKD patients before surgery can be addressed through the use of phosphate binders, vitamin D supplementation, and calcium altering medications, such as bisphosphonates and calcitriol. While calcitriol and other vitamin D analogues have been shown to reduce mortality in CKD patients, there are no data on perioperative outcomes with the use of these drugs specifically.[61,62] The use of bisphosphonates in CKD patients is controversial, as this population has typically been excluded from analysis.[63]

Hemoglobin

As kidney disease progresses, anemia can result from deficiency of erythropoietin, with commensurate diminished aerobic capacity and quality of life, as well as the potential for myocardial dysfunction.[64] Mild to moderate anemia has been associated with progression of renal injury, stroke, and death in surgical patients.[65] The degree of hemodilution during cardiopulmonary bypass was shown to be associated with worsening renal function necessitating renal replacement therapy in 9080 cardiac surgery patients, of whom 1818 had preexisting renal disease.[66] Additionally, incidences of myocardial infarction, shock, bleeding, multiple organ failure, and death were all increased in the setting of anemia (hematocrit <22%) in 5000 cardiac surgery patients, only 171 of whom had renal failure.[67] However, data on perioperative anemia in the CKD population are scant. A retrospective study of CKD patients undergoing hip and knee arthroplasty found that CKD patients, when compared with controls matched for age, gender, and type of orthopedic procedure, received significantly

more blood transfusions intraoperatively and during hospitalization.[68] The presence of CKD was independently associated with need for blood transfusion. Another prospective observational study analyzed preoperative hemoglobin and cardiac surgery outcomes in patients with CKD stages 3 to 5.[69] With every 1 g/dL decrease in preoperative hemoglobin, there was a higher risk of mortality, sepsis, cerebrovascular incident, and postoperative hemodialysis. Preoperative hemoglobin concentration below 12 g/dL was also an independent postoperative mortality risk factor. Therefore, blood transfusion, or alternatively treatment with erythropoietin-stimulating medications, may be appropriate perioperatively in the anemic CKD patient, but this practice is not data-driven and no randomized controlled trials exist to evaluate optimization of preoperative hemoglobin concentration in CKD patients.[23] Erythropoietin-stimulating medications have been used in the perioperative setting to reduce the need for blood transfusion, but these medications are associated with adverse cardiovascular, cerebrovascular, and thrombotic events.[70] Additional studies are needed to address the timing, dose, duration, and safety of erythropoietin-stimulating medications in the perioperative period.[71] Guidelines currently recommend transfusion of CKD patients to a hemoglobin level of 11–12 g/dL, although this recommendation is not specific to surgical populations.[72]

BUN

Patients with CKD are considered to have higher risk of bleeding from uremic platelet dysfunction, which can occur even though a coagulation evaluation is normal.[73] Some studies, however, suggest that blood from CKD patients is prothrombotic, and that concomitant anemia is responsible for perioperative bleeding. Red blood cell transfusion to a hematocrit of 26% has been shown to shorten bleeding time.[74] Correction of the effects of uremia, either by lowering BUN with dialysis or reversing the antiplatelet effects of uremia with deamino-8-D-arginine vasopressin (DDAVP), cryoprecipitate, or intravenous conjugated estrogens can address the risk of perioperative bleeding.[75] Dialysis acts to remove uremic toxins which are associated with coagulopathy, including urea, creatinine, phenol, phenolic acids, and guanidinosuccinic acid.[76–78] DDAVP is administered intravenously at a dose of 0.3 μg/kg and causes the release of von Willebrand factor from the vascular endothelium, which in turn enhances platelet aggregation.[78] DDAVP is effective within 30 minutes and lasts for four hours.[79] Estrogens do not become effective until 6 hours after administration, but effects last for 2–3 weeks.[75] The mechanism of action is thought to be related to interference with the nitric oxide synthetic pathway.[78] Importantly, aspirin-mediated platelet dysfunction in CKD patients with concomitant cardiovascular disease may be desired, and reversal of this effect with DDAVP, platelet transfusion, or estrogen therapy may increase the risk of perioperative acute coronary syndrome. Studies assessing the cost benefit of reversal of platelet dysfunction are lacking. Platelet mapping studies with thromboelastography (TEG) may assist the clinician in quantifying the level of platelet dysfunction and are more informative than the standard coagulation studies and platelet count.

Potassium

No specific recommendation exists regarding a safe potassium level before surgery. Historically, hyperkalemia has been associated with increased hospital mortality.[80,81] In CKD patients, hyperkalemia is likewise associated with increased mortality, although the presence and severity of CKD was associated with a lower odds ratio of potassium-related mortality compared with non-CKD patients.[82] Hyperkalemia is thought to be associated with up to 5% of all deaths among ESRD patients.[83] Studies on surgical mortality directly related to hyperkalemia, however, are lacking.[84–86] Singh Mangat et al. evaluated serum potassium (S[K]) levels perioperatively as a secondary endpoint and found no correlation between potassium levels and mortality.[12] Hyperkalemia is thought to predispose to ventricular arrhythmia, and sudden increases in S[K], such as encountered occasionally with the use of certain anesthetics or depolarizing agents, are generally best avoided. Consensus opinion is that most anesthesiologists avoid depolarizing anesthetic agents when S[K] is above 5.5 mEq/L. However, a number of studies report no adverse events with depolarizing agents, despite S[K] above this level.[87,88] Hypokalemia has likewise been evaluated in the perioperative setting and is associated with serious perioperative arrhythmias and the need for cardiopulmonary resuscitation.[34] Furthermore, low S[K] is associated with worsening renal function in the CKD population.[33] Evaluation of hyperkalemia or hypokalemia in the perioperative setting should be corroborated with evidence of myocardial instability by electrocardiography or rhythm monitoring.

Sodium

The loss of sodium regulation is a recognized risk factor for development of ESRD.[89,90] Hyponatremia may lead to worse surgical outcomes in patients with CKD. A retrospective study showed increased mortality and LOS in the ICU among patients with S[Na] <135 mEq/L compared with patients with S[Na] ≥135 mEq/L.[91] Logistic regression showed that hyponatremia was an independent risk factor for mortality and need for dialysis. Of note, although rates of congestive heart failure were similar in both groups, left ventricular dysfunction

was more prevalent in the hyponatremia group and may explain some of the risk seen with hyponatremia. A large retrospective cohort study by Leung et al. found that preoperative hyponatremia was associated with a higher risk of 30-day mortality (5.2% vs. 1.3%; adjusted odds ratio [aOR], 1.44; 95% CI, 1.38−1.50).[92] In subgroup analysis, dialysis-dependent patients exhibited a smaller but still significant increased risk of perioperative mortality.

Electrocardiography

Given the increased cardiac risk in CKD patients, an electrocardiogram (ECG) should be performed as part of the preoperative evaluation. Left ventricular hypertrophy (LVH) can signal long-standing or difficult-to-control hypertension. In ESRD patients, LVH on ECG was associated with cardiovascular mortality.[93] Evidence of myocardial electrical abnormality, such as peaked T waves in hyperkalemia or prolonged PR or QT segments as seen in hypokalemia can suggest electrolyte instability, although such ECG findings are unreliable.[94,95] ST segment changes and the presence of Q waves can signify current or prior myocardial infarction and the presence of coronary artery disease and may prompt an additional preoperative evaluation, such as echocardiogram or myocardial stress testing according to the ACC/AHA guidelines.[21]

Intraoperative Volume and Blood Pressure Management

The perioperative maintenance of euvolemia and adequate renal perfusion pressure is important in preventing postoperative AKI. At baseline, only 10−20% of the total renal blood flow of 1−1.5 L/min is filtered through the glomeruli, which still delivers adequate oxygen to the renal medullary parenchyma.[38] However, because of renal autoregulation and tubuloglomerular feedback mechanisms, reduced renal blood flow has a disproportionately large effect on GFR.[38] Hence, a drop in systolic blood pressure, either because of hypovolemia or vasodilation, can cause kidney hypoxia and ischemia, as well as render the kidney susceptible to further insult. On the other hand, fluid overload in the setting of CKD may be associated with progression of renal disease, as well as altered gut permeability and a maladaptive inflammatory response.[96] Patients with CKD have an impaired ability to excrete sodium, as well as dilute and concentrate urine in response to alterations in sodium and water intake.[97] As such, they are predisposed to the development of volume overload related to the dysregulation of free water distribution on receiving a sodium load.[37] Administration of saline solutions, as is common in the operative setting, can lead to the development of metabolic acidosis in patients with CKD.[98] In general, perioperative fluid administration has been associated with deleterious effects on cardiac, pulmonary, renal, and gastrointestinal function.[99] Therefore, it behooves the clinician to avoid *both* hypovolemia and hypervolemia in the perioperative setting. This is not always easy to do, as traditional signals of volume status may be misinterpreted in CKD patients. Intraoperative urine output repeatedly has been shown to poorly predict postoperative renal function.[100,101] Moreover, many of the anesthetics and analgesics as well as beta blockers may mask some of the features of hypovolemia, such as tachycardia.[40]

Determination of volume responsiveness (i.e. whether the patient's hemodynamic profile would improve with the administration of a volume challenge) can be made using a number of different dynamic tools, including the pulmonary artery catheter, pulse contour analysis, esophageal Doppler, or inferior vena cava diameter.[102] These tools have largely replaced the static measurements of volume status, such as central venous pressure and pulmonary artery occlusion pressure, which have been shown in numerous studies to poorly correlate with volume responsiveness.[103,104] There are a number of excellent review articles which explore volume management in the critical care environment.[102,105,106] The method of determining volume responsiveness is patient-, clinician-, and institution-specific.

Traditionally, perioperative fluid management has consisted of providing "maintenance" fluid with bolus administration in patients with hypotension or reduced urine output.[107] However, based on a number of studies that associate positive fluid balance with worse outcomes, emerging opinion is such that relative hypovolemia (i.e. a restrictive fluid balance) is a superior strategy in the perioperative setting.[108−112] A restricted crystalloid fluid strategy in thoracic surgery patients was not associated with development of AKI even in patients with decreased preoperative renal function.[113] Furthermore, a meta-analysis of patients undergoing colonic resection found that perioperative fluid restriction did not affect postoperative mortality, although this study was not conducted solely in CKD patients.[114] Commonly, the Enhanced Recovery After Surgery pathway may be used for fluid management during abdominal surgery.[115] This pathway facilitates euvolemia during surgery *via* a fluid replacement rate of 0.5 mL/kg/h, which is thought to be the insensible loss during abdominal surgery. Moreover, intraoperative dynamic measures of fluid responsiveness such as stroke volume variation are increasingly being used,[115] although these fluid management strategies have not been studied in randomized controlled trials in CKD patients. Nonetheless, it is reasonable to adopt a protocolized approach based on

frequently obtained objective measures in CKD patients undergoing major surgery.

In instances of hypovolemia and inadequate renal perfusion when fluid administration is needed, generally crystalloid or blood products are given. The choice of crystalloid is subject to debate, as recent data have emerged linking chloride-rich fluids to a higher incidence of AKI and renal replacement therapy.[116] Administration of balanced solutions, such as lactated ringers or Plasma-Lyte® 148 (Baxter Healthcare), may be associated with superior renal hemodynamics compared with administration of normal saline.[117] Administration of lactated ringers solution was compared with normal saline in patients undergoing renal transplantation and found to be associated with fewer incidents of hyperkalemia and metabolic acidosis.[98] Normal saline was compared with Plasma-Lyte® in an observational study of patients undergoing open abdominal surgery and found to be associated with higher mortality and perioperative complications.[118] Numerous studies have evaluated sodium bicarbonate solution as a resuscitative fluid strategy for the prevention or mitigation of AKI.[119–122] None of these, however, specifically focus on the CKD population.

Colloidal solutions may be preferred when the clinician desires to minimize extravascular volume, such as in cases of worsening pulmonary edema or abdominal compartment syndrome. The choice of colloids is also debatable. Starch solutions have been found to be associated with adverse outcomes (including bleeding, renal failure, and death).[123,124] In contrast, the SAFE Investigators evaluated normal saline vs. a 4% albumin solution and found no differences in death, organ failure, LOS, or days of renal replacement therapy.[125] Specialty solutions, such as mannitol or hypertonic saline, have been examined in CKD patients. Occasionally, mannitol is used in CABG patients to increase renal blood flow and appears to be effective.[126] In the authors' opinion, blood transfusion may be an appropriate colloidal resuscitative strategy in anemic CKD patients, in light of the impact of a low hematocrit on perioperative outcomes. Importantly, there is a paucity of research comparing clinical outcomes related with perioperative resuscitation with crystalloids compared with blood products. Moreover, the optimal fluid strategy in CKD patients has never been elucidated, and additional research is required on this topic.

Operative hypotension has been shown in multiple studies to be associated with the development of AKI.[127,128] Walsh et al. examined perioperative data for 33,330 patients undergoing noncardiac surgery and found that the probability of AKI increased with low MAP during surgery, an effect that was time sensitive.[127] Vasopressor therapy is frequently used in the perioperative setting, especially when fluid resuscitation is unable to achieve desired MAP goals or when a restrictive fluid resuscitation strategy may be desired. The choice of vasopressor agent may have clinical implications in the CKD population. Evidence is beginning to support the use of noncatecholamine therapy (vasopressin and angiotensin II) in patients at risk for AKI.[129–131] Subgroup and *post hoc* analyses of both the vasopressin vs. norepinephrine infusion in patients with septic shock (VASST) and the Angiotensin II for the Treatment of High Output Shock (ATHOS-3) trials both found improved kidney outcomes in septic shock patients treated with noncatecholamine pressors.[129,132] The Vasopressin vs. Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery (VANCS) randomized controlled trial found that postoperative cardiac surgery patients with vasoplegic shock treated with vasopressin exhibited significantly lower incidence of AKI (10.3% vs. 35.8%, OR 0.26 (0.15–0.46), $p < 0.0001$).[133] Importantly, there are no studies specifically evaluating the choice of vasopressor in the CKD population. However, the effects of intrinsic vasopressin and angiotensin II on kidney function are well described.[134,135]

The drug levosimendan, a calcium sensitizer, has shown some ability to mitigate AKI in an operative setting. A *post hoc* study evaluated renal outcomes in patients with circulatory shock or heart failure (preoperative LVEF <25% and/or perioperative hemodynamic support with intraaortic ballon pump or inotropes) who underwent mitral valve surgery.[136] A significant decrease in the incidence of AKI (30% vs. 52 %, $p = 0.035$) and major complications (39% vs. 66%, $p = 0.011$) was seen in the levosimendan group compared with the placebo group. Two other randomized controlled trials have evaluated levosimendan in the postoperative setting and found no major differences in renal biomarkers or renal outcomes.[137,138] As of the publication of this chapter, levosimendan is not approved by the US Food and Drug Administration for clinical use.

Intraoperative hypertension is common (up to 80% of the cardiac surgery population and up to 25% of the noncardiac surgery population) and can contribute to complications such as myocardial ischemia, stroke, neurocognitive dysfunction, and surgical bleeding.[139] Intraoperative stressors such as endotracheal intubation and surgical incision are associated with increased sympathetic tone and consequent hemodynamic responses. The intravenous beta blockers esmolol and labetalol are short acting, easily titrated, and well-tolerated in the operating theater and can attenuate the hemodynamic responses of these stimuli.[140] Nicardipine, a dihydropyridine calcium channel blocker, is an appropriate alternative when beta blockade is contraindicated (such as in patients with asthma or bradycardia). Little

data exist, however, comparing intraoperative antihypertensive strategies in the CKD population. An optimal intraoperative blood pressure is determined in part by the observed blood pressure in the preoperative setting and by the type of surgery contemplated.[141] Notably, a mean arterial pressure of 65–75 mm Hg may result in underperfusion of the kidneys in the chronically hypertensive patient.[40,73] A randomized trial evaluated outcomes after major abdominal surgery in elderly hypertensive patients who were stratified by different MAP goals (65–79 mm Hg, 80–95 mm Hg, or 96–110 mm Hg).[142] The group with the intermediate MAP goal experienced less AKI, a lower rate of ICU admission, shorter length of ICU stay, and a lower incidence of hospital acquired pneumonia compared with those randomized to other MAP goals. Although this study did not specifically evaluate CKD patients, the results may nonetheless support higher blood pressure goals in patients likely to suffer from CKD (the elderly and those with high AKI risk). The Intraoperative Norepinephrine to Control Arterial Pressure trial tested two intraoperative blood pressure strategies in patients with a high risk of AKI: an "individualized" approach (targeted systolic BP within 10% of the patients' resting systolic BP) or a "standard" approach (systolic BP above 80 mm Hg or within 40% of the patients' resting systolic BP).[143] At enrollment, renal impairment was present in 11.7% of the standard therapy group, and 19.1% of the individualized therapy group. At 30 days, organ dysfunction was lower in the individualized strategy group, and there was no difference in 30-day mortality. However, renal-specific organ dysfunction was not different between groups.

TABLE 79.1 Drugs With Active or Toxic Metabolites Dependent on Renal Excretion[144]

Drug	Metabolites	Activity
Morphine	Morphine-3-glucuronide	Antanalgesic
	Morphine-6-glucuronide	Analgesic (40 x morphine)
Meperidine	Normeperidine	Neuroexcitatory
Diazepam	Oxazepam	Sedative
Midazolam	1-Hydroxy-midazolam	Sedative
Sodium nitroprusside	Thiocyanate	Neurotoxic
Enflurane	Fluoride	Nephrotoxic
Vecuronium	Desacetyl-vecuronium	Relaxant
Pancuronium	3-Hydroxy-pancuronium	Relaxant
Procainamide	n-Acetyl-procainamide (NAPA)	Neurotoxic

ANESTHESIA, ANALGESIA, AND NEUROMUSCULAR BLOCKING AGENTS

Induction Agents

Patients with CKD are at risk for adverse drug responses related to abnormalities in drug metabolism and elimination. Lipid insoluble drugs may be partially or completely dependent on renal function for adequate elimination. Lipid insoluble metabolites of lipid soluble drugs normally metabolized hepatically may also accumulate in patients with diminished renal function.[144] Table 79.1 lists commonly used medications with impaired clearance in renal failure.

Induction of anesthesia must be tailored appropriately to avoid these complications. Propofol is commonly used for induction and maintenance of anesthesia and has been found to be safe in patients with ESRD as well as CKD.[145,146] However, a higher dose of propofol may be required to reach the desired level of hypnosis as a result of altered plasma volume.[147] Propofol-related infusion syndrome (PRIS) is a rare complication of propofol administration, with several toxic metabolic effects including anion gap metabolic acidosis, rhabdomyolysis, and hyperkalemia and is of special concern and consideration in advanced CKD and ESRD patients, due to impaired potassium management.[148] The risk of PRIS is increased with duration of propofol administration, as well as with bolus dosing as part of rapid sequence intubation. Etomidate is safe in CKD patients.[147] Ketamine, too, is considered safe, but physicians must be aware of the side effects of hypertension and tachycardia when using ketamine.[149] Benzodiazepines are extensively protein-bound, and their effect is potentiated in CKD patients (where uremia alters protein binding activity). Moreover, many benzodiazepines are excreted by the kidneys, and repeated doses can accumulate, causing respiratory and cardiac depression.[149] For example, midazolam is metabolized to a renally excreted active metabolite, which is slow to clear in patients with diminished GFR.[150] Diazepam, compared with other benzodiazepines, is more extensively unbound to proteins, and doses should be adjusted downward in patients with CKD.[144]

The choice of induction agent may be patient-specific, given underlying morbidities. A retrospective study of patients with ST-elevation myocardial infarction showed that during rapid sequence intubation after

revascularization, midazolam was associated with more hypotension than ketamine,[151] which may be of particular concern to normotensive patients with CKD who might otherwise be served well *via* induction with ketamine.

