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A New Era

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Nutrition and Kidney Disease: A New Era

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Hiromichi Suzuki *Saitama*
Paul L. Kimmel *Washington, D.C.*

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Hiromichi Suzuki
Department of Nephrology, School of Medicine
Faculty of Medicine, Saitama Medical University
38 Morohongo, Moroyama, Iruma
Saitama 350-0495 (Japan)

Paul L. Kimmel
Professor of Medicine
George Washington University
School of Medicine
Washington, DC 20037 (USA)

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Contents

Preface

Over the last decade, it has become clear that lowering blood pressure with renin-angiotensin inhibitors has become one of the sophisticated maneuvers for preventing progression of renal dysfunction in patients with chronic kidney disease (CKD). It is also however well-known that the daily diet plays an important role in the preservation and integrity of renal function in patients with CKD. However, there is currently controversy and confusion regarding the correct dietary prescription for individual CKD patients, in part because the Modification of Diet in Renal Disease (MDRD) study may be interpreted as showing that a low-protein diet does not have a major effect on the course of renal dysfunction. In addition, there is limited information regarding optimal diets for patients with different kidney diseases at different stages of disease.

To resolve this dilemma, researchers are developing frameworks for an appropriate dietary program which will significantly alter the understanding of the role of diet and, eventually, have important implications for the practice of nephrology. This publication provides an update on both laboratory and clinical research, including nutritional status and its assessment, and nutritional therapy in various CKD settings. It is the result of work by an international group of authors from three continents. The individual chapters examine the role of sodium, protein and phosphate in the diet, and concern patients with diabetic nephropathy, patients with CKD at early stages as well as those treated with hemodialysis, peritoneal dialysis and transplantation. Formats range from traditional reviews to up-to-the-minute research reports.

Part of a long-standing and continuing effort to improve patient outcomes, this book provides both a fundamental understanding of dietary therapies as

well as practical and up-to-date summaries of current knowledge and technology. It will therefore be a helpful tool for clinicians working with patients with CKD.

We deeply appreciate the contributions of all the authors. We acknowledge that the wisdom is theirs and the mistakes are our own. Obviously, much work still needs to be done, and one of the goals of this book is to stimulate further research in this area, in which so many sub-disciplines of medical science are involved.

We wish to express our appreciation to our many associates and colleagues, who, in their particular fields, have helped us with constructive criticism and helpful suggestions. This book could not have been produced without the dedicated help of our co-workers in the editorial offices of all the contributors. Finally, we continue to be indebted to the staff of Karger Publishers.

We dedicate this book to our patients and the clinicians who care for them.

Hiromichi Suzuki
Paul L. Kimmel

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Nutritional Status, Psychological Issues and Survival in Hemodialysis Patients

Scott D. Cohen, Paul L. Kimmel

Division of Renal Diseases and Hypertension, Department of Medicine, George Washington University School of Medicine, Washington, D.C., USA

Abstract

There is a high prevalence of protein-energy malnutrition in the end-stage renal disease population. There are a number of causes of malnutrition in hemodialysis patients, which can often be directly linked to the uremic state. Laboratory measures including albumin, prealbumin, and serum cholesterol, as well as anthropometric measures, have been used to assess malnutrition in this patient population. There is, however, no single accepted measure of malnutrition in patients with chronic kidney disease. Failure to achieve adequate nutritional goals may lead to protein-energy malnutrition, which has been linked to decreased survival. Several studies have also shown a direct association between psychosocial variables, including depression, and the nutritional status of hemodialysis patients, in particular the serum albumin concentration. Interventions such as oral nutritional supplements or intradialytic parenteral nutrition may be necessary to improve nutritional status if conservative measures such as nutritional counseling and regular dietician follow-up fail to produce the changes needed to sustain health. In addition, given the potential link between psychological conditions, such as depression, and overall nutritional status, interventions designed to screen for and treat psychiatric disorders may lead to improvements in nutritional status and therefore increased survival rates of patients with end-stage renal disease treated with hemodialysis. Further study is needed to evaluate the association between depression, malnutrition, and survival in patients with chronic kidney disease.

Malnutrition is associated with poor outcomes and increased mortality in patients with end-stage renal disease (ESRD). Unfortunately, protein-calorie malnutrition is quite prevalent in this patient population, with estimates ranging from 20 to 80% of ESRD patients [1–3]. As chronic kidney disease (CKD) progresses to advanced stages, appetite declines, predisposing patients to malnutrition. This chapter will present an overview of associations between nutritional

status and survival in patients with ESRD. In addition, we will discuss the impact psychosocial factors may have on an ESRD patient's overall nutritional status.