Volatile Anesthetics

Inhalational anesthetics, such as halothane, desflurane, sevoflurane, isoflurane, and nitrous oxide, are eliminated by the lungs and are generally considered safe for use in CKD patients.[144] Initial concerns regarding elevated fluoride levels with the use of sevoflurane have abated, as studies have not demonstrated any evidence of adverse outcomes in the clinical setting.[152] Both sevoflurane and enflurane biodegrade into inorganiic fluoride, which can be nephrotoxic at a concentration of 50 μmol/L. This far exceeds measured fluoride levels after anesthetic doses of isoflurane and halothane, which cause an increase of 3−5 μmol/L and 1−2 μmol/L, respectively.[147] Conzen et al. found that neither sevoflurane nor isoflurane caused worsening of renal function in patients with preexisting CKD.[153] Litz et al. compared desflurane and isoflurane in a population of patients with preexisting renal disease and also found no deterioration in renal parameters such as creatinine clearance, S[Cr], and BUN level.[154] However, enflurane is best avoided, as it can cause a concentration defect in kidneys of healthy volunteers and has been associated in case reports with renal failure in CKD patients.[155,156]

Neuromuscular Blocking Agents

Administration of the depolarizing neuromuscular blocking agent succinylcholine is associated with the development of hyperkalemia, and this drug should be used with caution in CKD patients. Historically, succinylcholine has been considered safe for induction of anesthesia in patients with CKD who have normal preoperative potassium levels.[157] In these patients, S[K] levels were observed to increase by approximately 0.5 mEq/L for 10−15 minutes without the occurrence of arrhythmia.[158] Large or prolonged doses of succinylcholine should be avoided, as the active metabolite succinylmonocholine is renally excreted.[149] Nondepolarizing agents are not associated with hyperkalemia, but still must be used with caution due to altered pharmacokinetics and decreased elimination in renal failure. Vecuronium and rocuronium are primarily excreted in the bile, but partially eliminated through the kidney, and can exhibit a prolonged effect due to reduced renal clearance.[159−161] They are, however, fairly safe and predictable in renal failure.[160] Atracurium and the derivative cisatracurium are both metabolized by spontaneous nonenzymatic (Hoffmann) degradation and ester hydrolysis, a process completely independent of kidney function. These muscle relaxants are considered safe in patients with renal failure, with the caveat that laudanosine (a metabolite of atracurium and to a lesser extent cisatracurium) has been shown to cause seizures in laboratory animals.[162]

Analgesics

Opioids are extensively used both for induction of anesthesia and analgesia and must be administered with caution in patients with CKD. Morphine is catabolized by the liver into several metabolites, including morphine-6-glucuronide, which has an analgesic potency 40 times that of the parent drug. Morphine-6-glucuronide is eliminated renally and may have a prolonged half-life of up to 27 hours in patients with renal failure.[163] Morphine-6-gluconoride can accumulate in renal dysfunction and can potentially lead to severe, life-threatening side effects including respiratory depression, altered mental status, and myoclonus.[164] Consequently, morphine doses should be reduced in the CKD patient. Fentanyl is metabolized extensively in the liver and does not have active metabolites. A small percentage of fentanyl is excreted in the urine and clearance is reduced in patients with CKD.[165,166] One potentially appealing opioid for use in CKD patients is remifentanil, which undergoes degradation by ester hydrolysis, independent of renal function.[149]

Other analgesics which are not used for induction of anesthesia but rather for perioperative pain control include other opioid derivatives, nonsteroidal antiinflammatory drugs (NSAIDs), and acetaminophen. Hydromorphone is an opioid which is extensively metabolized by the liver to several renally excreted metabolites including hydromorphone-3-glucuronide, which has been associated with cognitive dysfunction and myoclonus.[167] Meperidine is metabolized to an active metabolite normeperidine, which has been associated with seizure activity in CKD patients and hence should be avoided in kidney failure.[168] NSAIDs affect renal function and can precipitate AKI *via* inhibition of prostaglandin-mediated renal blood flow. As such, they may be unsafe in patients with CKD, especially after surgery.[22,23,37,38,40,73] NSAIDs have been associated with adverse cardiovascular events and are known to exacerbate hypertension, hyperkalemia, and progression of AKI.[37,169] Acetaminophen is considered safe in the CKD population and can be used as an adjunct in pain management or as monotherapy.[170]

POSTOPERATIVE MANAGEMENT

There is little research guiding postoperative management of the CKD patient. Rather, the intensivist should use sound clinical judgment and common sense. Extubation should not be contemplated before a complete assessment of vital signs and airway reflexes, due to the possibility of reduced clearance of anesthetics and paralytics. Volume status should be carefully determined, as diuresis may be challenging in the setting of reduced renal blood flow, and early extubation may be associated with pulmonary edema. Analgesia in the postoperative setting can be difficult to manage, owing to altered pharmacokinetics of many of the commonly used analgesics. Blood pressure, fluid status, and mineral metabolism are dysregulated in the CKD population, and outpatient medications should be resumed when possible. It is prudent to involve the nephrologist postoperatively in the event that the patient may require renal replacement therapy.[38] Nephrotoxic medications should be avoided, and radiocontrast dye exposure should be minimized in postoperative CKD patients. Immunosuppressive therapy, if needed, should be dose-adjusted and monitored by serum level in patients with CKD who experience change in renal function after surgery. These drugs can cause side effects, including hypertension, hyperlipidemia, hyperkalemia, diabetes mellitus, neurotoxicity, and worsening of renal function.[37] Other aspects of postoperative care, such as nutrition, early mobility, and transition to home and should be considered an important aspect of any postsurgical care plan.[171–173]

CONCLUSION

The perioperative management of CKD patients continues to provide a challenge to their physicians. Close consideration must be given to the fluid and electrolyte disturbances associated with the underlying renal insufficiency as well as altered drug clearance and metabolism. In addition, the presence of several comorbid conditions such as diabetes mellitus, systemic hypertension, and cardiovascular disease are associated with worse outcomes and must be factored into a perioperative risk assessment. The avoidance of AKI, the correction of electrolyte, mineral and volume abnormalities, and the improvement of perioperative anemia can mitigate an adverse postoperative course. A multidisciplinary approach, consisting of the nephrologist, primary care physician, surgeon, anesthesiologist, and intensivist is required to optimize surgical success in the CKD patient.

Disclosures

Dr. Busse has no disclosures to report.
Dr. Karambelkar has no disclosures to report.
Dr. Chawla is an employee of La Jolla Pharmaceutical Company.

References

1. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**(2 Suppl. 1):S1–266.
2. van der Velde M, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2011;**79**(12):1341–52.
3. Novis BK, et al. Association of preoperative risk factors with postoperative acute renal failure. *Anesth Analg* 1994;**78**(1):143–9.
4. Chertow GM, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005;**16**(11): 3365–70.
5. MedlinePlus. Surgery. http://www.nlm.nih.gov/medlineplus/surgery.html.
6. Noordzij PG, et al. Postoperative mortality in The Netherlands: a population-based analysis of surgery-specific risk in adults. *Anesthesiology* 2010;**112**(5):1105–15.
7. Anderson O, et al. Surgical adverse events: a systematic review. *Am J Surg* 2013;**206**(2):253–62.
8. Pearse RM, et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012;**380**(9847):1059–65.
9. Anderson RJ, et al. Renal failure predisposes patients to adverse outcome after coronary artery bypass surgery. VA Cooperative Study #5. *Kidney Int* 1999;**55**(3):1057–62.
10. Morabito S, et al. Acute renal failure following cardiac surgery. *G Ital Nefrol* 2006;**23**(Suppl. 36):S52–60.
11. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. *Clin J Am Soc Nephrol* 2006;**1**(1):19–32.
12. Singh Mangat K, et al. Is estimated peri-operative glomerular filtration rate associated with post-operative mortality in fractured neck of femur patients? *Injury* 2008;**39**(10):1141–6.
13. Azizzadeh A, et al. Glomerular filtration rate is a predictor of mortality after endovascular abdominal aortic aneurysm repair. *J Vasc Surg* 2006;**43**(1):14–8.
14. Jacob K. Inflammatory complications after cardiac surgery: atrial fribrillation and kidney injury. In: *Risk score for renal replacement therapy or death after cardiac surgery in patients with chronic kidney disease: development and external validation*; 2017. p. 131–55. Unpublished work.
15. Cooper WA, et al. Impact of renal dysfunction on outcomes of coronary artery bypass surgery: results from the Society of Thoracic Surgeons National Adult Cardiac Database. *Circulation* 2006; **113**(8):1063–70.
16. Holzmann M, et al. Long-term cardiovascular outcomes in patients with chronic kidney disease undergoing coronary artery bypass graft surgery for acute coronary syndromes. *J Am Heart Assoc* 2014;**3**(2):e000707.
17. Kertai MD, et al. Comparison between serum creatinine and creatinine clearance for the prediction of postoperative mortality in patients undergoing major vascular surgery. *Clin Nephrol* 2003;**59**(1): 17–23.
18. Ensrud KE, et al. Renal function and risk of hip and vertebral fractures in older women. *Arch Intern Med* 2007;**167**(2):133–9.
19. Schmid M, et al. Chronic kidney disease and perioperative outcomes in urological oncological surgery. *Int J Urol* 2014;**21**(12): 1245–52.

20. Lee TH, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999;**100**(10):1043–9.
21. Fleisher LA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 2002 guidelines on perioperative cardiovascular evaluation for noncardiac surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol* 2007;**50**(17):1707–32.
22. Joseph AJ, Cohn SL. Perioperative care of the patient with renal failure. *Med Clin N Am* 2003;**87**(1):193–210.
23. Carrasco LR, Chou JC. Perioperative management of patients with renal disease. *Oral Maxillofac Surg Clin N Am* 2006;**18**(2): 203–12. vi.
24. Bennett WM, et al. Drug prescribing in renal failure: dosing guidelines for adults. *Am J Kidney Dis* 1983;**3**(3):155–93.
25. Smith JW, Seidl LG, Cluff LE. Studies on the epidemiology of adverse drug reactions. V. Clinical factors influencing susceptibility. *Ann Intern Med* 1966;**65**(4):629–40.
26. Bertrand M, et al. Should the angiotensin II antagonists be discontinued before surgery? *Anesth Analg* 2001;**92**(1):26–30.
27. Comfere T, et al. Angiotensin system inhibitors in a general surgical population. *Anesth Analg* 2005;**100**(3):636–44 [table of contents].
28. Smith I, Jackson I. Beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers: should they be stopped or not before ambulatory anaesthesia? *Curr Opin Anaesthesiol* 2010;**23**(6):687–90.
29. Kobori H, et al. The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. *Pharmacol Rev* 2007;**59**(3):251–87.
30. Yoshitake I, et al. Renin-angiotensin system control for chronic kidney disease patients undergoing coronary surgery. *Ann Thorac Cardiovasc Surg* 2016;**22**(5):291–7.
31. Wolf A, McGoldrick KE. Cardiovascular pharmacotherapeutic considerations in patients undergoing anesthesia. *Cardiol Rev* 2011;**19**(1):12–6.
32. Fleisher LA, et al. ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for noncardiac surgery: focused update on perioperative beta-blocker therapy–a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to update the 2002 guidelines on perioperative cardiovascular evaluation for noncardiac surgery). *Anesth Analg* 2007;**104**(1):15–26.
33. Wang HH, et al. Hypokalemia, its contributing factors and renal outcomes in patients with chronic kidney disease. *PLoS One* 2013;**8**(7):e67140.
34. Wahr JA, et al. Preoperative serum potassium levels and perioperative outcomes in cardiac surgery patients. Multicenter Study of Perioperative Ischemia Research Group. *JAMA* 1999;**281**(23): 2203–10.
35. Yee J, Parasuraman R, Narins RG. Selective review of key perioperative renal-electrolyte disturbances in chronic renal failure patients. *Chest* 1999;**115**(5 Suppl.):149s–57s.
36. Tasker PR, MacGregor GA, De Wardener HE. Prophylactic use of intravenous saline in patients with chronic renal failure undergoing major surgery. *Lancet* 1974;**2**(7886):911–2.
37. Craig RG, Hunter JM. Recent developments in the perioperative management of adult patients with chronic kidney disease. *Br J Anaesth* 2008;**101**(3):296–310.
38. Carmichael P, Carmichael AR. Acute renal failure in the surgical setting. *ANZ J Surg* 2003;**73**(3):144–53.
39. Dunning J, et al. Guideline on antiplatelet and anticoagulation management in cardiac surgery. *Eur J Cardiothorac Surg* 2008; **34**(1):73–92.
40. Jones DR, Lee HT. Surgery in the patient with renal dysfunction. *Med Clin N Am* 2009;**93**(5):1083–93.
41. Friedrich JO, et al. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med* 2005;**142**(7):510–24.
42. Schenarts PJ, et al. Low-dose dopamine: a physiologically based review. *Curr Surg* 2006;**63**(3):219–25.
43. Holmes CL, Walley KR. Bad medicine: low-dose dopamine in the ICU. *Chest* 2003;**123**(4):1266–75.
44. Zangrillo A, et al. Fenoldopam and acute renal failure in cardiac surgery: a meta-analysis of randomized placebo-controlled trials. *J Cardiothorac Vasc Anesth* 2012;**26**(3):407–13.
45. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care* 2013; **17**(1):204.
46. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012;**2**(1):2–138.
47. Chen H, Busse LW. Novel therapies for acute kidney injury. *Kidney Int Rep* 2017;**2**(5):785–99.
48. Ambrosi N, et al. Alpha-lipoic acid protects against ischemia-reperfusion injury in simultaneous kidney-pancreas transplantation. *Transplantation* 2016;**100**(4):908–15.
49. Yoo YC, et al. Anesthetics influence the incidence of acute kidney injury following valvular heart surgery. *Kidney Int* 2014;**86**(2): 414–22.
50. Bang JY, et al. The influence of propofol and sevoflurane on acute kidney injury after colorectal surgery: a retrospective cohort study. *Anesth Analg* 2016;**123**(2):363–70.
51. Ammar AS, Mahmoud KM. Comparative effect of propofol versus sevoflurane on renal ischemia/reperfusion injury after elective open abdominal aortic aneurysm repair. *Saudi J Anaesth* 2016;**10**(3):301–7.
52. Furnary AP, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2003;**125**(5):1007–21.
53. Turina M, et al. Short-term hyperglycemia in surgical patients and a study of related cellular mechanisms. *Ann Surg* 2006;**243**(6): 845–51. discussion 851–3.
54. Oezkur M, et al. Chronic hyperglycemia is associated with acute kidney injury in patients undergoing CABG surgery–a cohort study. *BMC Cardiovasc Disord* 2015;**15**:41.
55. Nikolsky E, et al. Impact of chronic kidney disease on prognosis of patients with diabetes mellitus treated with percutaneous coronary intervention. *Am J Cardiol* 2004;**94**(3):300–5.
56. Snit M, et al. Impact of glycemic control on survival of diabetic patients on chronic regular hemodialysis: a 7-year observational study. *Diabetes Care* 2007;**30**(1):189. author reply 189–90.
57. Morioka T, et al. Glycemic control is a predictor of survival for diabetic patients on hemodialysis. *Diabetes Care* 2001;**24**(5): 909–13.
58. Finfer S, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;**360**(13):1283–97.
59. Ling Y, Li X, Gao X. Intensive versus conventional glucose control in critically ill patients: a meta-analysis of randomized controlled trials. *Eur J Intern Med* 2012;**23**(6):564–74.
60. Covic A, et al. Systematic review of the evidence underlying the association between mineral metabolism disturbances and risk of all-cause mortality, cardiovascular mortality and cardiovascular events in chronic kidney disease. *Nephrol Dial Transplant* 2009;**24**(5):1506–23.

61. Shoben AB, et al. Association of oral calcitriol with improved survival in nondialyzed CKD. *J Am Soc Nephrol* 2008;**19**(8):1613–9.
62. Duranton F, et al. Vitamin D treatment and mortality in chronic kidney disease: a systematic review and meta-analysis. *Am J Nephrol* 2013;**37**(3):239–48.
63. Toussaint ND, Elder GJ, Kerr PG. Bisphosphonates in chronic kidney disease; balancing potential benefits and adverse effects on bone and soft tissue. *Clin J Am Soc Nephrol* 2009;**4**(1):221–33.
64. Trainor D, Borthwick E, Ferguson A. Perioperative management of the hemodialysis patient. *Semin Dial* 2011;**24**(3):314–26.
65. Hare GM, Freedman J, David Mazer C. Review article: risks of anemia and related management strategies: can perioperative blood management improve patient safety? *Can J Anaesth* 2013; **60**(2):168–75.
66. Karkouti K, et al. Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. *J Thorac Cardiovasc Surg* 2005;**129**(2):391–400.
67. Habib RH, et al. Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: should current practice be changed? *J Thorac Cardiovasc Surg* 2003;**125**(6):1438–50.
68. Augustin ID, et al. Association between chronic kidney disease and blood transfusions for knee and hip arthroplasty surgery. *J Arthroplast* 2013;**28**(6):928–31.
69. Shavit L, et al. Preoperative hemoglobin and outcomes in patients with CKD undergoing cardiac surgery. *Clin J Am Soc Nephrol* 2014; **9**(9):1536–44.
70. Lin DM, Lin ES, Tran MH. Efficacy and safety of erythropoietin and intravenous iron in perioperative blood management: a systematic review. *Transfus Med Rev* 2013;**27**(4):221–34.
71. Tran DH, et al. Effectiveness and safety of erythropoiesis-stimulating agent use in the perioperative period. *Expert Opin Biol Ther* 2014;**14**(1):51–61.
72. IV. NKF-K/DOQI clinical practice guidelines for anemia of chronic kidney disease: update 2000. *Am J Kidney Dis* 2001;**37**(1 Suppl. 1):S182–238.
73. Dougherty M, Webb ST. Perioperative management of the patient with chronic kidney disease. *Surgery* 2010;**28**(9):433–6.
74. Fernandez F, et al. Low haematocrit and prolonged bleeding time in uraemic patients: effect of red cell transfusions. *Br J Haematol* 1985;**59**(1):139–48.
75. Livio M, et al. Conjugated estrogens for the management of bleeding associated with renal failure. *N Engl J Med* 1986; **315**(12):731–5.
76. Couch P, Stumpf JL. Management of uremic bleeding. *Clin Pharm* 1990;**9**(9):673–81.
77. Rabiner SF, Drake RF. Platelet function as an indicator of adequate dialysis. *Kidney Int Suppl* 1975;(2):144–6.
78. Galbusera M, Remuzzi G, Boccardo P. Treatment of bleeding in dialysis patients. *Semin Dial* 2009;**22**(3):279–86.
79. Zeigler ZR, Megaludis A, Fraley DS. Desmopressin (d-DAVP) effects on platelet rheology and von Willebrand factor activities in uremia. *Am J Hematol* 1992;**39**(2):90–5.
80. Moore ML, Bailey RR. Hyperkalaemia in patients in hospital. *N Z Med J* 1989;**102**(878):557–8.
81. Paice B, et al. Hyperkalaemia in patients in hospital. *Br Med J* 1983; **286**(6372):1189–92.
82. Einhorn LM, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med* 2009;**169**(12): 1156–62.
83. Han SW. Hyperkalemia in chronic kidney disease. *Electrolytes & Blood Pressure* 2005;**3**(2):71–8.
84. Acker CG, et al. Hyperkalemia in hospitalized patients: causes, adequacy of treatment, and results of an attempt to improve physician compliance with published therapy guidelines. *Arch Intern Med* 1998;**158**(8):917–24.
85. Lissoos I, et al. Surgical procedures on patients in end-stage renal failure. *Br J Urol* 1973;**45**(4):359–65.
86. Pinson CW, et al. Surgery in long-term dialysis patients. Experience with more than 300 cases. *Am J Surg* 1986;**151**(5):567–71.
87. Olson RP, et al. Absence of adverse outcomes in hyperkalemic patients undergoing vascular access surgery. *Can J Anaesth* 2003; **50**(6):553–7.
88. Schow AJ, et al. Can succinylcholine be used safely in hyperkalemic patients? *Anesth Analg* 2002;**95**(1):119–22 [table of contents].
89. Kovesdy CP, et al. Hyponatremia, hypernatremia, and mortality in patients with chronic kidney disease with and without congestive heart failure. *Circulation* 2012;**125**(5):677–84.
90. Han SW, et al. Serum sodium levels and patient outcomes in an ambulatory clinic-based chronic kidney disease cohort. *Am J Nephrol* 2015;**41**(3):200–9.
91. Shavit L, et al. Hyponatremia predicts poor outcomes in patients with chronic kidney disease undergoing heart operation. *Ann Thorac Surg* 2018;**106**(3):696–701.
92. Leung AA, et al. Preoperative hyponatremia and perioperative complications. *Arch Intern Med* 2012;**172**(19):1474–81.
93. Covic AC, et al. The prognostic value of electrocardiographic estimation of left ventricular hypertrophy in dialysis patients. *Ann Noninvasive Electrocardiol* 2013;**18**(2):188–98.
94. Aslam S, Friedman EA, Ifudu O. Electrocardiography is unreliable in detecting potentially lethal hyperkalaemia in haemodialysis patients. *Nephrol Dial Transplant* 2002;**17**(9):1639–42.
95. Green D, et al. The clinical significance of hyperkalaemia-associated repolarization abnormalities in end-stage renal disease. *Nephrol Dial Transplant* 2013;**28**(1):99–105.
96. Pecoits-Filho R, et al. Impact of residual renal function on volume status in chronic renal failure. *Blood Purif* 2004;**22**(3):285–92.
97. Bourgoignie JJ, et al. Sodium homeostasis in dogs with chronic renal insufficiency. *Kidney Int* 1982;**21**(6):820–6.
98. O'Malley CM, et al. A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. *Anesth Analg* 2005;**100**(5):1518–24 [table of contents].
99. Holte K, Sharrock NE, Kehlet H. Pathophysiology and clinical implications of perioperative fluid excess. *Br J Anaesth* 2002;**89**(4): 622–32.
100. Alpert RA, et al. Intraoperative urinary output does not predict postoperative renal function in patients undergoing abdominal aortic revascularization. *Surgery* 1984;**95**(6):707–11.
101. Knos GB, et al. Intraoperative urinary output and postoperative blood urea nitrogen and creatinine levels in patients undergoing aortic reconstructive surgery. *J Clin Anesth* 1989;**1**(3):181–5.
102. Busse L, et al. Hemodynamic monitoring in the critical care environment. *Adv Chron Kidney Dis* 2013;**20**(1):21–9.
103. Kumar A, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med* 2004;**32**(3):691–9.
104. Osman D, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med* 2007;**35**(1):64–8.
105. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest* 2002;**121**(6):2000–8.
106. Marik PE, et al. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med* 2009; **37**(9):2642–7.
107. Glassford NJ, Myles P, Bellomo R. The Australian approach to perioperative fluid balance. *Curr Opin Anaesthesiol* 2012;**25**(1):102–10.
108. de Aguilar-Nascimento JE, et al. Clinical benefits after the implementation of a protocol of restricted perioperative intravenous

crystalloid fluids in major abdominal operations. *World J Surg* 2009;**33**(5):925–30.
109. Warrillow SJ, et al. Perioperative fluid prescription, complications and outcomes in major elective open gastrointestinal surgery. *Anaesth Intensive Care* 2010;**38**(2):259–65.
110. Toraman F, et al. Highly positive intraoperative fluid balance during cardiac surgery is associated with adverse outcome. *Perfusion* 2004;**19**(2):85–91.
111. McArdle GT, et al. Preliminary results of a prospective randomized trial of restrictive versus standard fluid regime in elective open abdominal aortic aneurysm repair. *Ann Surg* 2009;**250**(1): 28–34.
112. Varadhan KK, Lobo DN. A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. *Proc Nutr Soc* 2010;**69**(4):488–98.
113. Ahn HJ, et al. The risk of acute kidney injury from fluid restriction and hydroxyethyl starch in thoracic surgery. *Anesth Analg* 2016; **122**(1):186–93.
114. Boland MR, et al. Perioperative fluid restriction in major abdominal surgery: systematic review and meta-analysis of randomized, clinical trials. *World J Surg* 2013;**37**(6):1193–202.
115. Miller TE, Roche AM, Mythen M. Fluid management and goal-directed therapy as an adjunct to Enhanced Recovery After Surgery (ERAS). *Can J Anaesth* 2015;**62**(2):158–68.
116. Yunos NM, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012;**308**(15): 1566–72.
117. Chowdhury AH, et al. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte(R) 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg* 2012; **256**(1):18–24.
118. Shaw AD, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. *Ann Surg* 2012;**255**(5):821–9.
119. Cho JS, et al. Effect of perioperative sodium bicarbonate administration on renal function following cardiac surgery for infective endocarditis: a randomized, placebo-controlled trial. *Crit Care* 2017;**21**(1):3.
120. Chen X, et al. Comparative efficacy of drugs for preventing acute kidney injury after cardiac surgery: a network meta-analysis. *Am J Cardiovasc Drugs* 2018;**18**(1):49–58.
121. Tian ML, et al. Efficacy and safety of perioperative sodium bicarbonate therapy for cardiac surgery-associated acute kidney injury: a meta-analysis. *J Cardiovasc Pharmacol* 2015;**65**(2): 130–6.
122. Bailey M, et al. Sodium bicarbonate and renal function after cardiac surgery: a prospectively planned individual patient meta-analysis. *Anesthesiology* 2015;**122**(2):294–306.
123. Brunkhorst FM, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008;**358**(2):125–39.
124. Perner A, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012;**367**(2):124–34.
125. Finfer S, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004;**350**(22): 2247–56.
126. Maitra G, et al. Renal dysfunction after off-pump coronary artery bypass surgery- risk factors and preventive strategies. *Indian J Anaesth* 2009;**53**(4):401–7.
127. Walsh M, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* 2013; **119**(3):507–15.
128. Sun LY, et al. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology* 2015;**123**(3):515–23.
129. Gordon AC, et al. The effects of vasopressin on acute kidney injury in septic shock. *Intensive Care Med* 2010;**36**(1):83–91.
130. Torgersen C, et al. Comparing two different arginine vasopressin doses in advanced vasodilatory shock: a randomized, controlled, open-label trial. *Intensive Care Med* 2010;**36**(1):57–65.
131. Gordon AC, et al. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial. *JAMA* 2016;**316**(5):509–18.
132. Tumlin JA, et al. Outcomes in patients with vasodilatory shock and renal replacement therapy treated with intravenous angiotensin II. *Crit Care Med* 2018;**46**(6):949–57.
133. Hajjar LA, et al. Vasopressin versus norepinephrine in patients with vasoplegic shock after cardiac surgery: the VANCS randomized controlled trial. *Anesthesiology* 2017;**126**(1):85–93.
134. Mavani GP, DeVita MV, Michelis MF. A review of the nonpressor and nonantidiuretic actions of the hormone vasopressin. *Front Med* 2015;**2**:19.
135. Turner JM, et al. Treatment of chronic kidney disease. *Kidney Int* 2012;**81**(4):351–62.
136. Zangrillo A, et al. Effect of levosimendan on renal outcome in cardiac surgery patients with chronic kidney disease and perioperative cardiovascular dysfunction: a substudy of a multicenter randomized trial. *J Cardiothorac Vasc Anesth* 2018;**32**(5): 2152–9.
137. Ristikankare A, et al. Effects of levosimendan on renal function in patients undergoing coronary artery surgery. *J Cardiothorac Vasc Anesth* 2012;**26**(4):591–5.
138. Baysal A, et al. Levosimendan improves renal outcome in cardiac surgery: a randomized trial. *J Cardiothorac Vasc Anesth* 2014;**28**(3): 586–94.
139. Aronson S, et al. The ECLIPSE trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. *Anesth Analg* 2008;**107**(4):1110–21.
140. Cucchiara RF, et al. Evaluation of esmolol in controlling increases in heart rate and blood pressure during endotracheal intubation in patients undergoing carotid endarterectomy. *Anesthesiology* 1986;**65**(5):528–31.
141. Weiss SJ, Longnecker DE. Perioperative hypertension: an overview. *Coron Artery Dis* 1993;**4**(5):401–6.
142. Wu X, et al. Optimal blood pressure decreases acute kidney injury after gastrointestinal surgery in elderly hypertensive patients: a randomized study: optimal blood pressure reduces acute kidney injury. *J Clin Anesth* 2017;**43**:77–83.
143. Futier E, et al. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA* 2017;**318**(14):1346–57.
144. Sladen RN. Anesthetic considerations for the patient with renal failure. *Anesthesiol Clin N Am* 2000;**18**(4):863–82.
145. de Gasperi A, et al. Pharmacokinetic profile of the induction dose of propofol in chronic renal failure patients undergoing renal transplantation. *Minerva Anestesiol* 1996;**62**(1–2):25–31.
146. Ickx B, et al. Propofol infusion for induction and maintenance of anaesthesia in patients with end-stage renal disease. *Br J Anaesth* 1998;**81**(6):854–60.
147. Verma VK, K A, Bhardwaj G, Kumar S, Kumar M, Kumar KC. Anaesthesia for chronic renal disease and renal transplant: an update. *J Evol Med Dent Sci* 2005;**4**(19):3346–64.
148. Virmani S, et al. Propofol induced hyperkalemia and its management in end stage renal disease patients. *Conn Med* 2016;**80**(8): 491–3.

149. Stafford-Smith M, Shaw A, Sandler A, Kuhn C. The renal system and anesthesia for urologic surgery. In: *Clinical anesthesia*. Philadelphia, PA: Lippincott Williams & Wilkins; 2013.
150. Vinik HR, et al. The pharmacokinetics of midazolam in chronic renal failure patients. *Anesthesiology* 1983;**59**(5):390–4.
151. Zuin M, et al. Ketamine and midazolam differently impact post-intubation hemodynamic profile when used as induction agents during emergency airway management in hemodynamically stable patients with ST elevation myocardial infarction. *Heart Vessel* 2018;**33**(3):213–25.
152. Nishiyama T, Aibiki M, Hanaoka K. Inorganic fluoride kinetics and renal tubular function after sevoflurane anesthesia in chronic renal failure patients receiving hemodialysis. *Anesth Analg* 1996; **83**(3):574–7.
153. Conzen PF, et al. Low-flow sevoflurane compared with low-flow isoflurane anesthesia in patients with stable renal insufficiency. *Anesthesiology* 2002;**97**(3):578–84.
154. Litz RJ, et al. Renal responses to desflurane and isoflurane in patients with renal insufficiency. *Anesthesiology* 2002;**97**(5): 1133–6.
155. Conzen PF, et al. Renal function and serum fluoride concentrations in patients with stable renal insufficiency after anesthesia with sevoflurane or enflurane. *Anesth Analg* 1995;**81**(3):569–75.
156. Mazze RI, Calverley RK, Smith NT. Inorganic fluoride nephrotoxicity: prolonged enflurane and halothane anesthesia in volunteers. *Anesthesiology* 1977;**46**(4):265–71.
157. Miller RD, et al. Succinylcholine-induced hyperkalemia in patients with renal failure? *Anesthesiology* 1972;**36**(2):138–41.
158. Thapa S, Brull SJ. Succinylcholine-induced hyperkalemia in patients with renal failure: an old question revisited. *Anesth Analg* 2000;**91**(1):237–41.
159. Cooper RA, et al. Time course of neuromuscular effects and pharmacokinetics of rocuronium bromide (Org 9426) during isoflurane anaesthesia in patients with and without renal failure. *Br J Anaesth* 1993;**71**(2):222–6.
160. Della Rocca G, et al. Atracurium, cisatracurium, vecuronium and rocuronium in patients with renal failure. *Minerva Anestesiol* 2003; **69**(7–8). 605–11, 612, 615.
161. Szenohradszky J, et al. Pharmacokinetics of rocuronium bromide (ORG 9426) in patients with normal renal function or patients undergoing cadaver renal transplantation. *Anesthesiology* 1992;**77**(5): 899–904.
162. Fahey MR, et al. Effect of renal failure on laudanosine excretion in man. *Br J Anaesth* 1985;**57**(11):1049–51.
163. Murphy EJ. Acute pain management pharmacology for the patient with concurrent renal or hepatic disease. *Anaesth Intensive Care* 2005;**33**(3):311–22.
164. Koncicki HM, Unruh M, Schell JO. Pain management in CKD: a guide for nephrology providers. *Am J Kidney Dis* 2017;**69**(3):451–60.
165. Launay-Vacher V, et al. Treatment of pain in patients with renal insufficiency: the World Health Organization three-step ladder adapted. *J Pain* 2005;**6**(3):137–48.
166. Koehntop DE, Rodman JH. Fentanyl pharmacokinetics in patients undergoing renal transplantation. *Pharmacotherapy* 1997;**17**(4): 746–52.
167. Babul N, Darke AC, Hagen N. Hydromorphone metabolite accumulation in renal failure. *J Pain Symptom Manag* 1995;**10**(3):184–6.
168. Szeto HH, et al. Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure of cancer. *Ann Intern Med* 1977;**86**(6):738–41.
169. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2001;**286**(8): 954–9.
170. Berg KJ, et al. Acute effects of paracetamol on prostaglandin synthesis and renal function in normal man and in patients with renal failure. *Clin Nephrol* 1990;**34**(6):255–62.
171. Abunnaja S, Cuviello A, Sanchez JA. Enteral and parenteral nutrition in the perioperative period: state of the art. *Nutrients* 2013; **5**(2):608–23.
172. Mistiaen P, Francke AL, Poot E. Interventions aimed at reducing problems in adult patients discharged from hospital to home: a systematic meta-review. *BMC Health Serv Res* 2007;**7**:47.
173. Pashikanti L, Von Ah D. Impact of early mobilization protocol on the medical-surgical inpatient population: an integrated review of literature. *Clin Nurse Spec* 2012;**26**(2):87–94.
174. Ronald A, et al. Can the use of TEG predict and decrease bleeding and blood product requirements in adult patients undergoing cardiac surgery? *Inter CV Thorac Surg* 2005;**4**:456–63.
175. Madsen DE, Ingerslev J, Sidelmann JJ, Thorn JJ, Gram J. Intraoperative blood loss during orthognathic surgery is predicted by thromboelastography. *J Oral Maxillofac Surg* 2012;**70**(10): e547–52. https://doi.org/10.1016/j.joms.2012.06.182.

QUESTIONS AND ANSWERS

Question 1

A 54-year old man is admitted with ischemic colitis and is scheduled for a right hemicolectomy. The patient has a history of diabetes mellitus, hypertension, and stage 4 CKD. Urinary protein excretion is less than 500 mg protein per day. On physical examination, his blood pressure is 190/80 mm Hg and pulse is 80 beats per minute. His jugular venous pressure is 10 cm, lungs are clear, heart sounds are normal, and abdomen is soft with slightly tender right lower quadrant. There is 1+ peripheral edema. The following labs are obtained:

S[Na] 129 mEq/L
S[K] 5.2 mEq/L
S[Cl] 105 mEq/L
tCO2 18 mEq/L
BUN 38 mg/dL
S[Cr] 2.7 mg/dL
Glucose 82 mg/dL

Which of the following intravenous fluids should be used during the operative case?

A. 3% hypertonic saline
B. The patient should not be given any fluid unless signs of hypotension become apparent
C. Normal saline
D. Lactated Ringer's solution
E. Balanced isotonic salt solution (e.g. Plasmalyte or Isolyte)

Answer: E

Chloride-rich solutions cause acidemia, and in this patient are likely to exacerbate the patient's hyperkalemia. Therefore, A and C are wrong. Maintenance fluid during exploratory laporatomy is standard of care. Waiting for hypotension to occur before intervening is not appropriate perioperative care. Therefore, B is wrong. Lactated Ringer's solution is not an optimal choice because the solution is hypotonic and the patient is already hyponatremic. Therefore, Answer D is wrong.

Question 2

Which of the following platelet function tests predicts bleeding in CKD patients?

A. Bleeding time
B. Thrombin time
C. TEG
D. Blood smear

Answer: C

Bleeding time is an invasive test characterized by high interoperator variability. In addition, it does not predict bleeding. Thrombin time is not a platelet assessment. The blood smear is qualitative and does not predict bleeding. The answer is C, TEG, which can elucidate platelet dysfunction and other bleeding diatheses.[174,175]

Question 3

Which of the following antihypertensive agents can be safely administered to CKD patients before surgery?

A. ACEIs
B. Beta blockers
C. ARBs
D. Nifedipine

Answer: B

Beta blockers can be safely prescribed to CKD patients before surgery. Both ACEI and ARB have been associated with AKI during the perioperative period and their continued use throughout the perioperative period is controversial. There are no data on the use of nifedipine in CKD patients in the perioperative setting.

Question 4

Which of the following paralytic agents should be avoided in a patient with stage 4 CKD who is about to undergo burn debridement surgery?

A. Pancuronium
B. Cisatracurium
C. Succinylcholine
D. Vecuronium

Answer: C

Succinylcholine is a depolarizing paralytic and is associated with hyperkalemia. In general, avoidance of this drug in a patient population that has a tendency to develop acidemia and hyperkalemia is warranted. In burn injuries, in particular, the development of hyperkalemia should be anticipated, due to extensive tissue damage.