Protein-energy malnutrition (PEM) can be defined as 'the state of decreased body pools of protein with or without fat depletion or a state of diminished functional capacity, caused at least partly by inadequate nutrition intake relative to nutrient demand and/or which is improved by nutritional repletion' [1]. PEM is common in ESRD patients treated with maintenance hemodialysis (HD). However, PEM appears to begin at stages well before dialysis is initiated. In the Modification of Diet in Renal Disease (MDRD) study, once GFR fell below 60 ml/min, mean serum albumin levels began to decline [1, 4].

A number of factors are associated with the decreased nutritional status of ESRD patients. There are obligate losses of amino acids during dialysis therapy, with generally higher losses of amino acids during peritoneal dialysis (PD) [1, 5]. It is estimated that 5–8 g of amino acids are lost during HD, and approximately 5–12 g/day of amino acids are lost during PD [1, 5]. In addition, there can be induction of the inflammatory cascade during dialysis treatments from bioincompatible HD membranes [1, 5]. ESRD patients often have a number of underlying comorbid conditions that are associated with malnutrition, including diabetes mellitus, gastrointestinal diseases, inflammatory or autoimmune disorders, and side effects of frequent polypharmacy [1, 5].

Nutritional Parameters in Chronic Kidney Disease Patients

A single evaluation is not available to assess the nutritional status of medical patients, including those with renal disease. Traditionally, multiple measures have been used to evaluate the nutritional status of ESRD patients (table 1). Current guidelines endorse the use of several tools to completely evaluate nutritional status in patients with CKD [6]. The laboratory parameters used include serum concentrations of albumin, prealbumin, creatinine, cholesterol, transferrin, potassium, phosphate, and trace metals. In addition, dry weight and interdialytic weight gain (IDWG) have been used to assess overall nutritional status.

Serum albumin concentration has frequently been used as a measure of nutritional status in ESRD patients [6–10]. Albumin levels typically decline with a decrease in dietary protein and/or energy intake and increase when protein and/or energy intake increases [6]. However, hypoalbuminemia is common during inflammation, infection, and stress, and is therefore not necessarily a reliable indicator of changes in nutritional status in ESRD patients [6]. In addition,

Table 1. Selected laboratory values to assess protein energy malnutrition in HD patients

Albumin
Prealbumin
Transferrin
Cholesterol, triglycerides
Creatinine
Serum urea nitrogen
Insulin-like growth factor (IGF-1)
CBC (lymphocyte count)

underlying comorbid conditions such as nephrotic syndrome and dialysis therapeutic modality must be considered when evaluating the serum albumin level [6, 8, 9]. Hypoalbuminemia has been linked to increased mortality in ESRD patients treated with HD [10]. Therefore, albumin remains an important marker to follow on a monthly basis in dialysis patients. Interventions to sustain or increase albumin levels could be associated with improved survival. However, more research is needed in this area.

Serum prealbumin levels can also be used to assess the nutritional status of ESRD patients. Because of its shorter half-life, changes in prealbumin concentration may be used to detect earlier changes in nutritional status [6, 11]. The half-life of prealbumin is approximately 2–3 days, compared to that of albumin, which is 20 days [6]. A prealbumin level less than 30 mg/dl is associated with higher patient mortality, and correlates with other measures of poor nutritional status in ESRD patients [6, 12]. However, like albumin, the metabolism of prealbumin is influenced by other factors, such as infection and inflammation, and its serum levels typically decline during these conditions. In addition, because prealbumin is cleared by the kidneys, caution in interpreting these values in patients with CKD must be exercised [11].

Predialysis serum creatinine concentration in HD patients is determined in part by dietary protein intake (DPI) and skeletal muscle mass [6]. However, one must consider the level of any residual renal function when interpreting this value. The creatinine index is used to estimate creatinine production and fat-free body mass [6, 13]. In patients treated with HD, predialysis serum creatinine and the ratio of urea to creatinine are associated with differential survival [6, 10]. Mortality risk increases with serum creatinine levels less than 9–11 mg/dl in maintenance HD patients [6, 10, 14].

Patients undergoing HD who have nonfasting serum cholesterol levels of 150–180 mg/dl or lower have a decreased survival rate, compared to individuals with increased cholesterol levels [6, 10, 14]. There is an increasing risk of

mortality as the serum cholesterol rises above the range of 200–300 mg/dl or decreases below 200 mg/dl [6, 10, 14]. Cholesterol is an independent predictor of mortality in patients treated with HD [6, 10]. In conjunction with other nutritional parameters, evaluation of cholesterol levels may be useful.

Another marker of nutritional status is the protein equivalent of total nitrogen appearance (PNA). The PNA is equivalent to the protein catabolic rate (PCR). Initially a total nitrogen appearance (TNA) must be determined. TNA is calculated as the sum of the postdialysis rise in blood urea nitrogen plus the losses of nitrogen in the urine, feces, and dialysate [6]. The PNA is obtained by transformation of the TNA using standard formulae, including a correction factor involving the weight of the patient [6]. However, the PNA is not a perfect measure of DPI [6]. PNA estimates DPI only when an individual is in steady state [6]. Evaluation using the PNA should be undertaken with caution during hypercatabolic or anabolic states [6]. Nevertheless, when used in conjunction with some of the other nutritional parameters mentioned above, including albumin, prealbumin, and creatinine, the PNA is a useful measure of nutritional status.