Question 5

A 64-year-old woman is admitted with wet gangrene of the lower left extremity and is being taken to the operating room for debridement and possible amputation. The patient has a history of diabetes mellitus, hypertension, obstructive sleep apnea, and stage 3 CKD. Urine protein excretion is less that 100 mg/day. On physical examination, her blood pressure is 90/60 mm Hg and pulse is 130 beats per minute. The patient's lungs are clear, heart sounds are normal, tachycardic, and abdomen is soft. Left lower extremity from the ankle

down is dark, cool, and edematous with purulence and crepitus. The following labs are obtained:

Serum electrolytes:

S[Na] 139 mEq/L
S[K] 6.2 mEq/L
S[Cl] 105 mEq/L
tCO2 12 mEq/L
BUN 38 mg/dL
S[Cr] 3.5 mg/dL
Glucose 82 mg/dL
S[Cr] 2 months ago was 2.2 mg/dL.

The anesthesiologist indicates that he prefers colloid to crystalloid and but wants to preserve kidney function and avoid adverse events during and after surgery. The most appropriate treatment strategy is

A. There are no data to indicate benefit or harm for any colloidal solution compared with any crystalloid solution, so avoid hypotension, dose the medications appropriately, and avoid aminoglycosides
B. Use renal dose dopamine along with a balanced salt solution
C. Noncatecholamine vasopressor agents should be avoided, and resuscitation should be accomplished with blood products
D. While perioperative starch solutions have been shown to improve perioperative outcomes in surgical patients, for this patient any form of starch should be avoided due to the risk of nephrotoxicity

Answer: D

Answer A is wrong because the use of many colloids (i.e. startch solutions) has been shown to be potentially harmful. Answer B is wrong, as there is no role for renal dose dopamine in the preservation of renal function in CKD patients. Noncatecholmine vasopressor agents may confer benefit over catecholamines so Answer C is wrong. The answer is D, as multiple colloidal solutions compared with crystalloids have been preferentially used in the perioperative period with improved outcomes; however, starch is a known nephrotoxic agent and should be avoided in a patient with AKI superimposed on CKD.

Question 6

A 77-year-old man is admitted with worsening heart failure from ischemic cardiomyopathy. He has noticed increasing shortness of breath with exertion, orthopnea, and swelling of his lower extremities. On physical examination, his blood pressure is 90/60 mm Hg and pulse is 110 beats per minute. His jugular venous pressure is 18 cm, rales are heard bilaterally, S1, S2, and an S3 gallop are present, abdomen is soft and nontender but his liver is enlarged, and there is 4+ peripheral edema. Cardiac catheterization shows multivessel disease, and the patient is scheduled for bypass surgery.

The following laboratory tests are obtained:

Serum electrolytes:

S[Na] 142 mEq/L
S[K] 3.4 mEq/L
S[Cl] 107 mEq/L
tCO2 18 mEq/L
BUN 38 mg/dL
S[Cr] 1.7 mg/dL
Glucose 82 mg/dL
Hemoglobin: 7.5 g/dL
Platelets: 150,000 mm^3

Which **one** of the following is the most appropriate recommendation?

A. As the patient is volume overloaded, the patient should have a catheter placed intraoperatively and be started on ultrafiltration postoperatively
B. The patient is severely anemic and should be started on erythropoietin
C. The patient is volume overloaded and should be immediately diuresed before undergoing surgery
D. The patient should be placed on fenoldopam during the perioperative period
E. The patient has CKD and has been exposed to radiocontrast, thus the perioperative management should avoid NSAIDs if possible.

Answer: E

Administration of erythropoietin is not indicated and has been associated with thrombotic events; thus, Answer B is wrong. The management of fluid overload remains controversial, but preoperative dialysis has not been shown to be superior to standard expectant management, so Answers A and C are wrong. D is incorrect because fenoldopam has not been shown to alter outcomes in patients undergoing CABG.

CHAPTER

80

Ethical Issues in Chronic Kidney Disease Patients

Alvin H. Moss

Center for Health Ethics and Law, Robert C. Byrd Health Sciences Center, West Virginia University, Morgantown, WV, United States

Abstract

Patients with stage 3–5 chronic kidney disease (CKD) have increased rates of cardiovascular mortality and cognitive impairment and are more likely to die than progress to end-stage renal disease. Because of their distinctly worse prognosis compared with age-matched patients in the general population, treatment of these patients raises ethical issues which require special consideration. These include matters pertaining to informed consent, shared decision-making, advance care planning with the completion of advance directives and Physician Orders for Life-Sustaining Treatment (POLST) forms as appropriate, the "biomedicalization" of aging, conflicts of interest in clinical practice guideline development for patients with CKD, and the ethical responsibility for particularly careful management of patients with CKD. Shared decision-making is the model for advance care planning and emphasizes an individualized patient-centered approach focusing on the patient's goals of care vs. a disease-oriented approach to treatment of CKD patients. Informed consent is especially important for older stage 5 CKD patients with multiple comorbidities because they may not benefit from dialysis. The "biomedicalization" of aging as it relates to the use of dialysis in older Americans is a key concern. Palliative care is appropriate for CKD patients with a poor prognosis and for whom the nephrologist would not be surprised if the patient died in the next year. Palliative care should be instituted early in their course so that they experience an optimal quality of life.

A critical population for nephrologists is stage 3–5 chronic kidney disease (CKD) patients who would not be considered candidates for kidney transplantation. There is a maxim in ethics, "Good ethics starts with good facts." The starting point for an ethical discussion of CKD is that the CKD population is distinctly different from age-matched patients in the general population, and this difference forms the basis for an approach to their treatment that is ethically directed and takes into account the unique nature of CKD. This uniquely different approach is justified by a foundational principle in medical ethics, the principle of formal justice, which states that people who are equal in relevant respects should be treated equally, and that people who are unequal in relevant respects should be treated differently.[1] In three large studies of CKD populations, death is a more common outcome than end-stage renal disease (ESRD).[2–4] Compared with the age-matched population without CKD, patients at all stages of CKD have increased rates of all-cause mortality and cardiovascular mortality that progress with advancing CKD.[5] Cognitive impairment is also highly prevalent in CKD patients. Epidemiologic data suggest that individuals at all stages of CKD have a higher risk of developing cognitive disorders and dementia.[6] Consequently, the ethical questions of "Who should decide?" and "What should be decided?" as they relate to decisions about initiating or forgoing dialysis are particularly germane.

Key ethical tasks exist in the treatment of patients with CKD. CKD is a life-limiting illness which should trigger an informed consent process and advance care planning long before the initiation of dialysis. Shared decision-making is the model for advance care planning which emphasizes an individualized patient-centered approach focusing on the patient's goals of care rather than using a disease-oriented approach to treatment of CKD patients. The communication of decisions reached as a result of shared decision-making to family and loved ones and their implementation by completion of advance directives and Physician Orders for Life-Sustaining Treatment (POLST) Paradigm forms is appropriate. The influence of our culture, in which there has been a "biomedicalization" of aging as it relates to the use of "life-extending" dialysis in older Americans, needs to be recognized and explicitly addressed in decision-making. Conflicts of interest in the treatment of CKD, including in the creation of the Kidney Disease Outcomes

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00080-2

Quality Initiative (KDOQI) clinical practice guidelines, need to be appreciated, and the ethical concerns raised by industry funding of clinical practice guideline development need to be factored into decisions regarding whether to comply with the guidelines for all patients. Considerations regarding conflicts of interest must be taken into account in the creation of kidney-specific clinical practice guidelines in the future. Because of the range of choices, there is an ethical obligation to include patients in decision-making about the treatment for their kidney disease and to offer the options of active medical management without dialysis and palliative care for CKD patients who decide to forgo dialysis.[7,8]

ILLUSTRATIVE CASES

The following cases require the ethical tasks identified above to be implemented into the patients' treatment for them to receive the best care possible.

The first case is that of Mr. A, a 90-year-old man who has hypertensive nephrosclerosis as a cause of stage 4 CKD with an estimated glomerular filtration rate (eGFR) of 20 mL/min/1.73 m^2. He is referred from his primary care physician for predialysis planning when his S[Cr] reaches 3.0 mg/dL. According to the accompanying medical records, his S[Cr] has been rising very slowly over the last few years. His hemoglobin is 10.5 g/dL, and he is not iron deficient. Aside from hypertension and anemia, he has no other comorbidities, and he is fully functional. He still drives and is the primary caregiver for his 87-year-old wife who has moderate to severe Alzheimer disease. They have no children, and there are no other family who live nearby. When asked if he would want dialysis in the future if he were to progress to ESRD, he says "Yes" because he wants to continue to be able to care for his wife. He was a member of the National Kidney Foundation for a few years and read a newsletter some time back about the KDOQI guidelines. He asks if he should be referred for placement of an arteriovenous fistula to prepare him for dialysis and if he should be started on erythropoietin injections to raise his hemoglobin level and improve his quality of life.

The second case is that of Ms. B, a 76-year-old woman with diabetic nephropathy, retinopathy, and peripheral neuropathy. She has stage 3 CKD with an eGFR of 34 mL/min/1.73 m^2. One year ago, she had a right above-the-knee amputation for peripheral arterial disease. After rehabilitation therapy, she has been residing in an assisted living facility. At the time of the vascular surgery, she had a myocardial infarction. She had three coronary artery stents placed during that admission. In the last 18 months, she has had increasing periods of confusion and memory loss. An MRI of the brain shows cortical volume loss greater than would be expected for her age, with changes of chronic microvascular disease. She was recently hospitalized for sepsis from pneumonia and required a prolonged period of mechanical ventilation in the intensive care unit. Her CKD progressed to near ESRD and has not recovered. Her eGFR is now 9 mL/min/1.73 m^2 and is progressively decreasing. She was discharged to a skilled nursing facility because she is more confused, deconditioned, and malnourished (S [Alb] 2.7 g/dL). She is no longer able to care for herself. She has a Karnofsky Performance Score of 40.

In her younger life, she was a school teacher and very independent. Ms. B never married or had children. She did not like people making a fuss over her. As her diabetes took more and more of a toll on her, she repeatedly said she did not want to be a burden on others. Ms. B has good days and bad days with her vascular dementia, but she lacks sufficient decision-making capacity to decide about dialysis initiation.

Her closest living relative is a niece, her sister's daughter. The niece was appointed the patient's healthcare surrogate. The nephrologist has recommended insertion of an arteriovenous graft to prepare Ms. B for dialysis, but at the same time he admits that her prognosis for long-term survival is not good. The niece is not sure what she should decide about starting dialysis for her aunt.

INFORMED CONSENT FOR TREATMENT OF CKD

Informed consent is the accepted medical practice for reaching decisions with patients about treatment. It is based on the well-established ethical principle of respect for patient autonomy and the legal doctrine of patient self-determination.[1] Informed consent is to be obtained from the patient if he/she has decision-making capacity or else from the person designated in the patient's advance directive to be the patient's designated decision-maker in the event the patient loses decision-making capacity. If the patient has not completed an advance directive naming a substitute decision-maker (called a healthcare proxy, medical power of attorney, durable power of attorney for healthcare, or healthcare agent, depending on the state), most state laws specify that a healthcare surrogate should be appointed to participate with the physician in an informed consent process to make decisions for the patient according to the patient's expressed wishes or best interest.

The elements of informed consent have been clearly articulated.[1] The elements include the following:

1. A patient with decision-making capacity (or his/her substitute decision-maker),
2. Voluntary nature of the decision,

3. Disclosure of the benefits and risks of the proposed and alternative treatments including no treatment,
4. Recommendations by the physician based on the patient's overall condition and values,
5. Assuring patient understanding of the recommendations and the reasons for supporting the recommendations,
6. The patient makes an informed decision, and
7. The patient authorizes the chosen plan (often including signing a consent form)

Informed consent for predialysis CKD patients needs to acknowledge that most dialysis patients have a poor prognosis. *The Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis* clinical practice guideline recommends that in the informed consent process each patient should be given a patient-specific estimate of prognosis.[7] Based on the US Renal Data System (USRDS) report, age-adjusted all-cause mortality is 6–8 times higher for dialysis patients than for individuals in the general population. Among dialysis patients 65 years of age and older, mortality is twice as high as for patients in the general population who have diabetes, cancer, congestive heart failure, stroke, or acute myocardial infarction.[9] According to the 2018 USRDS Annual Data Report for 2013 incident patients, only 60% are still alive three years after the start of dialysis.[10]

The informed consent process for Mr. A would include a review of the patient's overall condition and the likelihood that he is much more likely to die from a nonrenal cause than to progress to the need for dialysis.[4] The physician would need to explain that more recent evidence since the KDOQI guidelines indicates that placement of an arteriovenous fistula is unnecessary because of the slow rate of CKD progression in the elderly[4] and that for the patient's degree of anemia treatment with erythropoietin is not beneficial.[11] Control of the patient's hypertension, monitoring his CKD and anemia, and treatment of other problems as they develop would constitute a reasonable treatment plan for which the physician should obtain verbal consent.

Studies have identified a population of CKD patients for whom the prognosis is particularly poor and for whom informed consent needs to be more detailed. This population has been found to include patients with two or more of the following characteristics: (1) elderly (defined by research studies identifying poor outcomes in patients who are 75 years and older); (2) patients with high comorbidity scores (modified Charlson Comorbidity Index score of 8 or greater); (3) marked functional impairment (Karnofsky Performance Status Scale score less than 40); and (4) severe chronic malnutrition (S[Alb] less than 2.5 g/dL using the bromcresol green method).[7]

Elderly patients, aged 75 years and older, with stage 4 or 5 CKD constitute a group for whom the informed consent process regarding initiation of dialysis requires special consideration of the risk:benefit ratio. Because of the severe comorbidities, functional impairment, and malnutrition of some elderly CKD patients, nephrologists should not take an "age-neutral" approach to the management of CKD patients. On the other hand, age alone should not constitute a contraindication to starting dialysis because comorbidity is an important determinant of outcome in dialysis patients. Age and comorbidity are additive in predicting dialysis patient survival.

Ms. B is a patient who has a particularly poor prognosis, and for whom informed consent needs to be more detailed. She has a number of factors that predict poor prognosis for long-term survival on dialysis, including comorbidities such as coronary artery disease, peripheral arterial disease, and dementia, her functional status, and her nutritional status with a low S[Alb]. Using an integrated prognostic model developed for patients with stage 4 and 5 CKD, she is calculated to have a 6-month predicted survival of 53.5% and a 1-year survival of 41.4% (https://qxmd.com/calculate/calculator_446/Predicting-12-Month-Mortality-in-CKD-patients). Given this predicted limited survival, her nephrologist should engage the niece in a discussion of whether dialysis is something Ms. B would want based on her prior expressed wishes.

As recommended by the American Society of Nephrology in the Choosing Wisely Campaign, before placement of an arteriovenous access or peritoneal dialysis (PD) catheter, elderly patients with stage 4 or 5 CKD and severe comorbidities should have a shared decision-making conversation about the benefits and burdens of dialysis for a patient in their particular condition.[12] Ms. B's case is a perfect example of a patient for whom this recommendation is appropriate. Adapted from the surgical literature, researchers have suggested using the "Best Case/Worst Case" approach to discussing renal replacement therapy options, including medical management without dialysis with older advanced CKD patients.[13] The "Best Case" for such patients on dialysis has been described as patients being tired but having some good days in between dialysis treatment days and experiencing more complications over time with an estimated survival of one to three years.[13] The purpose of the shared decision-making conversation is for nephrologists to learn their patients' values, preferences, and goals and to make treatment recommendations in alignment with them. Some older patients, especially those with a good support system who place a high value on life extension, may find PD at home an attractive renal replacement therapy option.

As part of the discussion, nephrologists should inform patients of the following information:

- Dialysis may not confer a survival advantage.
- Patients with their level of illness who are not already uremic are more likely to die than live long enough to progress to ESRD.[4]
- Life on dialysis may entail significant burdens that may detract from their quality of life, and many dialysis patients experience a deterioration of their quality of life once dialysis is started.[14]
- They may not experience functional improvement with dialysis and may undergo significant functional decline during the first year after dialysis initiation.[15]
- The burdens of dialysis include surgery for vascular or PD access placement and complications from the vascular access or PD catheter.
- They may experience adverse physical symptoms on dialysis such as dizziness, fatigue, and cramping, and a feeling of "unwellness" after dialysis.
- There will be travel time and expense to and from dialysis, long hours spent on dialysis, and a reduction in the time available for physical activity.
- Dialysis may entail an "unnecessary medicalization of death" resulting in invasive tests, procedures, and hospitalizations.[7]

SHARED DECISION-MAKING IN THE PROCESS OF ADVANCE CARE PLANNING

Shared decision-making is the recognized preferred model for medical decision-making because it addresses the ethical need to fully inform patients about the risks and benefits of treatments, as well as the need to ensure that patients' values and preferences play a prominent role. It is the recommended process by which healthcare professionals and patients come to agreement on a specific course of action based on a common understanding of the goals of treatment and the risks and benefits of the chosen course compared with any reasonable alternative.[7] Shared decision-making has been referred to as the pinnacle of patient-centered care.[16]

In shared decision-making, the healthcare provider is the expert in diagnosis, prognosis, and treatment alternatives, and the patient is the expert in his or her own history, values, preferences, and goals. Physicians and patients work together to reach decisions that are individualized to the patient's particular circumstances and preferences (see also Figure 80.1).

Advance care planning represents one way in which shared decision-making is implemented. Advance care planning is inherently patient-centered rather than disease-oriented because its purpose is to identify and respect an individual patient's future medical treatment wishes (Table 80.1). The purpose of advance care planning is to help patients understand their condition, identify their goals for care, and prepare them for the decisions that may have to be made as the condition progresses over time. Because complex comorbid conditions, impaired functional status, and limited life expectancy are more common among older patients with CKD, older CKD patients especially are less likely to benefit from a disease-oriented approach.[17] A disease-oriented approach would lead to automatic referral of older stage 5 CKD patients with comorbid conditions for dialysis evaluation and access placement. This present default with regard to CKD care leads to poor outcomes of CKD patients 75 years of age or older. They have a five-year survival on dialysis of about 15%, and their deaths are often characterized by very aggressive treatment including hospitalization, frequent intensive care unit admissions, and late referral, if at all, to hospice.[18]

The proposed goal of advance care planning for CKD patients is to align the treatment they receive with their preferences and to begin the process long before end-of-life treatment decisions are necessary. Commentators have proposed that advance care planning be a required portion of the kidney disease education benefit.[19] Another has suggested that for older CKD patients with a heavy burden of comorbid illness, active medical management without dialysis or what has been called "planned conservative management" be the default choice rather than HD or even a 90-day time-limited trial of HD. It is during the 90-day time-limited trial that such patients experience the highest morbidity and mortality risk from vascular access complications, infection, and other hospital-acquired disease.[20]

COMPLETION OF ADVANCE DIRECTIVES AND MEDICAL ORDER FORMS TO IMPLEMENT ADVANCE CARE PLANNING DECISIONS

Advance care planning may vary with the patient's clinical situation and level of involvement of family as well as intrafamily communication dynamics. Gillick has proposed four components of advance care planning:

1. Patient and family understanding of the patient's current overall medical condition.
2. Elicitation of the patient's goals of care based on an understanding of the patient's condition and obtainable goals.
3. Identification of the patient's preferred decision-maker in the event of incapacity and completion of an advance directive naming that person.