The Subjective Global Assessment (SGA) is another measure of nutritional status in patients on maintenance HD [6]. The SGA consists of a four-item scale including questions regarding 'dietary intake and gastrointestinal symptoms, change in weight over the previous 6 months, muscle mass, and visual assessment of subcutaneous tissue [6]'. Higher scores connote 'better dietary intake,' increased appetite, and absence of symptoms attributable to gastrointestinal dysfunction [6]. Evaluation of subcutaneous tissue and muscle mass is also part of the scoring [6]. The different components are summed to determine the total SGA score [6].

Another measurement tool is the comprehensive Malnutrition-Inflammation Score (MIS) [15]. Given the known links between malnutrition, inflammation and increased mortality in HD patients, Kalantar-Zadeh et al. [15] developed this measure to quantitatively assess the severity of this condition. The score consists of portions of the SGA and the Dialysis Malnutrition Score (DMS), as well as the body mass index (BMI), serum albumin, and total iron-binding capacity [15]. The MIS ranges from 0 to 30, with higher scores signifying worsening malnutrition and inflammation [15]. The authors evaluated the MIS score and compared it to SGA and DMS scores. MIS was associated with length and frequency of hospitalization, with higher correlation coefficients achieved with MIS compared to SGA and DMS [15]. The investigators concluded that the MIS 'may be superior to the conventional SGA and DMS, as well as to individual laboratory values, as a predictor of dialysis outcome and an indicator of malnutrition inflammation complex syndrome [15]'.

Malnutrition-Inflammation Complex Syndrome

PEM and inflammation significantly contribute to the increased mortality rate among patients on HD. There are several pieces of evidence to support a link between PEM and inflammation. Firstly, tumor necrosis factor (TNF)-α, a cytokine known to participate in the inflammatory cascade, is associated with decreased appetite [1, 16]. Levels of TNF-α and other proinflammatory cytokines are increased in well-dialyzed maintenance HD patients [17]. Secondly, HD patients with underlying inflammatory states lose weight and go into hypercatabolic states with associated breakdown of proteins [1, 18]. Thirdly, albumin levels are decreased when C-reactive protein levels rise [1]. Finally, inflammatory states have been associated with hypocholesterolemia, which is another indicator of malnutrition [1, 19]. The close link between these two conditions has lead to use of the term 'Malnutrition-Inflammation Complex Syndrome' or MICS [1, 15]. MICS has been linked to refractory anemia, coronary artery disease, decreased quality of life, and increased mortality [1]. Kalantar-Zadeh et al. [1] suggest the following therapies that may be tried in an effort to ameliorate MICS: statins, angiotensin-converting enzyme inhibitors, Vitamin E, and intensification of dialysis treatments. However, there have not been randomized controlled trials yet to suggest improved outcomes with these approaches.

Anthropometric Measures to Assess Nutritional Status in Hemodialysis Patients

Over more than 30 years, anthropometry has been used as a marker of nutritional status and body composition in patients with and without renal disease [20–24]. Anthropometry consists of a group of noninvasive and simple methods to estimate body composition [6, 20–24]. Anthropometric measures used to estimate overall nutritional status in HD patients include skeletal frame size, body weight, height, skinfold thickness, mid-arm muscle circumference, percent of body mass that is fat, percent of usual body weight, percent of standard body weight, and the BMI [6, 20–24] (table 2). Anthropometric measures provide an estimate of body composition by tissue distribution, including the bone, muscle, and fat compartments [6, 20–24].

Percent of UBW is determined by a thorough review of prior weight values [6]. Percent of SBW is defined as 'the patient's actual weight (postdialysis) expressed as a percentage of normal body weight for healthy Americans of similar sex, height, and age range and skeletal frame size [6]'. Data from the National Health and Nutritional Examination Survey (NHANES) are used to

Table 2. Selected anthrompometric measures to measure nutritional status

Body weight
Height
Skeletal frame size
Skinfold thickness
Mid-arm muscle circumference
Percent of fat body mass
Percent of usual body weight
Percent of standard body weight
Body mass index

compare dialysis patients with age and sex matched individuals [6]. Maintenance HD patients with higher levels of weight have increased survival rates [6]. Individuals with lower than 90% of normal body weight have mild to moderate malnutrition [6]. Patients with less than 70% of normal body weight are severely malnourished [6]. The goal percent of SBW for patients on HD is 90–110% [6]. Limitations of these measures are their lack of precision and accuracy, since they are operator dependent.

BMI is another anthropometric measure frequently used to assess nutritional status in HD patients. BMI is estimated by dividing weight (in kilograms) by height (in squared meters). ESRD patients treated with HD with higher BMI have increased survival over a 1-year period [6, 12, 25–27]. In the general population, patients with lower BMI usually have increased survival [6, 12, 28]. Further research is needed in this area to explain the reasons for the differences between the findings in the general population and ESRD patients.

Skinfold thickness is another anthropometric measure used to evaluate malnutrition. It is important to evaluate skinfold thickness at four separate sites [29]. Measurement at just one site is not accurate, since responses to malnutrition at the different sites varies [29]. It is possible to estimate the skinfold thickness and total body fat using skinfold calipers at the suprailiac, subscapular, triceps and biceps skinfold areas [6].

Mid-arm muscle area, diameter, and circumference are measures that estimate total body muscle protein [6]. It is possible to estimate the muscle mass of an individual and compare this with a reference population from the NHANES database [6]. By assessing mid-arm circumference and the triceps skinfold, the mid-arm muscle circumference can be evaluated [6].

Kimmel et al. [20] studied the association between anthropometric measures, cytokines, and laboratory measures of nutritional status, including serum albumin and transferrin, in 240 urban HD patients. Arm muscle area (AMA) was associated with patient age, but arm fat area (AFA), BMI, percent ideal

weight (PIW), serum albumin, and serum transferrin were not correlated with age [20]. AMA, BMI, PIW, and serum albumin correlated with Kt/V [20]. AMA, AFA, BMI, and PIW were not associated with PCR [20]. The anthropometric measures did not correlate with cytokine levels, including log TNF-α, log interleukin-1 (IL-1), or log interleukin-6 (IL-6) [20]. In addition, serum albumin and transferrin were not associated with log TNF-α, log IL-1, or log IL-6 [20]. The AFA, AMA, and BMI were associated with PIW [20], and AFA and AMA were correlated with each other [20]. The AMA, AFA, and PIW were not associated with serum albumin or serum transferrin levels [20]. BMI was associated with serum transferrin, but was not associated with serum albumin [20].

Whole body dual energy X-ray absorptiometry (DEXA) is another tool used to evaluate malnutrition in ESRD patients [6, 30, 31]. Like anthropometric measures, DEXA is a method to evaluate body composition, including bone mineral mass and density, and fat and fat-free mass [6]. DEXA is more precise and accurate when compared to anthropometry in HD patients [30, 31]. Anthropometric measures may be subject to variation due to changes in volume status that typically occur in ESRD patients [20, 31]. In addition, anthropometric measurements are operator-dependent [30, 31]. However, higher costs must be considered before ordering this study [30, 31]. Further study of the relationship of DEXA measures with other factors in this patient population, including outcomes, is needed.

Protein Nutrition for Hemodialysis Patients

There are many reasons for PEM while on maintenance HD. Decreased intake is believed to be the main factor [6]. There are numerous causes for anorexia in the HD population including uremia, the HD procedure itself, side effects of multiple medications, the presence of multiple comorbid illnesses and acidemia [1, 5, 6]. DPI is frequently decreased in patients on HD [6]. The mean DPI in patients on HD ranges between 0.94 and 1.0 g protein/kg/day [6, 32]. The relationships between DPI and outcomes such as hospitalizations, perception of quality of life and mortality have not been assessed in rigorously designed randomized controlled trials [6]. It has been recommended that a DPI of approximately 1.2 g/kg/day is needed to maintain nitrogen balance in the majority of maintenance of HD patients [6, 33, 34]. It is recommended that at least half of the DPI should consist of proteins of high biological value [6, 33]. Low DPI in HD patients was linked with worsened outcomes in two retrospective studies [6, 35]. Other studies have not been able to confirm associations between DPI and ESRD patient morbidity and mortality [6, 36].

Energy Intake for ESRD Patients Treated with HD

The mean daily energy intake needed to maintain nitrogen balance and body composition is approximately 35 kcal/kg/day in patients treated with HD [33]. However, HD patients often have lower energy intakes, which has been associated with decreased survival. This guideline applies to individuals who are less than 60 years old. In older individuals there is a reduction in energy requirements. Therefore, a daily energy intake of 30–35 kcal/kg/day may be a reasonable goal [6]. If these goals are not reached, supplementary measures such as dietary counseling, oral nutritional supplements, tube feeds, and parenteral nutrition may be needed.

Several recent reports provide support for the use of oral nutritional supplements in malnourished HD patients [37, 38]. Using an isotope tracer to measure protein balance, Veneeman et al. [38] evaluated the effects of oral feedings during HD. Their study showed that enteral feeding resulted in a positive protein balance to the same degree as a nondialysis day [38]. Cagler et al. [39] administered oral nutritional supplements over a 6 month period to 85 patients during HD, and found that they had significantly higher albumin, prealbumin, and SGA levels compared to levels during a 3-month baseline period during which they received 'conventional nutritional counseling' without nutritional supplements. Larger randomized controlled trials are needed to confirm these findings.