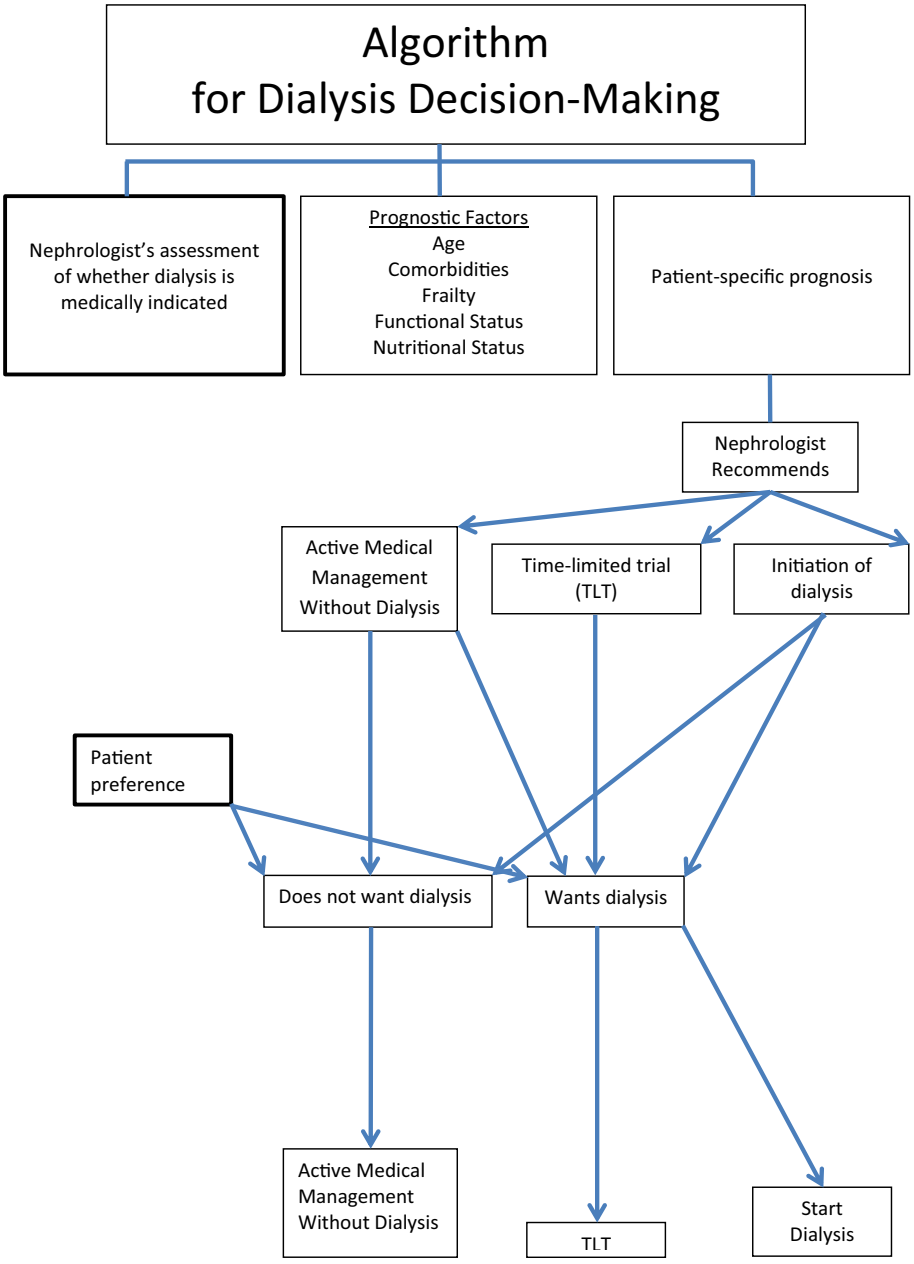


FIGURE 80.1 Implementation of the process of shared decision-making in deciding whether to initiate dialysis.

4. Completion of a POLST Paradigm form for seriously ill patients to translate the patient's wishes into medical orders that are respected throughout the healthcare system.[21]

POLST has been adopted by multiple states and regions (www.POLST.org) in response to inadequacies in general written advance directives.[22] Unlike living wills (instruction directives) or documents naming legal agents (proxy directives), POLST forms are signed physician orders directing treatments based on patient choice. In some states, nurse practitioners or physician assistants are authorized to sign POLST forms. POLST forms are especially appropriate for patients for whom the nephrologist would not be surprised if the patient died in the next year. The "surprise" question has been validated in primary care, CKD, and dialysis populations.[23,24] POLST forms have been shown to be effective in honoring patients' end-of-life treatment preferences, in part because they ensure continuity of orders for the patient across treatment settings. Where available, such documents are particularly applicable to many CKD patients and help to ensure that patients receive the treatment they want (Table 80.2).[25,26]

TABLE 80.1 Suggested Steps for Implementing Advance Care Planning in CKD Patients

- Recommend advance care planning at the initiation of overall treatment for patients with stage 3 or higher CKD
- Use a "No" response to the "surprise" question[24] as a trigger for advance care planning for CKD patients for whom it has not yet been conducted
- Assess decision-making capacity to determine if patient can complete an advance directive. Appoint a healthcare surrogate according to state law for patients who lack capacity
- Encourage patient-centered advance care planning among patients and families with completion of an advance directive as appropriate. Revisit advance care planning with each patient hospitalization and/or significant change in medical status
- Discuss advance care planning by asking:
  - What are your most important goals if your health gets worse?
  - What are your biggest fears and worries with regard to medical treatment?
  - If you become unable to make decisions for yourself, whom do you want to make decisions for you?
  - If you had to choose between being kept alive as long as possible regardless of personal suffering or living a shorter time to avoid suffering which would you choose?
  - In your condition, what is your understanding of the benefits and burdens of dialysis for you?
  - What are your current thoughts with regard to starting dialysis?
  - If you choose to start dialysis, under what circumstances, if any, would you want to stop it?
  - If your heart stops beating or you stop breathing, would you want to allow a natural death?
  - Under what circumstances, if any, would you not want to be kept alive with medical means such as cardiopulmonary resuscitation, a feeding tube, or mechanical ventilation?
  - Where do you prefer to die and who do you wish to be with you when you die?
- Document provider's discussion and understanding of patient's preferences in the medical record in a form in which it can be found on subsequent visits
- Where available, for seriously ill patients for whom the surprise question answer is "No" complete a Physician Orders for Life-Sustaining Treatment (POLST) or similar form to translate patients' wishes into medical orders (see www.polst.org)
- Place a copy of advance directives, DNR order card, and/or POLST form in multiple medical records as appropriate, including electronic medical record, statewide electronic advance directive and medical order registry, commonly attended clinics, hospital, nursing home, and home
- Encourage the patient, family, and/or legal agent to carry a current copy of the patient's advance directive, do not resuscitate order card, and/or POLST form whenever traveling or being admitted for overnight medical care

TABLE 80.2 Desired Outcomes of Advance Care Planning for CKD Patients[22]

- Enhance patient and family understanding about the patient's illness and end-of-life issues, including prognosis and likely outcomes of alternative plans of care
- Define the particular patient's key priorities in end-of-life care and develop a care plan that addresses these issues and identifies the patient's overall goals of care
- Enhance patient autonomy by shaping future clinical care to fit the patient's preferences and values
- Improve the process of healthcare decision-making generally, including (1) patient and family satisfaction with the advance care planning process; (2) healthcare provider understanding of advance care planning and advance directives; and (3) provider comfort in participating in advance care planning
- Help patients find hope and meaning in life and achieve a sense of spiritual peace
- Explore ways to ease the emotional and financial burdens borne by patients and families
- Strengthen relationships with loved ones
- Complete written advance directives, particularly those identifying a legal agent, do not resuscitate documents, and POLST documents where available
- Honor advance directives, do not resuscitate orders, and POLST orders at the end of life

THE "BIOMEDICALIZATION" OF AGING AND CONSEQUENCES FOR DIALYSIS DECISION-MAKING IN ELDERLY STAGE 5 CKD PATIENTS

Older patients are more likely to have CKD.[27] Of the estimated 29.7 million US residents with stage 3 and 4 CKD in 2011–2012, 31.5% of the 65- to 79-year olds and 65% of the 80 and older patients had CKD. Guidelines typically do not stratify their recommendations for older patients compared with younger adults, or consider the burden of comorbid illness. Older adults tend to have more comorbidities, increased mortality risk, and an increased risk of treatment-related adverse events. These factors are likely to alter guideline-projected benefits and harms of treatment for a single disease such as CKD. Simply said, most guidelines for CKD and ESRD patients underestimate the risk and overestimate the benefit for older patients.[28]

In this context, the processes of informed consent, shared decision-making, and advance care planning are particularly important to individualize decision-making and not take an "age-neutral" approach for older CKD patients.[4] Unfortunately, the US culture is moving in the opposite direction, and medical interventions such as dialysis are being normalized as necessary and appropriate to treat the problem of ESRD.[29] Old age is being transformed through clinical practices and medical innovations that lie at the heart of biomedicalization in the US.[30]

Effective clinical treatments for ever-older persons have led to an interesting turn in the biomedicalization of aging. There are said to no longer be technological or biological limits to what can be done, medically or surgically, for older persons. Biomedicalization has

resulted in an aged body being seen as a diseased entity in need of restoration and improvement. Medical anthropologists have described an incremental creep upward in the acceptable "normal" age range for aggressive, invasive medical interventions. The technological imperative—"If it can be done, it must be done"—has become a moral imperative for patients, families, and physicians. A diagnostic test confirms the "need" for an intervention. The performance of the intervention becomes routinized based on its clinical indication. Reasoned choice is said to be obfuscated by the need to treat, the routinization of the intervention, and the specter of future risk if the intervention is not undertaken. The aggressive dialysis treatment for an older stage 5 CKD patient with multiple severe comorbidities becomes standard practice. Commentators have described a new ethical field in our social fabric, the difficulty or impossibility of saying "no" to life-extending medical interventions. This new "field" has resulted in a blurring of the focus in medicine between cure, life enhancement, and life prolongation on the one hand and reducing the burden of disease and promoting comfort on the other. There is a new "ethics of normalcy" in which expectations about long lives and routine medical treatments have come together. It is no longer acceptable to die at age 91 if there is a medical treatment that might be able to prevent death regardless of what suffering might be entailed in the continued life.

Observers of the application of the technological imperative to implantable cardioverter-defibrillators (ICDs), another life-sustaining technology like dialysis, note that in the US two cultural moves—from new technique to standard technique, and then, from standard technique to ethical necessity—are evident in the growing trend to use aggressive interventions like dialysis and ICDs for older or sicker patients. The irony is that such interventions prolong debilitation, suffering, and the dying process, something which patients report they want to avoid.[31]

CONFLICTS OF INTEREST IN THE TREATMENT OF CKD

The National Kidney Foundation KDOQI clinical practice guidelines published in 2002 and updated in 2006[32] shifted the concept of kidney disease from that of an uncommon life-threatening condition requiring care by nephrologists to that of a common condition with a range of severity meriting attention by general internists. The guidelines not only had a major effect on clinical practice, research, and public health but also generated substantial controversy.[33,34]

There were four significantly controversial guideline recommendations. First, the extension of the diagnosis of CKD to a large percentage of the US population (10% at the time). Second, a recommendation for early preparation for arteriovenous fistula placement at 30 mL/min/1.73 m^2 eGFR, which resulted in many older CKD patients prematurely receiving surgery for access placement. Third, the recommendation of the upper range of the target for erythropoietin of 13 g/dL, which subsequently was shown to be not beneficial and possibly harmful.[11] Finally, the recommendation that patients be started on dialysis when their eGFR dropped to 10.5 mL/min/1.73 m^2, which subsequently was unsubstantiated by further research.[35]

Where there was insufficient evidence on which to base a recommendation, the National Kidney Foundation KDOQI workgroups used consensus opinion. Amgen, Inc. was the founding and principal sponsor of KDOQI. Additional support was provided by Baxter Healthcare Corporation, Fresenius USA, Inc., Genentech, Inc., and Watson Pharmaceuticals, Inc. There were disclosures provided for each workgroup member, but it was not possible to tell from the disclosures the extent of the relationships between the KDOQI guideline workgroup members and Amgen, Baxter, Fresenius, Genentech, and Watson.

The concern with regard to the development of KDOQI is that recommendations in the absence of solid evidence require subjective judgments. Such judgments naturally leave room for error and bias.[36] The process of the KDOQI guideline development has been criticized for its failure to adequately account for the influence of conflicts of interest and bias in the recommendations.[37,38] In their report on physician financial conflicts of interest in clinical care, the Association of American Medical Colleges cited the results of psychological research on how financial interests can distort medical decision-making.[39] They noted that when physicians stand to gain by reaching a particular conclusion, they tend to unconsciously and unintentionally weigh evidence in a biased fashion that favors that conclusion. Such weighing of the evidence can happen beneath the individual's level of awareness, such that a biased individual will sincerely claim objectivity. These studies explain how well-intentioned physicians can succumb to conflicts of interest and why the effects of such conflicts are so insidious and difficult to combat.[39]

In a study of the relationship between clinical practice guideline developers and the pharmaceutical industry, the majority of authors were found to have financial conflicts of interest, and 38% had served as employees or consultants for pharmaceutical companies.[40] The authors concluded that there was a high degree of interaction between authors of clinical practice guidelines and the pharmaceutical industry and that these interactions may influence the practice of a very large number of

physicians. They recommended a formal process for discussing the conflicts of interest before clinical practice guideline development.

The concern about trustworthiness of clinical practice guidelines prompted the Institute of Medicine at the request of the US Congress to develop eight standards for objective, scientifically valid, and consistent approaches to the establishment of guidelines.[41] A subsequent study of 114 guidelines demonstrated poor adherence to the Institute of Medicine standards, but the Institute of Medicine standards themselves have been criticized as being too inflexible and impractical to achieve.[42] The bottom line on clinical practice guideline development has yet to be found, but the need for an explicit, transparent process seems to be clear.[40]

The National Kidney Foundation KDOQI guidelines were created before there were standards for guideline development. It is not possible to assess to what extent, if any, KDOQI recommendations were biased by financial conflicts of interest. Subsequent continuing work by the Kidney Disease: Improving Global Outcomes effort, the successor to the KDOQI process, can take advantage of the scientific and ethical scrutiny that has occurred in the first decade of the 21st century with regard to guideline development.

THE ETHICAL RESPONSIBILITY FOR CAREFUL MANAGEMENT OF CKD PATIENTS

Because compared with the age-matched population without CKD, patients with all stages of CKD have increased rates of all-cause mortality, cardiovascular mortality, cognitive impairment, and dementia that progress with advancing CKD, physicians treating these patients are ethically obligated to do everything they can to identify and treat the risk factors for CKD, cardiovascular mortality, and cognitive impairment. This task is more difficult than it appears because in at least one study CKD was strongly associated with the incidence of dementia independent of age, sex, education, and other vascular risk factors.[43] Controlling hypertension to the recommended MDRD level of less than 130/80 mm Hg,[44] and treating hyperlipidemia and diabetes to achieve the target ranges to reduce the risk of atherosclerosis, are a good start, but may not be adequate to prevent the progression of CKD. Nephrologists and others treating CKD patients will need to keep abreast of the research to determine how best to slow the progression of CKD.

For patients with stage 5 CKD who choose to forgo dialysis, nephrologists will need to provide generalist palliative care and consult specialist palliative care as needed for refractory pain and symptom management; management of more complex depression, anxiety, grief, and existential despair; and assistance with conflict resolution regarding goals or methods of treatment.[45] Palliative and end-of-life care for CKD patients including systematic screening for symptoms provides them with the most optimal care (Table 80.3).[46]

TABLE 80.3 Recommendations for Palliative and End-of-Life Care in Chronic Kidney Disease

1. Identify patients who would benefit from palliative care interventions.
   a. Those with significant pain and symptoms. Screen with a simple tool such as the Edmonton Symptom Assessment Scale (ESAS)[46] which has been validated in ESRD.
   b. High risk of death within the next year. Consider using the "surprise" question, "Would I be surprised if this patient died in the next year?"[24]
2. Screen for and manage emotional, psychosocial, and spiritual distress; refer to allied health professionals as appropriate.
   a. The ESAS-Renal is also appropriate for screening for anxiety and depression. The PHQ-4 has also been validated and is brief.[45,47]
   b. A simple question such as "Do you have any spiritual needs or concerns that your healthcare providers may help address?" may be appropriate for screening for spiritual distress.
3. Assess patients' desire for prognostic information.
4. Enhance predialysis education.
   a. Educate regarding active medical management without dialysis option as appropriate
   b. Describe available palliative care and hospice services.
5. Provide routine advance care planning as described in Table 80.1.
   a. Ensure patients and families are aware of the relevance of these discussions (i.e. have an understanding of their overall health state and prognosis).
   b. Consider initiating advance care planning at the time that patients are being educated with respect to renal replacement options if not done already.
   c. Include discussions of patients' goals of care, health states for which the patient would not want or no longer want dialysis, and preferred location of death.
   d. Establish a substitute decision-maker in an advance directive.
   e. Ensure that family and other important people (as identified by the patient) are present for these discussions, especially the substitute decision-maker.
6. Increase access to specialist palliative care, including hospice.
7. Develop relationships with hospice providers that focus on sharing of care in active medical management without dialysis and transition of care from dialysis to hospice, bridging patients into hospice by decreasing frequency of dialysis treatments, and having the patient be in control of when they are ready to stop palliative dialysis.
8. Provide bereavement support to patients' families directly or through hospice services.

CONCLUSION

For patients with advanced CKD with progressive loss of kidney function, particularly those who are not candidates for kidney transplantation, nephrology professional societies and the medical literature recommend a shared decision-making discussion before the initiation of dialysis with a discussion of all renal replacement therapy options, including medical management without dialysis. In this discussion, particular attention needs to be devoted to the likelihood of benefits and burdens of dialysis for the patient based on the patient's prognosis and values, preferences, and goals. For older patients with significant comorbidities, a decision to initiate dialysis should not be automatic, because dialysis may not offer a survival benefit. Whether the patient chooses to start dialysis or not, a palliative care approach not only to the goals of care discussion but to meticulous pain and symptom management can improve patients' quality of life and satisfaction with care.