Parenteral nutrition given during HD can lead to improvements in nutritional status [40]. Pupim et al. [40] studied the effect of intradialytic parenteral nutrition (IDPN) on nutritional status of HD patients by directly measuring specific components of protein and energy metabolism using radioisotopes. IDPN was associated with a 96% increase in whole body protein synthesis, and a 50% decrease in whole body protein degradation when compared to the control group [40]. In addition, results showed that patients went from a catabolic to an anabolic state during the course of the study, despite ongoing HD, in which amino acids are lost in the dialysate [40]. More research is needed to evaluate the effects of IDPN in larger patient populations.

IDPN can be administered during HD, which adds to patient convenience and reduces the possibility of development of volume overload. However, the therapy can be costly, and it is not clear that sufficient calories are provided because the IDPN is administered only on dialysis days [37, 40]. Further data are needed comparing enteral nutritional supplementation and IDPN before definitive recommendations can be made for or against its use [37, 40].

Rocco et al. [41] evaluated the nutritional status of the first 1,000 patients selected for the HEMO study, and compared these values to the NKF-KDOQI guidelines for protein/energy intake. Twenty-nine percent of patients had a serum albumin <3.5 g/dl, 76% had dietary energy intake <28 kcal/kg/day, and

61% of patients had DPI < 1.0 g/kg/day [41]. A majority of patients had nutritional levels below KDOQI guideline standards [41]. These data support the importance of alternative means to promote nutritional status in maintenance of HD patients.

Increasing dialysis frequency or intensity through daily HD treatments or longer treatment times has been shown to increase appetite and protein/energy intake in uncontrolled studies [42, 43]. The mechanisms by which increased dialysis intensity may improve appetite are likely multifactorial, and may be related to clearance of uremic toxins [42, 43]. Daily HD has been associated with higher serum albumin levels [37]. Bossola et al. [37] discussed the potential decreased use of phosphate and potassium binders with increased dialysis. Both of these drugs can impair appetite [37]. Recommendations regarding the use of frequent dialysis modalities to modify nutritional status await the performance of properly designed randomized controlled trials.

Appetite stimulants such as megestrol acetate may be necessary to improve the nutritional status of HD patients [37]. Megestrol is a synthetic derivative of progesterone [37]. There are limited data regarding the use of this drug in HD patients [37]. A trial by Burrowes et al. [44] suggested an increase in fat mass and a decrease in fat-free mass after the use of the drug. However, a study by Boccanfuso et al. [45] suggested numerous side effects, including potential hypercoagulability states, adrenal insufficiency, and hypertension associated with administration of megestrol acetate to dialysis patients. Therefore, more data are needed before recommendations for use of megestrol acetate can be made in such populations.

Mineral, Vitamin, and Trace Elements in Hemodialysis Patients

Water soluble vitamins may be depleted in HD patients, as a result of decreased intake and clearance during dialysis [5]. Multivitamin supplementation is important in this patient population to ensure adequate supply of these essential nutrients. With the exception of vitamin D, the other fat soluble vitamins A, E, and K usually do not require additional supplementation [5].

Dietary sodium intake of HD patients should be limited to avoid volume overload and hemodynamic instability [5]. In addition, patients should strictly adhere to a low potassium diet of less than 2 g/day, to avoid the potential complications of hyperkalemia [5]. Phosphorus restriction to 600–800 mg/day is also essential to avoid the potential complications of hyperphosphatemia, including hypocalcemia, vascular calcification and calciphylaxis [5]. Phosphate binders taken with each meal are often necessary, since phosphate is not easily cleared by conventional HD.

Nutrition in Elderly Hemodialysis Patients

In the US, about half of ESRD patients are more than 65 years old [46]. Sustaining adequate nutritional intake in this growing patient population presents a unique challenge. Socioeconomic and psychological factors may play an increasing role in limiting the elderly's access to food. Protein intake in elderly HD patients should be 1.2 g/kg body weight/day, based on KDOQI practice guidelines [6]. The elderly have slightly decreased energy requirements. The recommended energy intake is 30 kcal/kg body weight/day [6]. Multivitamin supplementation is particularly important in the HD patient population. Attention should be paid to calcium and phosphorus metabolism in order to promote bone health.

Role of Dietary Counseling

Nutritional counseling is essential, given the high prevalence of malnutrition in this patient population. Counseling may lead to improved dietary compliance [6]. The dietician should develop a plan that addresses the preferences and previous diet history of each patient. A nutritional prescription is then formulated which becomes part of the overall patient care plan. The care plan involves patients, nurses, physicians, dieticians, social workers, and administrators as part of a multidisciplinary team [6]. Depending on the patient's overall medical condition, more frequent dietary counseling may be necessary, especially if the patient has undergone recent hospitalizations where increased catabolism may occur. For example, maintenance HD patients who are acutely ill should receive DPI of approximately 1.2 g/kg/day and energy intake of 35 kcal/kg/day [6].

Nutritional Status and Mortality in HD Patients

There is a link between measures of PEM and increased mortality in patients treated with maintenance HD. This section will review the most recent literature to support this association.

A recent subgroup analysis of the HEMO study supports an association between improved nutritional status indicators and reductions in mortality [47]. Dwyer et al. [47] evaluated 12 nutritional parameters measured in the HEMO study at baseline and calculated relative mortality risks at less than and greater than 6 months of follow-up. There was a higher relative risk of mortality in the low serum creatinine, low serum albumin, low serum cholesterol, low arm

circumference, low calf circumference, and low BMI groups [47]. The authors concluded from this study that nutritional parameters are associated with mortality in a 'time-dependent manner' [47].

Dwyer et al. [48] also evaluated the impact overall nutritional status has on the quality of life of patients enrolled in the HEMO study. Quality of life was assessed using the Medical Outcomes Study Short Form-36 (SF-36) [48]. This instrument has two summary measures, a physical component score and a mental component score [48]. They found associations between physical component scores and dietary energy intake, appetite level, serum albumin, and serum creatinine, after controlling for underlying comorbid and demographic variables [48].

Another analysis of the HEMO study done by Rocco et al. [49] evaluated whether the dose of dialysis and membrane flux affect nutritional parameters. Serum albumin, equilibrated PCR, and postdialysis weights were recorded every month [49]. Protein and energy intake, appetite assessment, upper arm circumference, and calf circumference were measured yearly [49]. During 3 years of follow-up, serum albumin and postdialysis weights were not significantly affected by the dialysis dose or membrane flux [49]. There was also no meaningful difference in the energy or protein intake in patients receiving the different interventions [49]. The authors concluded from this study that neither dose of dialysis nor membrane flux significantly impacts nutritional status of maintenance HD patients [49].

Abbott et al. [50] evaluated the association of BMI and survival in HD and PD patients through a retrospective cohort study of the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality Wave II Study. HD patients in the lowest quartile of BMI, defined as less than 21.9, had the lowest survival. Early in the study follow-up period, HD patients with BMI between 25 and 29.9 had the best survival [50]. After 2 years of observation, patients with BMI $>$ 29.9 had similar survival rates to those with BMI between 25 and 29.9 [50]. Survival over time was uniformly higher for patients with BMI $>$ 30 kg/m^2 [50]. However, in PD patients there was no statistically significant association between higher BMI and survival [50].

IDWG is another potential measure of nutritional status, and a number of studies have investigated whether increased IDWG was associated with decreased survival rates. Sezer et al. [51] evaluated this potential association by dividing HD patients into two groups: Group I had IDWG $<$ 3% of dry weight/day and Group II had IDWG $\geq$ 3% of dry weight per day. Nutritional status was evaluated through albumin, prealbumin, cholesterol, creatinine, predialysis potassium and phosphorus levels, nPCR, and anthropometry [51]. There was a statistically significant increase in mortality for Group I compared to Group II, with 74% 2 year survival in Group I compared to 92.6% survival in

Group II ($p < 0.03$) [51]. Group I patients with the lowest albumin levels had a 2 year survival rate of only 57.1% [51].

Another observational multicenter longitudinal study of 283 urban HD patients evaluated whether IDWG was associated with survival in patients treated with HD [52]. IDWG was associated with several nutritional variables, and with parameters associated with survival on HD [52]. In this study, patients were stratified according to the presence of diabetes. Higher IDWG was associated with mortality in the diabetic HD patients, but there was no association of IDWG and survival in patients without diabetes mellitus [52].

Prealbumin is another key measure of nutritional status. Chertow et al. [53] recently investigated the association between serum prealbumin levels and mortality in 7,815 HD patients. The investigators found that 'relative risk of death was inversely related to the serum prealbumin concentration' [53]. The relative risk of death was 2.4-fold greater for patients with a prealbumin level of less than 15 mg/dl [53]. They also found a link between relative risk of hospitalization from infection and decreased prealbumin levels [53]. The relative risk of hospitalization was 2.97 for patients with a prealbumin level less than 15 mg/dl [53].

While serum albumin is believed to be associated with survival in HD patients, we found in a longitudinal, observational study of HD patients that anthropometric measures did not predict survival [20]. AMA, AFA, BMI, and PIW were evaluated in a longitudinal multicenter study of urban HD patients [20]. Baseline values of these anthropometric measures were not associated with statistically significant increases in mortality risk after controlling for age, illness severity, serum albumin, and dialyzer type [20].