References

1. Beauchamp TL, Childress JF. *Principles of biomedical ethics*. 5th ed. New York: Oxford University Press; 2001. p. 227.
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**:1296–305.
3. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004;**164**:659–63.
4. O'Hare AM, Choi AI, Bertenthal D, Bacchetti P, Garg AX, Kaufman JS. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol* 2007;**18**(10):2758–65.
5. Dennis VW. Coronary heart disease in patients with chronic kidney disease. *J Am Soc Nephrol* 2005;**16**:S103–6.
6. Bugnicourt J-M, Godefroy O, Chillon J-M, Choukron G, Massy ZA. Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. *J Am Soc Nephrol* 2013;**24**:353–63.
7. Renal Physicians Association. *Shared decision-making in the appropriate initiation of and withdrawal from dialysis*. 2nd ed. Rockville, MD: Renal Physicians Association; 2010.
8. Ladin K, Pandya R, Perrone RD, Meyer KB, Kannam A, Loke R, Oskoui T, Weiner DE, Wong JB. Characterizing approaches to dialysis decision making with older adults: a qualitative study of nephrologists. *Clin J Am Soc Nephrol* 2018;**13**:1188–96.
9. U.S. Renal Data System. *USRDS 2012 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
10. U.S. Renal Data System. *USRDS 2018 annual data report: atlas of chronic kidney disease and end-stage renal disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2018. Available at: https://www.usrds.org/adr.aspx.
11. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;**355**:2085–98.
12. Williams AW, Dwyer AC, Eddy AA, Fink JC, Jaber BL, Linas SL, Michael B, O'Hare AM, Schaefer HM, Shaffer RN, Trachtman H, Weiner DE, Falk AR, American Society of Nephrology Quality, and Patient Safety Task Force. Critical and honest conversations: the evidence behind the "Choosing Wisely" campaign recommendations by the American Society of Nephrology. *Clin J Am Soc Nephrol* 2012;**7**:1664–72.
13. Grubb V. Time to recast our approach for older patients with ESRD: the best, the worst, and the most likely. *Am J Kidney Dis* 2018;**71**:605–7.
14. Da Silva-Gane M, Wellsted D, Greenshields H, Norton S, Chandna SM, Farrington K. Quality of life and survival in patients with advanced kidney failure managed conservatively or by dialysis. *Clin J Am Soc Nephrol* 2012;**7**:2002–9.
15. Kurella Tamura M, Covinsky KE, Chertow GM, Yaffe K, Landefeld CS. Functional status of elderly adults before and after initiation of dialysis. *N Engl J Med* 2009;**361**(16):1539–47.
16. Barry MJ, Edgman-Levitan S. Shared decision making – pinnacle of patient-centered care. *N Engl J Med* 2012;**366**:780–1.
17. Bowling CB, O'Hare AM. Managing older adults with CKD: individualized versus disease-based approaches. *Am J Kidney Dis* 2012;**59**(2):293–302.
18. Wong SP, Kreuter W, O'Hare AM. Treatment intensity at the end of life in older adults receiving long-term dialysis. *Arch Intern Med* 2012;**172**(8):661–3.
19. Patel UD, Schulman KA. Can we begin with the end in mind? End-of-life care preferences before long-term dialysis. *Arch Intern Med* 2012;**172**:663–4.
20. Carson R. Deny dialysis or "D-NI" dialysis? The case for "do not initiate; do not ignore" orders. *Clin J Am Soc Nephrol* 2012;**7**:1924–6.
21. Gillick MR. Reversing the code status of advance directives? *N Engl J Med* 2010;**362**:1239–40.
22. RAND Health, Wenger NS, Shugarman LR, Wilkinson A. *Advance directives and advance care planning: report to congress*. US Department of Health and Human Services; 2007.
23. Schmidt RJ, Landry DL, Cohen L, Moss AH, Dalton C, Nathanson BH, Germain MJ. Derivation and validation of a prognostic model to predict mortality in patients with advanced chronic kidney disease. *Nephrol Dial Transplant* 2019. Epub ahead of print. PMID: 30395311.
24. Moss AH, Ganjoo J, Sharma S, Gansor J, Senft S, Weaner B. Utility of the "surprise" question to identify dialysis patients with high mortality. *Clin J Am Soc Nephrol* 2008;**3**:1379–84.
25. Citko J, Moss AH, Carley M, Tolle SW. *The national POLST Paradigm initiative*. 2nd ed. Fast Facts and Concepts; September 2010. p. 178 Available at: https://www.mypcnow.org/blank-k2dh9.
26. Hickman SE, Nelson CA, Moss AH, Tolle SW, Perrin NA, Hammes BJ. The consistency between treatments provided to nursing facility residents and orders on the physician orders for life-sustaining treatment (POLST) form. *J Am Geriatr Soc* 2011;**59**(11):2091–9.
27. Murphy D, McCulloch CE, Lin F, Banerjee T, Bragg-Gresham JL, Eberhardt MS, Morgenstern H, Pavkov ME, Saran R, Powe NR, Hsu CY, Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Trends in prevalence of chronic kidney disease in the United States. *Ann Intern Med* 2016;**165**:473–81.
28. Uhlig K, Boyd C. Guidelines for the older adult with CKD. *Am J Kidney Dis* 2011;**58**:162–5.
29. Kaufman SR, Shim JK, Russ AJ. Revisiting the biomedicalization of aging: clinical trends and ethical challenges. *Gerontol* 2004;**44**:731–8.
30. Clarke AE, Shim JK, Mamo L, Fosket JR, Fishman JR. Biomedicalization: technoscientific transformations of health, illness and U.S. biomedicine. *Am Sociol Rev* 2003;**68**:161–94.
31. Kaufman SR, Mueller PS, Ottenberg AL, Koenig BA. Ironic technology: old age and the implantable cardioverter defibrillator in US health care. *Soc Sci Med* 2011;**72**:6–14.

32. National Kidney Foundation. Kidney disease outcomes quality initiative. Available at: http://www.kidney.org/professionals/kdoqi/index.cfm.
33. Bauer C, Melamed ML, Hostetter TH. Staging of chronic kidney disease: time for a course correction. *J Am Soc Nephrol* 2008;**19**:844.
34. Glassock RJ, Winearls C. An epidemic of chronic kidney disease: fact or fiction? *Nephrol Dial Transplant* 2008;**23**:1117–21.
35. Cooper BA, Branley P, Bulfone L, Collins JF, Craig JC, Fraenkel MB, IDEAL Study. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med* 2010;**363**:609–19.
36. Detsky AS. Sources of bias for authors of clinical practice guidelines. *CMAJ* 2006;**175**:1033.
37. Coyne D. Influence of industry on renal guideline development. *Clin J Am Soc Nephrol* 2007;**2**:3–7.
38. Coyne D. Conflicts of interest and viewpoint bias in KDOQI and KDIGO workgroups. *Nephrol Dial Transplant* 2008;**23**:4071.
39. AAMC report of the task force on financial conflicts of interest in clinical care. In: *The interest of patients: recommendations for physician financial relationships and clinical decision making*. Washington, DC: AAMC; 2010.
40. Choudhry NK, Stelfox HT, Detsky AS. Relationships between authors of clinical practice guidelines and the pharmaceutical industry. *J Am Med Assoc* 2002;**287**:612–7.
41. Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E. Clinical practice guidelines we can trust. In: Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E, editors. *Clinical practice guidelines we can trust*. Washington, DC: National Academies Press; 2011.
42. Ransohoff DF, Pignone M, Sox HC. How to decide whether a clinical practice guideline is trustworthy. *J Am Med Assoc* 2013;**309**:139–40.
43. Sasaki Y, Marioni R, Kasai M, Ishii H, Yamaguchi S, Meguro K. Chronic Kidney Disease: a risk factor for dementia onset: a population-based study. The Osaki-Tajiri project. *J Am Geriatr Soc* 2011;**59**:1175–81.
44. Peterson JC, Adler S, Burkart JM, Greene T, Hebert LA, Hunsicker LG. Blood pressure control, proteinuria, and the progression of renal disease. The modification of diet in renal disease study. *Ann Intern Med* 1995;**123**(10):754–62.
45. Quill TE, Abernethy AP. Generalist plus specialist palliative care – creating a more sustainable model. *N Engl J Med* 2013;**368**:1173–6.
46. Davison SN, Jhangri G, Johnson JA. Cross-sectional validity of a modified Edmonton symptom assessment system in dialysis patients: a simple assessment of a symptom burden. *Kidney Int* 2006;**69**(9):1621–5.
47. Kroenke K, Spitzer RL, Williams JB, Löwe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics.* 2009;**50**(6):613–21.
48. Lok CE, Allon M, Moist L, Oliver MJ, Shah H, Zimmerman D. Risk equation determining unsuccessful cannulation events and failure to maturation in arteriovenous fistulas (REDUCE FTM I). *J Am Soc Nephrol* 2006;**17**:3204–12.
49. Lazarides MK, Georgiadis GS, Antoniou GA, Staramos DN. A meta-analysis of dialysis access outcome in elderly patients. *J Vasc Surg* 2007;**45**:420–6.

QUESTIONS AND ANSWERS

Question 1

Which one of the following is an advantage of the POLST form compared with an advance directive?

A. It is legal in all fifty states
B. It is an immediately actionable medical order
C. Checklist format prevents contradictory orders from being issued
D. It is appropriate for patients in all stages of CKD

Answer: B

The POLST form or a variant is legal in 15 states at present. Contradictory orders could be written between Sections A and B such that the patient is to receive CPR in Section A and comfort measures in Section B of the form. The form is only appropriate for patients who are seriously ill and for whom the physician would not be surprised if the patient died in the next year. B is the correct answer.[25]

Question 2

Which one of the following is true regarding the creation of clinical practice guidelines such as the Kidney Disease Outcomes Quality Initiative?

A. The exhaustive literature review minimizes the effect of financial conflicts of interests
B. Disclosure of financial conflicts of interests prevents subjectivity in guideline recommendations
C. Studies on clinical practice guidelines have found that most authors have financial relationships to pharmaceutical industries
D. The clinical practice guideline process guards against bias in the resulting recommendations

Answer: C

An exhaustive literature review does not guard against subjectivity and bias in the interpretation of the literature. Disclosure also has not been found to limit subjectivity in guideline recommendations. Most authors involved in clinical practice guideline development have financial conflicts of interest. C is the correct answer.[36,40]

Question 3

Which one of the following statements best summarizes the role of shared decision-making for patients with CKD?

A. Shared decision-making is an outmoded concept from the 1980s
B. Shared decision-making fits well with a disease-oriented approach to CKD patient treatment
C. Shared decision-making for CKD patients defaults to dialysis modality choices
D. Shared decision-making is the recognized preferred model for medical decision-making

Answer: D

Shared decision-making was introduced in the 1980s as a process to promote informed consent and decisions which adequately take account of patients' preferences. It fits well with an individualized, patient-centered approach to decision-making, not a disease-oriented approach. Shared decision-making for CKD patients encompasses decisions about whether to start or stop dialysis, not just dialysis modality. D is the correct answer.[7,16]

Question 4

An 87-year-old woman is approaching the need for dialysis. She has dementia and is no longer capable of making her own decisions. Her family would like her to start dialysis because they point out that she is healthy apart from the dementia which is progressing slowly and the kidney disease which she has known about for a number of years. The family is hopeful that she will be able to live to her 90th birthday as her mother did before her. Which one of the following is true with regard to informed consent for dialysis for an older stage 5 CKD patient with significant comorbid conditions?

A. An "age-neutral" approach is appropriate to avoid discrimination
B. Informed consent should include disclosure that dialysis may not confer a survival advantage
C. Consent for dialysis may only be obtained from the patient
D. Physicians are to provide information, not make a recommendation

Answer: B

Age is a major effect modifier in patients with CKD. Older CKD patients have higher rates of death and lower rates of dialysis initiation. For this reason, an age-neutral approach has not been recommended for decision-making with CKD patients. If patients lack decision-making capacity, consent for dialysis may be obtained from the patient's designated healthcare proxy on an advance directive or a healthcare surrogate appointed according to state law. The physician recommendation with regard to treatment is one of the seven elements of informed consent. Older CKD patients with significant comorbidities may not live any longer with dialysis than without. B is the correct answer.[1,4,7]

Question 5

An 86-year-old stage 5 CKD patient has mild vascular dementia and has had several TIAs and one myocardial infarction in the past 5 years. He has experienced a decline in eGFR from 20 to 17 mL/min/1.73 m^2 since being referred for nephrology evaluation three years ago. He has expressed an interest in HD as his preferred dialysis modality. What recommendation with regard to dialysis access should his nephrologist make?

A. Placement of an access now is indicated to ensure that it has time to mature before use
B. Access placement should be scheduled for six months from now
C. The nephrologist should not recommend access placement as the patient is unlikely to progress to ESRD*
D. The nephrologist should recommend placement of an arteriovenous graft as an arteriovenous fistula is unlikely to mature in an elderly patient in time for use

Answer: C

In one large study not one of the CKD patients over the age of 85 progressed to ESRD. They all died of other causes, most commonly cardiovascular, first. Placement of a working arterivenous fistula is challenging in many older CKD patients. There is an association between greater age and failure of fistula maturation.[4,48,49]

Question 6

A 78-year-old woman with stage 5 CKD is approaching the need for dialysis. She has hypertensive nephrosclerosis, a long smoking history, and severe COPD requiring oxygen 24 hours per day. She also has peripheral arterial disease with a below-the-knee amputation in the left leg. Which one of the following has been found to be the single best predictor of survival in such CKD patients?

A. Comorbid conditions
B. Age
C. Functional status
D. Nutritional status

Answer: A

All four answers are statistically significant independent predictors of poor prognosis in CKD and ESRD patients. Based on an extensive review of the literature, of the four, comorbid conditions have been found to be the single best predictor. A is the correct answer.[7]

CHAPTER

81

Imaging the Chronic Kidney Disease Patient

David C. Wymer[a], *David T.G. Wymer*[b]

[a]University of Florida, Malcom Randall VAMC, Gainesville, FL, United States; [b]Mount Sinai Medical Center, Miami Beach, FL, United States

Abstract

Imaging plays an increasingly vital role in measuring both renal function and structure in patients with chronic kidney disease. Diagnosis, disease status, disease progression, and development of complications of renal failure are monitored clinically as well as with laboratory studies and radiologic imaging. Although ultrasound and nuclear medicine have historically played a vital first role, newer magnetic resonance imaging (MRI) technologies promise to provide safe advanced functional renal analysis. With the sophisticated new MRI sequences, we are on the verge of major change in the evaluation and follow-up of patients with renal disease. The indications for evaluating the kidneys include evaluating for treatable cause of failure (such as hydronephrosis), documenting renal size, identifying renal position (for example, for biopsy), monitoring progression of disease, and identifying or confirming a specific disease entity (such as renal vascular or polycystic kidney disease).

INTRODUCTION

Other than to document renal size and some complications of chronic disease such as kidney stones, imaging has historically had a limited role in chronic kidney disease (CKD) patients, with most evaluation based on laboratory tests and renal biopsies. However, with newer modalities, imaging plays an increasingly vital role in assessing both renal function and structure in CKD. Diagnosis, disease status, disease progression, and development of complications of CKD are monitored clinically as well as with laboratory studies and radiologic imaging. While ultrasound and nuclear medicine have historically played a vital first role, newer magnetic resonance imaging (MRI) technologies promise to provide safe advanced functional renal analysis. With sophisticated new MRI sequences and techniques, we are on the verge of major changes in the evaluation and follow-up of patients with renal disease.

Patients with CKD can be broadly separated into those with chronic but potentially controllable bilateral or unilateral disease processes, such as arteriosclerotic vascular disease, infections, and stone disease, and those who have a systemic, progressive, and bilateral process such as diabetes, hypertension, and collagen vascular diseases.

The indications for evaluating the kidneys include assessments of treatable causes of kidney disease (such as hydronephrosis), documentation of renal size, identification of the position of the kidneys (for biopsy), monitoring progression of disease, or identification or confirmation of a specific disease entity (such as polycystic kidney disease or renal vascular disease).

UTILITY OF IMAGING MODALITIES

Modality Selection

There are many clinical scenarios which bring a CKD patient in for radiologic evaluation. The testing is specific for patient complaints. Guidelines for imaging are available online through the American College of Radiology. These are regularly updated (http://www.acr.org/Quality-Safety/Appropriateness-Criteria). The website is organized by signs and symptoms and suggests the most useful modality as well as contraindications, relative contraindications, and caveats for each modality.

Ultrasound

Ultrasound is often the first imaging modality used in evaluating the kidneys, especially in patients with decreased renal function because it is inexpensive, quick, safe, and easily accessible. In chronic renal infections and stone disease, ultrasound shows findings

Chronic Renal Disease, Second Edition
https://doi.org/10.1016/B978-0-12-815876-0.00081-4

referable to the disease process—such as abscesses, calculi, and hydronephrosis.[1]

Early in the course of systemic renal failure, the ultrasound exam is often normal. Depending on the underlying disease state, later imaging shows variable changes. Obstruction causing renal failure is readily identified by demonstration of hydronephrosis. Ultrasound allows measurements of kidney size and cortical thickness. Both are important measures in CKD. Plain films (KUB) and intravenous urography overestimate renal size, because X-ray procedures have an inherent magnification of approximately 25%. Because of operator dependence, it is generally felt that computed tomography (CT) and MRI give more accurate overall renal measurements than ultrasound. Nevertheless, ultrasound is readily available, rapid, and accurate enough for screening and following renal size. Although there are size differences related to age, gender, and body mass index, in the average adult the kidneys should measure about 11−12 cm in greatest length. Width measurements are variable and are not generally considered clinically useful. The cortex from renal margin to calyx should be about 1.5 cm in the mid-kidney and 3 cm at the poles. Lower measurements represent atrophy.

The ultrasound appearance of normal kidneys typically shows well-marginated kidneys with a uniform cortex which is less echogenic than adjacent liver. The renal hilus is of increased echogenicity due to the presence of renal sinus fat and fibrous tissue (Figure 81.1).

In most cases of CKD, ultrasound of the kidneys shows nonspecific small and echogenic kidneys (Figure 81.2). However, the ultrasound in patients with chronic polycystic kidney disease shows enlarged kidneys which are nearly completely replaced with cysts (Figure 81.3). Most patients with CKD are middle aged and older. It is estimated that approximately 50% of adults have an incidental renal lesion. The most common incidental renal lesion is a cyst. Renal cysts are common and seen in otherwise normal patients. These are readily demonstrated and evaluated with ultrasound. Benign cysts are sharply circumscribed and may have thin internal septations (Figure 81.4).[2]

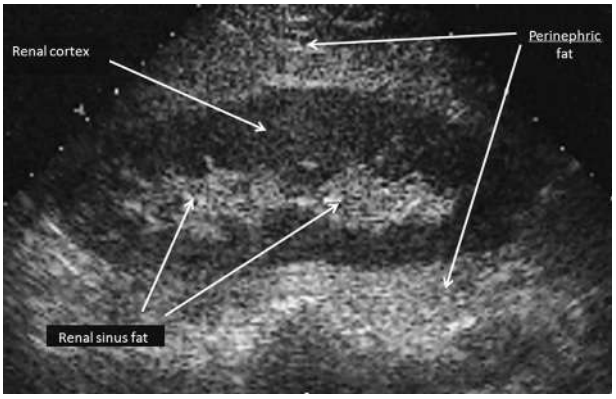


FIGURE 81.1 Normal renal ultrasound.

Contrast-enhanced ultrasound of the kidney with microbubbles is being used in other parts of the world, but it is an off-label use in the US at this time. Contrast-enhanced ultrasound with microbubbles is useful in evaluating renal blood flow (such as for the evaluation for renal artery stenosis) and more especially the degree of vascularity of complex real cysts and masses, allowing classification for malignant potential without the use of iodinated or gadolinium-based contrast agents and cost of CT or MRI.[3−5]

Nuclear Medicine

Nuclear scintigraphy techniques evaluate renal function and to a lesser extent anatomy. Because of the extremely small quantities injected and the benign nature of the radionuclides, these scans can be safely performed even in the face of markedly reduced renal function. Radioactive tracers are used which accumulate in renal tissues based on the underlying physiologic functions of the differing renal structures. For example, glomerular filtration rate (GFR) is evaluated with ^{99m}Tc-DTPA, tubular secretion with ^{99m}Tc-MAG3, general cortical integrity with ^{99m}Tc-DMSA, and renal parenchymal inflammation with ^{67}Ga-citrate.

One of the historic strengths of nuclear imaging is that, unlike the relative contraindications for contrast-enhanced CT and MRI, it can be used even in the face of declining renal function. Because of the relative preservation of tubular function and increased extraction efficiency compared with ^{99m}Tc-DTPA, ^{99m}Tc-MAG3 continues to provide information in the face of declining renal function. ^{67}Gallium-citrate has been used to diagnose interstitial nephritis as well as chronic infection of the kidneys.[6,7]

The usual functional renal scan is performed with ^{99m}Tc-MAG3 and can be studied in three phases of scanning. Following bolus intravenous injection of the nuclide, rapid sequential images are obtained to evaluate blood flow, which may be unilaterally or bilaterally compromised. Subsequent continued static imaging provides information on renal cortical function, both of the individual kidneys and the differential function between the kidneys. On subsequent delayed imaging, the excretion through the collecting system to the urinary bladder is displayed to evaluate the presence of obstructive uropathy. The renogram curve reflects abnormalities of vascular flow, renal function, and the presence of urinary tract obstruction. A normal curve of renal activity obtained during scanning is seen in Figure 81.5.

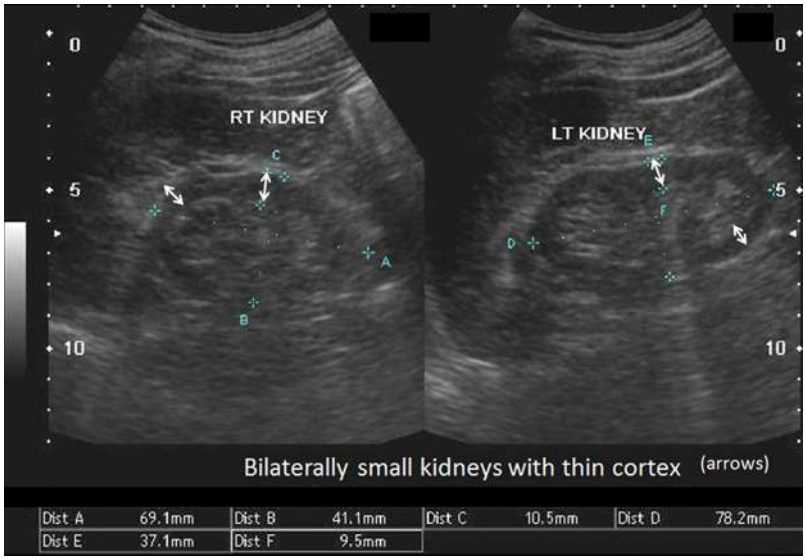


FIGURE 81.2 Bilaterally small kidneys with thinned cortex.

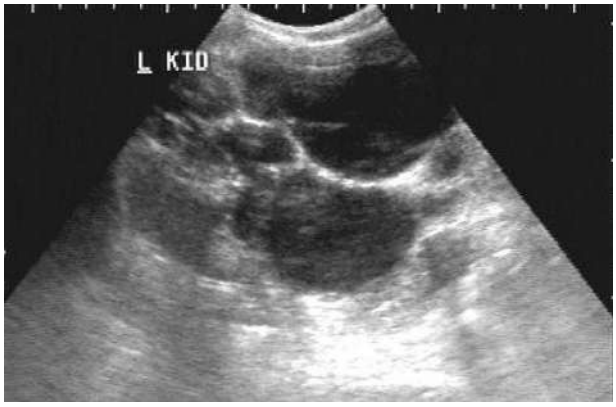


FIGURE 81.3 Numerous simple cysts replacing the renal parenchyma.

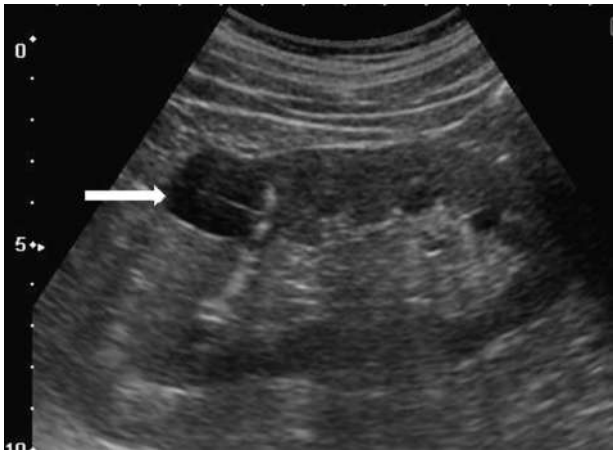


FIGURE 81.4 Benign renal cortical cyst with single thin internal septation.

Computed Tomography

CT has historically had a limited role in patients in the later stages of CKD. This has become more controversial recently, as research has demonstrated that intravenous administration of newer iso-osmolar or low osmolar iodinated contrast agents has no significant negative effect on CKD patients' short- or long-term renal function.[8] However, it is still standard of care that if the estimated GFR (eGFR) is below 30 mL/min/1.73 m^2, contrast material should be avoided if adequate diagnostic information can be obtained by other means. Contrast can be used judiciously and safely if the eGFR is 30–60 mL/min/1.73 m^2. If contrast is administered, patients should be hydrated before, during, and after contrast with intravenous saline and/or bicarbonate solution to reduce the risk of contrast-induced nephropathy (CIN). The use of other agents has shown questionable benefit in multiple studies, particularly N-acetylcysteine, which has shown to simply decrease S[Cr] even in normal volunteers without changing cystatin-C.[9–12] The recent 2018 Preserve Trial of 5177 patients failed to show any benefit on primary or secondary endpoints (renal or nonrenal adverse events) of any interventions beyond simple intravenous sodium chloride infusion.[12] The American College of Radiology manual on contrast media, which is regularly updated online (https://www.acr.org/Clinical-Resources/Contrast-Manual), recommends against routine use of N-acetylcysteine for prophylaxis or premedication.

Another disadvantage of CT scanning which is increasingly recognized as important is the associated radiation dose. Protocols are being changed to reduce dose exposure and new data reconstruction software is now available which has significantly reduced the

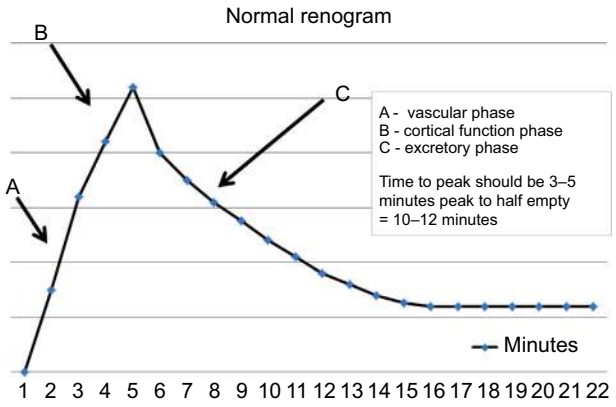


FIGURE 81.5 Normal renogram diagram showing different phases of renal nuclide clearance.

overall radiation exposures, but imaging with ultrasound and MRI which do not involve ionizing radiation is preferred whenever possible.

In earlier stages of chronic infectious kidney disease, such as in patients with xanthogranulomatous pyelonephritis, noncontrast CT can aid in determining extent of disease and for preoperative planning. Noncontrast CT is also used in evaluating, diagnosing, and following renal stone disease and nephrocalcinosis, and in guiding procedures such as renal biopsy and percutaneous nephrostomies.

Newer CT equipment has dual-energy scanning capability. This refers to simultaneous scanning using two distinct CT X-ray energies. Using the differential energy absorption of various renal stones, the mineral content of the stone can be noninvasively determined and appropriate therapy instituted, without having to physically remove and test the stone.

Magnetic Resonance Imaging

While it is not the usual first test in evaluation of the chronically diseased kidney, MRI is undergoing rapid technological change which is making it attractive as a renal imaging agent even in patients with CKD.[13,14] The ability to directly image in multiple planes allows excellent morphologic analysis. Imaging is based on the magnetic spin of hydrogen atoms, which are abundant in water-based tissues. Different sequences are used to highlight different structures such as cysts (water), fat, or other soft tissues.

Magnetic resonance angiography (MRA) visualizes flowing blood and can even quantitate the velocity and flow rate in vessels.[15–17] MRA can be performed with or without the intravenous administration of contrast material, although use of contrast usually provides better images. However, some of the new noncontrast sequences provide excellent vascular definition without the risk of contrast toxicity. By varying contrast injection timing and type of sequences, the abdominal venous structures can be visualized in addition to arteries. MRA is performed to evaluate the renal arteries for stenosis. MRA is less invasive than catheter angiography. With newer equipment and software, MRA now gives sensitivity of 97% and specificity of 93%, compared with digital subtraction angiography for contrast-enhanced MRA in the detection of renal artery stenosis. MRA without gadolinium historically has had a lower sensitivity (53%–100%) and specificity (65%–97%) for detection of renal artery stenosis, but this difference is becoming less with development of new noncontrast sequences. This makes MRA without gadolinium one of the best available tests for evaluating the renal vasculature in patients with hypertension, poor renal function, or allergies to intravenous contrast. With the appropriate timing of dialysis, CT angiography using contrast material can be performed in patients with severe decrements in renal function for surgical planning. However, MR imaging is often preferred before renal transplantation to evaluate the arteries (number and location), veins (number and location), and ureters (possible duplicated systems).

Multiple other sophisticated sequences have been developed and are being studied. While functional analysis used to require intravenous gadolinium, which is relatively contraindicated in severe renal failure, there are new sequences and contrast agents which do not have these drawbacks.

One sequence called diffusion-weighted imaging (DWI) displays the relative rate of diffusion of hydrogen atoms (mainly as water) through tissue. Various tissues have different diffusibility characteristics, which give different imaging appearances. Diffusion imaging has historically been most extensively studied in the brain and has been shown to be sensitive to both cellular edema and cellular atrophy, and hence to the tissue damage typically induced by acute or chronic hypoxia. Many causes of CKD have relationships with relative hypoxia, such as that seen in diabetes. This relationship is being studied with the idea of using DWI MRI to evaluate and follow disease processes in the kidney. Several studies have already shown DWI abnormalities in the renal cortex and medulla in patients with CKD as well as in states of obstructive uropathy.[18,19] Abnormalities are also seen in renal allografts, suggesting its use in transplant follow-up without the need for contrast.

Research is ongoing to assess how this technique can be used clinically to differentiate various benign and malignant processes, as well as to potentially evaluate systemic disease states of the renal parenchyma.

Another developing tool in MRI is blood oxygen level–dependent (BOLD) imaging. BOLD contrast

imaging sequences can noninvasively demonstrate the level of intrarenal oxygen tension. Because oxygen delivery correlates with reserve capacity of the kidney and renal tubular workload capacity, BOLD imaging provides further analysis of underlying renal parenchymal function in normal and disease states.[20,21] The clinical utility of BOLD imaging awaits further experimental validation.

Magnetic resonance elastography (MRE) is a technique that images the propagation of shear waves through tissue. Tissue motion is mechanically induced by an external source (such as a pneumatically driven pad) and the resultant tissue displacement is measured by the MR scanner. The degree of displacement is proportional to the elastic properties of the imaged tissue. An MRI parametric image map can be displayed which correlates with organ "stiffness." Ultrasound elastography is analogous and is also being investigated for evaluation of CKD patients. In CKD, one of the common final pathogenic pathways is interstitial fibrosis, which can be semiquantitatively analyzed with MRE. Elastography with MR and ultrasound is not in common use for kidney studies and are still being studied experimentally.[22]

One final developing tool is used in evaluating intrarenal inflammation. In current clinical practice, the degree of inflammatory response in the kidney can be demonstrated only by renal biopsy. Infiltration of the glomeruli and interstitium by inflammatory cells is a common finding in both glomerulosclerosis and tubulointerstitial nephritis. Diffuse interstitial macrophage infiltration of the parenchyma is well documented in many chronic renal diseases and has good correlation with renal transplant graft rejection. There are developing methods of imaging the inflammatory response with MRI by taking advantage of the fact that macrophages take up particles, such as ultrasmall particles of iron oxide (USPIO). Being paramagnetic, these particles result in fairly pronounced decreased signal intensity on MRI in any tissues in which they accumulate. Delayed imaging following USPIO intravenous injection with MR imaging in cases of intrarenal inflammation demonstrates a diffuse but significant decrease of signal intensity throughout the kidney, slightly more pronounced in the cortex. To date, the majority of studies have been in animal models, but some human trials are ongoing.[23]

Imaging to Diagnose Disease States

The normal aging kidney does not demonstrate significant pathologic changes other than a very minor decrease in size. Therefore, any variation from the normal appearance seen on imaging reflects some disease state. The challenge is to diagnose disease or at least to exclude some differential considerations. There are a few classic renal appearances seen, such as the large echogenic kidneys of HIV nephropathy[24,25] (Figure 81.6), the large cystic kidneys of polycystic kidney disease (Figure 81.3), and the renal vascular stenosis of renal artery hypertension.

The majority of renal disease states, however, have similar end results, such as parenchymal abnormalities which give similar imaging findings of small kidneys, increased ultrasound echogenicity, intrarenal arterial flow restriction due to interstitial processes, and general decreased functional clearance of contrast or radionuclides.

Renal angiography typically plays a limited role in CKD except in the evaluation and treatment of renal vascular disease—especially stenosis which may cause hypertension or even eventual renal failure from decreased blood flow. Other than the finding of renovascular stenosis, long-standing renal failure is angiographically seen as pruned and tortuous intrarenal vessels, diminished overall flow, and thinned cortex. Certain systemic diseases which lead to CKD have characteristic microaneurysms, such as seen in Wegener's granulomatosis, polyarteritis nodosa, and systemic lupus erythematosus.

Imaging can also be helpful for monitoring disease progression, and in some cases to corroborate a diagnosis or differentiate between possible diagnoses. This involves imaging organs other than the kidney, which may demonstrate diagnostic changes in certain diseases. For example, in the cardiorenal syndrome, the chest X-ray, echocardiogram, chest CT, or cardiac MRI can show changes of congestive failure, dilated nonischemic cardiomyopathy, or dilated ischemic cardiomyopathy,

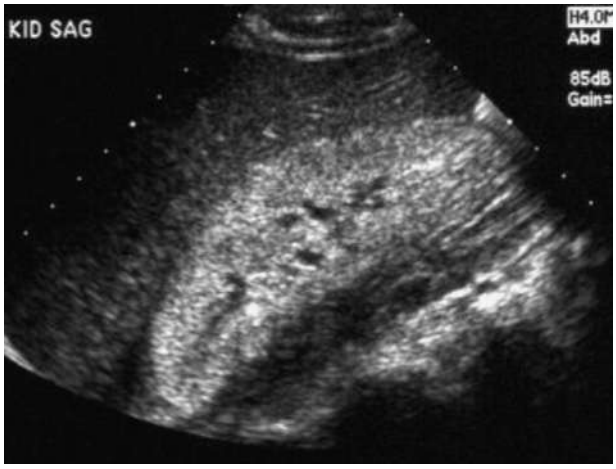


FIGURE 81.6 Large, intensely echogenic kidney with HIV nephropathy.

as well as specific causes of heart failure such as cardiac sarcoidosis or amyloidosis. In the hepatorenal syndrome, the liver is usually expected to show a small, irregular, dense, fibrotic cirrhotic appearance, with flow abnormalities in the portal system and portal venous hypertension. Patients with sickle cell disease, in its advanced stages, can show splenic and bone infarctions as well as other classic bone changes such as the "fish mouth" vertebral appearance. Many of the collagen vascular diseases have other organ involvement, especially lung parenchymal infiltrates or pulmonary fibrosis.

IMAGING CKD COMPLICATIONS

The most commonly associated complication of CKD discerned radiologically is renal calcifications. Calcifications can occur in the collecting systems as nephrolithiasis and in the renal parenchyma as nephrocalcinosis. Most renal calculi are calcium oxalate, calcium phosphate, urate, struvite, or cystine. The majority of stones contain calcium and are radioopaque. Ultrasound is relatively insensitive to stone detection, but when seen, the stones are very echogenic and classically demonstrate "shadowing" distal to the stone due to blocking of the ultrasound wave (Figure 81.7). Color Doppler can result in a characteristic turbulent signal called the "twinkle" artifact. Stones can be reasonably differentiated using CT scanning by dual-energy CT (DECT). Ultrasound is noninvasive without associated radiation and can be used in the initial evaluation of renal stones, especially in looking for hydronephrosis. Ultrasound, however, has a low sensitivity, particularly for small stones and ureteral stones. Noncontrast CT is the imaging method of choice for evaluating the location and size of renal calculi, as well as obstructive uropathy. These parameters affect treatment options.

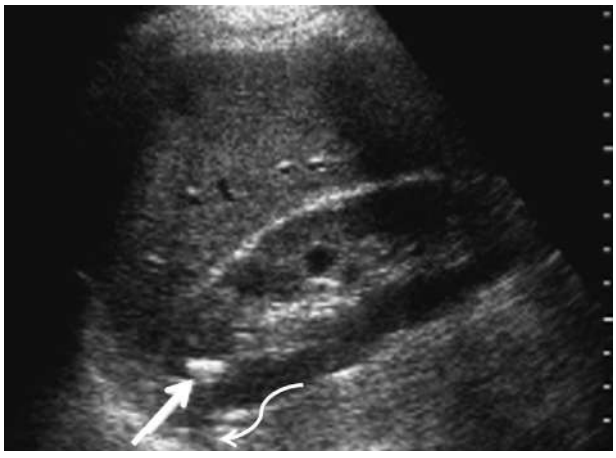


FIGURE 81.7 Large upper pole renal stone with distal acoustical shadowing.

In differentiation from nephrolithiasis, nephrocalcinosis refers to more diffuse intrarenal calcium. This process is commonly bilateral and can be seen with medullary deposition in such states as hyperparathyroidism, renal tubular acidosis, medullary sponge kidney, and in some medication complications such as patients treated with acetazolamide. Cortical nephrocalcinosis is usually dystrophic in nature and is secondary to parenchymal tissue destruction, such as seen with infarction and infection. Common etiologies include chronic glomerulonephritis, cortical necrosis, and transplant rejection.

Osseous abnormalities are common in patients with CKD. These bone abnormalities can have various radiographic findings. Osteitis fibrosa is a manifestation of hyperparathyroidism from CKD and results in the formation of cyst-like areas of brown tumors. Other typical findings in hyperparathyroidism include osteosclerosis of the vertebra (giving an X-ray appearance of the so-called rugger jersey spine), subperiosteal bone resorption (seen especially in the digits and clavicles), and skull changes (with scattered lytic and ground glass appearance). Extraskeletal calcifications from abnormalities of calcium-phosphate metabolism result in vascular, lung, and periarticular calcium deposition. Osteomalacia results from abnormal mineralization. Osteomalacia can result in looser zones or pseudofractures, usually seen in the long bones of the extremities.