Psychosocial Variables, Nutritional Status, and Hemodialysis

Depression is associated with lassitude and anorexia, which might result in decreased DPI, PEM and a vicious cycle of provision of inadequate dialysis therapy [54–56]. One could therefore propose an interaction between psychosocial status and malnutrition in HD patients. Koo et al. [57] evaluated the potential relationship between depression and nutritional status in patients treated with HD. Specific measures used included the Beck Depression Inventory (BDI), DSM IV criteria for depression, serum albumin, SGA, and anthropometric measures [57]. There were negative correlations between the BDI and serum albumin levels, SGA, as well as a number of anthropometric measures [57]. This led the authors to conclude that depression was associated with nutritional status in patients on HD [57].

Another study evaluating links between depression and malnutrition in ESRD was performed by Kalender et al. [58]. In this study, the correlation

between depressive affect, C-reactive protein, ferritin, serum albumin, and hemoglobin was assessed [58]. Sixty-eight patients treated with HD, 47 patients treated with continuous ambulatory peritoneal dialysis and 26 patients with CKD participated [58]. Similar to the results of Koo et al., there was a negative correlation between serum albumin level and BDI score [58].

Taskapan et al. [59] found a link between depression and IDWG. Forty patients with chronic renal failure were enrolled in this study that evaluated depression, nutritional status using serum albumin, SGA, predialysis phosphorus, potassium levels and IDWG [59]. In patients found to have a depression disorder as assessed by the Hamilton Depression Rating Scale, the IDWG was significantly higher than those without depression [59].

If increased depressive affect and malnutrition are linked, then it is possible to conclude that interventions aimed at treating depression may help to improve nutritional status. Koo et al. [60] investigated this possibility by evaluating the effect antidepressant treatment had on the nutritional status of patients on HD. Sixty-two ESRD patients were recruited [60]. Thirty-four patients who fulfilled the DSM IV criteria for depression were enrolled in the treatment arm, which consisted of Paroxetine 10 mg daily and psychotherapy for 8 weeks [60]. Twenty-eight patients were placed in the placebo arm [60]. Those patients assigned to the treatment arm had a statistically significant decrease in the magnitude of their depression score, as measured by the Hamilton Depression Rating Scale [60]. They also had a statistically significant increase in the normalized PCR, serum albumin level, and predialysis blood urea nitrogen level, when compared to the control group [60]. This study provides further support for an association between depression and malnutrition, especially in the ESRD population [60].

We evaluated the link between psychosocial variables and nutritional status in a study which included 295 urban HD patients [61]. We found that serum albumin level was not related to the BDI score, the Illness Effects Questionnaire score (which measures perception of burden of illness), or the Multidimensional Scale of Perceived Social Support (which measures perception of social support) [61].

We found BDI scores were associated with higher phosphate levels, a mortality risk factor (unpublished data). Higher levels of perceived social support were associated with lower PCR (unpublished data). Lower AMA was associated with higher rates of shortening behavior, a form of noncompliance (unpublished data). All measures of behavioral compliance were associated with serum phosphate level in Spearman analyses, including shortening and skipping behaviors, total time compliance, and percent attendance rates (unpublished data). The higher the compliance, the lower was the level of depression, as measured by the BDI ([61] and unpublished data).

Summary

PEM is quite common in the ESRD population, approaching 80% prevalence in some estimates [1]. There are a number of causes of PEM in this patient population, including conditions directly related to the uremic state. Laboratory measures including albumin, prealbumin, and serum cholesterol, as well as anthropometric measures have been used to assess malnutrition in HD patients. The recommended DPI for HD patients is approximately 1.2 g/kg/day, and the recommended energy intake to maintain stable body composition is 35 kcal/kg/day [6]. Failure to achieve these nutritional goals may lead to PEM which has been linked to decreased survival in this patient population. In addition, several studies have shown a direct association between psychosocial factors, including depression, with nutritional status, particularly albumin concentration.

Conclusions

Nephrologists must be aware of the high prevalence of PEM in the HD population and institute appropriate screening techniques to ensure their patients are receiving adequate nutrition. Interventions such as oral nutritional supplements or IDPN may be necessary to improve nutritional status if conservative measures such as nutritional counseling and regular dietician follow-up fail to produce the changes needed to sustain health. In addition, given the potential link between psychological conditions, such as depression, with overall nutritional status, interventions designed to screen for and treat psychiatric disorders may lead to improvements in nutritional status, and therefore increased survival rates on HD. Further study is needed to evaluate the potential links between psychosocial factors, malnutrition, and survival.