Osteopenia and osteoporosis with abnormal bone density is common in patients with CKD. Imaging with dual-energy X-ray absorptiometry is excellent at diagnosing demineralization, but it cannot differentiate the demineralization specific to CKD from other more common causes of osteoporosis. Bone biopsy is required for further differentiation and diagnosis.

There are multiple neurologic abnormalities associated with CKD, but imaging is of little help in the specific evaluation and diagnosis of CKD-induced changes. MRI of the brain can show white matter changes in some cases with uremic encephalopathy. Such changes can reverse following regular dialysis.

Cardiovascular abnormalities result from vascular inflammation as well as abnormal calcium metabolism, with accelerated progression of arteriosclerotic disease of vessels throughout the body as well as coronary vessels and cardiac valves. Screening for cardiac disease as well as risk stratification is possible with coronary calcium scoring with CT, cardiac CTA, stress echocardiography, and nuclear myocardial perfusion imaging. These studies have been validated as independent predictors of cardiac morbidity and/or mortality.

CONTRAST USE IN CKD

Caution should be exercised in the use of both the iodinated intravascular contrast used for CT and angiography and the gadolinium-based contrast used in MRI. While it is considered controversial, new data suggest that the concern over intravenous iodinated contrast agents is overexaggerated. Many experts suggest the risks of adverse events with iodinated contrast can be ameliorated with hydration and judicious use of dialysis as needed. However, the complications of nephrogenic systemic fibrosis (NSF), seen in patients following gadolinium contrast injection in patients with advanced renal insufficiency can be devastating. The first cases of NSF clinical findings were identified in 1997.[26] An international NSF registry was developed at Yale University which maintains records on over 215 patients with NSF worldwide.

NSF with pathological descriptions was reported in 2000. Evidence for a link between NSF and gadolinium was first described in a case series of 13 patients, all of whom developed NSF after being exposed to gadodiamide.[27] The background and history of NSF is nicely discussed in a review article from 2009.[28]

The reported incidence of NSF varies with individual gadolinium-based agents, primarily related to the degree of binding of the gadolinium chelate. Older, less stably bound agents are more directly implicated in the development of NSF.[29] Some of the newer agents are so tightly bound that it is suggested that they can be used safely in patients with advanced renal failure. Some large studies have demonstrated that certain newer agents have caused no cases of NSF even in patients treated with peritoneal and hemodialysis.[30]

The Contrast Media Safety Committee (CMSC) of the European Society of Urogenital Radiology (ESUR) updated their consensus guidelines in 2012. In summary, those guidelines suggest that gadolinium-based agents can be separated by risk of NSF, based on the molecular structure of the individual contrast agents. In contrast to NSF, there are concerns about the long-term retention of gadolinium in body tissues, especially the brain, even in patients with normal renal function. This is an ongoing area of investigation.[31]

Conservative strategies for administration of gadolinium-based contrast agents include contraindication in patients with stage 4 and 5 CKD (GFR<30 mL/min/1.73 m^2), acute renal injury, and pregnant women (gadolinium agents are pregnancy class C) and neonates, and use with caution in stage 3 CKD (GFR 30–60 mL/min/1.73 m^2) and children less than 1-year old. There should be at least 7 days between two injections. Lactating women should stop breastfeeding for 24 hours. The dose should not exceed 0.1 mmol/kg per examination.

The committee states that newer gadolinium agents which are more tightly bound in the molecular structure such as gadobutrol, gadoterate, and gadoteridol may be used with caution in patients with stage 4 and 5 CKD, because there are no well-documented unconfounded cases of NSF reported with these agents.

The 2011 ESUR guidelines for use of iodinated contrast identify patients as being at risk for CIN as those with eGFR below 60 mL/min/1.73 m^2, before intraarterial injections, and eGFR less than 45 mL/min/1.73 m^2 before intravenous injections.[32] There is additional concern when the patient has underlying diabetic nephropathy, dehydration, congestive heart failure, is over the age of 70, or has had concurrent use of nephrotoxic drugs.

In patients at risk, it is still recommended that alternative imaging methods be explored if reasonable. If contrast is to be used, low or iso-osmolar contrast at the lowest possible dose is recommended. Volume expansion has shown some protective effects. One general protocol suggests 1.0–1.5 mL/kg/h of intravenous saline for at least 6 hours before and after contrast administration. It is notable that to date prophylaxis with renal vasodilators, cytoprotective drugs, or other pharmacologic interventions has not proven efficacious against CIN. Early small studies suggested that the use of bicarbonate solutions helped to reduce the incidence of CIN. However, the largest trial to date showed no benefit of sodium bicarbonate nor acetylcysteine over normal saline.[12,33]

Specific guidelines have also been defined for contrast use in patients with reduced renal function taking metformin. This is because of the possibility of metformin-induced lactic acidosis. Because metformin is cleared by the kidneys, any reduction in renal function prolongs the biologic half-time of metformin and increases the subsequent risk of life-threatening acidosis. For these reasons, drug guidelines contraindicate the use of metformin in patients with eGFR less than 30 mL/min/1.73 m^2. The guidelines recommend that patients receiving IV contrast and with eGFR greater than 45 mL/min/1.73 m^2 can continue taking metformin normally. However, patients receiving intraarterial contrast and those with eGFR between 30 and 45 mL/min/1.73 m^2 should stop metformin before the study and not begin metformin again until 48 hours after the study, and then only after determining that renal function has not deteriorated.

Although it is still recommended to seek alternatives to imaging with intravenous iodinated contrast in patients with CKD, multiple recent studies and meta-analyses have demonstrated that the relative risk to these patients has been overestimated.[12,34–36] This should be taken into account in the decision process

for diagnostic imaging if there is significant potential benefit to using iodinated contrast in the patient's medical or surgical management, especially in emergent settings. For anuric end-stage renal disease patients without a functioning transplant treated with dialysis, the American College of Radiology manual on contrast media asserts that intravenous contrast material can be used safely without the risk of osmotic load. Low or iso-osmolar contrast media are recommended, and immediate postcontrast administration dialysis is not indicated.[37]

CONCLUSION

Imaging plays an increasingly vital role in measuring both renal function and structure in patients with CKD. Diagnosis, disease status, disease progression, and development of complications of renal failure are monitored clinically as well as with laboratory studies and radiologic imaging. Although ultrasound and nuclear medicine have historically played a vital first role, newer MRI technologies promise to provide safe advanced functional renal analysis. With sophisticated new MRI sequences, we are on the verge of major changes in the radiologic evaluation and follow-up of patients with CKD.

The indications for evaluating the kidneys include evaluation of treatable causes of renal failure (such as hydronephrosis), documentation of renal size, identification of the position of the kidneys, monitoring progression of disease, and identification or confirmation of a specific renal disease.

References

1. Buturović-Ponikvar J, Višnar-Perovič A. Ultrasonography in chronic renal failure. *Eur J Radiol* 2003;**46**(2):115–22.
2. Ascenti G, Mazziotti S, Zimbaro G, Settineri N, Magno C, Melloni D. Complex cystic renal masses: characterization with contrast-enhanced US. *Radiology* 2007;**243**(1):158–65.
3. Tamai H, Takiguchi Y, Oka M, Shingaki N, Enomoto S, Shiraki T. Contrast-enhanced ultrasonography in the diagnosis of solid renal tumors. *J Ultrasound Med* 2005;**24**(12):1635–40.
4. Dietrich C, Averkiou M, Nielsen M, et al. How to perform contrast-enhanced ultrasound (CEUS). *Ultrasound Int Open* 2017; **3**:E2–15.
5. Tenant S, Gutteridge C. The clinical use of contrast-enhanced ultrasound in the kidney. *Ultrasound* 2016;**24**(2):94–103.
6. Border WA, Holbrook JH, Peterson MC. Gallium citrate Ga 67 scanning in acute renal failure. *West J Med* 1995;**162**:477–8.
7. Joaquim AI, Mendes GEF, Ribeiro PFF, Baptista MAF, Burdmann EA. Ga-67 scintigraphy in the differential diagnosis between acute interstitial nephritis and acute tubular necrosis: an experimental study. *Nephrol Dial Transplant* 2010;**25**(10): 3277–82.
8. McDonald R, McDonald J, Carter R, et al. Intravenous contrast material exposure is not an independent risk factor for dialysis or mortality. *Radiology* 2014;**273**(3):714–25.
9. Durham J, Caputo C, Dokko J, et al. A randomized controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography. *Kidney Int* 2002;**62**(6):2202–7.
10. Vaitkus P, Brar C. N-acetylcysteine in the prevention of contrast-induced nephropathy: publication bias perpetuated by meta-analyses. *Am Heart J* 2007;**153**(2):275–80.
11. Stenstrom D, Muldoon L, Armijo-Medina H, et al. N-acetylcysteine use to prevent contrast medium-induced nephropathy: premature phase III trials. *J Vasc Interv Radiol* 2008;**19**(3):309–18.
12. Weisbord SD, Gallagher M, Jneid H, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. Preserve trial group. *NEJM* 2018;**378**(7):603–14.
13. Grenier N, Hauger O, Delmas Y, Combe C. MR imaging of nephropathies. *Abdom Imag* 2006;**31**(2):213–23.
14. Cheong B, Muthupillai R, Rubin MF, Flamm SD. Normal values for renal length and volume as measured by magnetic resonance imaging. *CJASN* 2007;**2**(1):38–45.
15. Tan KT, van Beek EJ, Brown PW, van Delden OM, Tijssen J, Ramsay LE. Magnetic resonance angiography for the diagnosis of renal artery stenosis: a meta-analysis. *Clin Radiol* 2002;**7**(7):617–24.
16. Grenier N, Trillaud H. Comparison of imaging methods for renal artery stenosis. *BJU Int* 2000;**86**(Suppl. 1):84–94.
17. Marcos HB, Choyke PL. Magnetic resonance angiography of the kidney. *Semin Nephrol* 2000;**20**:450–5.
18. Namimoto T, Yamashita Y, Mitsuzaki K, Nakayama Y, Tang Y, Takahashi M. Measurement of the apparent diffusion coefficient in diffuse renal disease by diffusion-weighted echo-planar MR imaging. *J Magn Reson Imaging* 1999;**9**:832–7.
19. Bozgeyik Z, Kocakoc E, Sonmezgoz F, Diffusion-weighted MR. Imaging findings of kidneys in patients with early phase of obstruction. *Eur J Radiol* 2009;**70**:138–41.
20. Thoeny HC, Zumstein D, Simon-Zoula S, Eisenberger U, De Keyzer F, Hofmann L. Functional evaluation of transplanted kidneys with diffusion-weighted and BOLD MR imaging: initial experience. *Radiology* 2006;**241**:812–21.
21. Prasad PV, Edelman RR, Epstein FH. Noninvasive evaluation of intrarenal oxygenation with BOLD MRI. *Circulation* 1996;**94**: 3271–5.
22. Nihar SS, Scott AK, Donna JL, Gerard F, John CL, Bernard FK. Evaluation of renal parenchymal disease in a rat model with magnetic resonance elastography. *Magn Reson Med* 2004;**52**: 56–64.
23. Hauger O, Grenier N, Deminère C, Lasseur C, Delmas Y, Merville P. USPIO-enhanced MR imaging of macrophage infiltration in native and transplanted kidneys: initial results in humans. *Eur Radiol* 2007;**17**(11):2898–907.
24. Herman ES, Klotman PE. HIV-associated nephropathy: epidemiology, pathogenesis, and treatment. *Radiographics* 2008;**28**: 1339–54.
25. Herman ES1, Klotman PE. HIV nephropathy secondary to direct renal infection, complications (cancer) or secondary to antiviral Tx. *Semin Nephrol* 2003;**23**(2):200–8.
26. Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. *Lancet* 2000;**356**:1000–1.
27. Marckmann P, Skov L, Rossen K, Dupont A, Damholt MB, Heaf JG. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol* 2006;**17**(9):2359–62.
28. Thomsen HS. Nephrogenic systemic fibrosis: history and epidemiology. *Radiol Clin N Am* 2009;**47**(5):827–31.
29. Thomsen HS, Marckmann P, Logager VB. Update on nephrogenic systemic fibrosis. *Magn Reson Imag Clin N Am* 2008; **16**:551–60.
30. Nandwana S, Moreno C, Osipow M, Sekhar A, Cox K. Gadobenate dimeglumine administration and nephrogenic systemic fibrosis: is

there a real risk in patients with impaired renal function? *Radiology* 2015;**276**(3):741–7.
31. McDonald R, McDonald J, Kallmes D, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. *Radiology* 2015;**275**(3):772–82.
32. Stacul F, van der Molen AJ, Reimer P, Webb JA, Thomsen HS, Morcos SK. Contrast induced nephropathy: updated ESUR contrast media safety committees guidelines. *Eur Radiol* 2011;**21**:2527–41.
33. Brar SS, Shen AY, Jorgensen MB, Kotlewski A, Aharonian VJ, Desai N. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. *J Am Med Assoc* 2008;**300**(9):1038–46.
34. Davenport M, Cohan R, Khalatbari S, Ellis J. The challenges in assessing contrast-induced nephropathy: where are we now? *Am Journal Rev* 2014;**202**:784–9.
35. Garfinkle M, Stewart S, Basi R. Incidence of CT contrast agent-induced nephropathy: toward a more accurate estimation. *Am Journal Rev* 2015;**204**:1146–51.
36. McDonald R, McDonald J, Bida J, et al. Intravenous contrast material-induced nephropathy: causal or coincident phenomenon? *Radiology* 2013;**267**(1):106–18.
37. Younathan C, Kaude J, Cook M, et al. Dialysis is not indicated immediately after administration of nonionic contrast agents in patients with end-stage renal disease treated by maintenance dialysis. *Am J Roentgenol* 1994;**163**(4):969–71.

QUESTIONS AND ANSWERS

Question 1

What is the most common and classic ultrasound appearance of the kidneys in CKD?

A. Multiple cortical cysts
B. Hypoechoic cortex in large kidneys
C. Hyperechoic cortex in small kidneys
D. Lobulated margins with mixed hyperechoic and hypoechoic cortex
E. Normal cortex with medullary calcifications

Answer: C

The classic appearance is small echogenic kidneys (C) with thinned cortices as the end result in most renal processes leading to renal failure. Hyperechoic large kidneys are the classic appearance of HIV-associated nephropathy. While multiple renal cortical cysts are a common finding in normal kidneys, enlarged kidneys with innumerable cysts are typical of adult polycystic kidney disease. Various calcifications (renal stones, cortical calcifications of cortical necrosis, and medullary calcifications of medullary sponge kidney) are seen in CKD but are not the most common finding.

Question 2

Renal stone content can be differentiated with which imaging technique?

A. Diffusion-weighted MRI
B. Ultrasound with microbubbles
C. DECT
D. MRI with BOLD imaging
E. Standard intravenous urogram

Answer: C

Using the physics principles of differing X-ray absorption of different X-ray energies by materials of different chemical structure, DECT can differentiate stones into basic categories—the correct answer is (C). DWI measures ease of diffusion of water molecules in tissues. BOLD imaging uses MRI to measure relative blood oxygen level. Microbubbles evaluate perfusion and the urogram evaluates renal function.

Question 3

With an eGFR of 50 mL/min/1.73 m^2 which statement regarding metformin use in conjunction with iodinated contrast is most correct?

A. No restriction to metformin use with intravenous contrast
B. Stop metformin 48 hours before contrast
C. There is no difference in recommendations between intravenous and intraarterial injections
D. Metformin can be continued only if the patient is pretreated for 6 hours with normal saline
E. Metformin should be withheld for at least 72 hours after contrast administration

Answer: A

The latest consensus from the CMSC of the ESUR in 2012 states that metformin can be used normally during intravenous contrast administration as long as the eGFR is above 45 mL/min/1.73 m^2. Therefore, the correct answer is A. Patients with an eGFR between 30 and 45 mL/min/1.73 m^2 and those receiving intraarterial contrast should stop metformin for 48 hours before contrast administration to avoid possible lactic acidosis. Additionally, they should not restart metformin for 48 hours after contrast, and then, only after determining that renal function has not deteriorated. Pretreatment with normal saline is suggested as a renal protective agent against CIN but has no direct bearing on the use of metformin.

Question 4

Which statement regarding contrast use in CKD is most correct?

A. Nephropathy is only seen with iodinated contrast and not gadolinium agents
B. Use of gadolinium agents is contraindicated in patients with eGFR< 30 mL/min/1.73 m^2
C. There are no restrictions to breastfeeding following gadolinium administration
D. Prophylaxis with renal vasodilators is renal protective
E. Volume expansion with normal saline is not as effective as bicarbonate infusion

Answer: B

Contrast nephropathy has been reported with both iodinated and gadolinium-based agents; however, the incidence is much lower with gadolinium. While there are some cyclic gadolinium agents which to date have not been associated with NSF even in patients in renal failure, the incidence of NSF is significantly increased with the use of some gadolinium agents when the eGFR is less than 30 mL/min/1.73 m^2, so gadolinium agents should not routinely be used in these cases. (The correct answer is B.) Gadolinium is secreted in breast milk, so breastfeeding should be stopped for 24 hours after gadolinium contrast to avoid possible adverse effects in the immature newborn kidneys as well as possible persistent accumulation of gadolinium in other fetal tissues. There is evidence that volume expansion with normal saline has some renal protective

effect, and bicarbonate infusion has shown some efficacy; however, the effects with bicarbonate are not as clear as simple normal saline. There is no proven renal prophylactic protective effect with renal vasodilators, cytotoxic agents, or other pharmacologic interventions.

Question 5

Which imaging techniques can be used to measure relative renal hypoxia?

A. DECT
B. Diffusion-weighted MRI
C. BOLD MRI
D. Microbubble ultrasound
E. Nuclear medicine gallium scanning

Answer: C

BOLD imaging with MRI can be used to measure relative renal oxygen levels; however, BOLD imaging is not in regular clinical use, due to the sophistication of the equipment and protocol sequences. (The correct answer is C.) DECT is useful for evaluating the chemical make up of renal stones. DWI evaluates tissue structure by measuring the rate of water diffusion in tissues. Ultrasound microbubbles are used to measure relative blood flow.

Question 6

Secondary hyperparathyroidism seen in CKD can result in what classic X-ray finding?

A. Osseous brown tumors
B. Interstitial lung disease
C. Small shrunken liver with cirrhosis
D. "Fish mouth" vertebra
E. Echogenic liver of steatohepatitis

Answer: A

The osteitis fibrosa of hyperparathyroidism can result in focal bone replacement with development of "brown tumors" (A). "Fish mouth" vertebra are classic in sickle cell anemia. The other three possibilities have no relationship to hyperparathyroidism.

Index

'*Note:* Page numbers followed by "f" indicate figures and "t" indicate tables.'

B

C

D

F

G

H

J

K

L

M

N

Q

S

U

V