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Paul L. Kimmel, MD, FACP, FASN
Division of Renal Diseases and Hypertension
Department of Medicine
George Washington University School of Medicine
2150 Pennsylvania Avenue NW
Washington, DC 20037 (USA)
Tel. +1 202 741 2283, Fax +1 202 741 2285, E-Mail pkimmel@mfa.gwu.edu

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Body Protein Index Based on Bioelectrical Impedance Analysis Is a Useful New Marker Assessing Nutritional Status: Applications to Patients with Chronic Renal Failure on Maintenance Dialysis

Toshiyuki Nakao, Yoshie Kanazawa, Yume Nagaoka, Hideaki Iwasawa, Asako Uchinaga, Hiroshi Matsumoto, Tomonari Okada, Maki Yoshino

Department of Nephrology and Dialysis, Tokyo Medical University, Tokyo, Japan

Abstract

Background: Evaluation and monitoring of nutritional status is a fundamental concept in providing nutritional care to patients with end-stage renal failure. There have been, however, few practically available indices assessing whole body protein stores of patients. **Methods:** We enrolled 448 end-stage renal disease patients, 394 on maintenance hemodialysis (HD) and 54 on continuous ambulatory peritoneal dialysis (PD) in this study. 83 Age- and sex-matched subjects (controls) whose creatinine clearance was more than 70 ml/min and urinary protein excretion was less than 1.0 g/day were also recruited for comparison. To assess whole body somatic protein stores, we devised the body protein index (BPI). The volume of body protein mass was measured by multifrequency bioelectrical impedance analysis and then BPI was calculated as body protein mass (kg) divided by height in meters (m^2). Based on BPI, we defined the nutritional status of the patients as normal if the value was within −10% of the mean value of control subjects, −10 to −14% as mild malnutrition, −15 to −19% as moderate malnutrition, and <−20% as severe malnutrition. **Results:** The required time for measurement was 5.2 ± 1.3 min and coefficient of variation of measurements was 0.8 ± 0.2%. Among men the mean BPI in both HD and PD patients was significantly lower than those of control subjects (4.25 ± 0.37, 4.38 ± 0.34 vs. 4.72 ± 0.37 kg/m^2, $p < 0.001$). In women, BPI was significantly lower in HD patients than in control subjects (3.65 ± 0.34 vs. 4.00 ± 0.34 kg/m^2, $p = 0.033$), whereas only a non-significant lower tendency was found in PD patients (3.83 ± 0.39 kg/m^2, $p = 0.067$). There were no significant differences in BPI values between diabetic and non-diabetic subjects, both in men (4.26 ± 0.41 vs. 4.25 ± 0.36 kg/m^2) and women (3.69 ± 0.36 vs. 3.65 ± 0.34 kg/m^2). Based on BPI nutritional categories, 113 (28.7%) of all HD patients were classified as having mild malnutrition, 57 (14.5%) as having moderate malnutrition, 40 (10.1%) as having

severe malnutrition, and 184 (46.7%) were classified as normal. The patients of longer dialysis history groups showed a tendency of lower BPI compared to those of shorter dialysis history groups ($p < 0.05$), although the ages of the patients of the two groups did not significantly differ. No correlations were found between BPI and serum albumin or transferrin concentrations. Only weak correlations were found with albumin in male and transferrin in female HD patients. **Conclusion:** BPI calculated from measurement of multifrequency bioelectrical impedance analysis could evaluate whole body somatic protein stores, and is a potentially useful new marker assessing nutritional status in patients with chronic renal failure. Decreased body somatic protein stores, mainly due to muscle wasting, was prevalent in end-stage renal failure patients on maintenance dialysis.

Protein-energy malnutrition (PEM) is one of the most prevalent complications in patients with end-stage renal disease (ESRD), and is a strong predictor of poor clinical outcomes, especially among patients commencing maintenance dialysis [1–4]. The pathogenesis of PEM among these patients is multifactorial. Inadequate nutrient intake, dialysis-related nutrient losses, alterations in protein metabolism, acidosis and inflammation are considered to be the major causes of PEM [5, 6]. In this context, assessment and monitoring of nutritional status are crucial to prevent, diagnose and treat malnutrition.

There are a variety of parameters and methods to assess nutritional status of ESRD patients. However, since no definitive single method has been established for the assessment of nutritional status and responses to nutritional treatment, a number of proposed methods are currently being used concomitantly and then evaluated collectively to ascertain the nutritional status of the patients.

Examination of dietary nutrient intake is important for the evaluation of nutrition. Subjective global assessment is a simple assessment method that draws on the experience of a clinician to make an overall assessment of nutritional status in a standardized way [7]. However, a major essential element for judging nutritional status would be assessment of body composition, such as protein mass. There are two major categories in the assessment of protein mass, visceral protein stores and somatic protein stores. Concentrations of circulating proteins are markers that estimate the size of the visceral protein stores in the body [8]. The most readily available and commonly used laboratory tests for circulating protein concentrations are serum albumin, transferrin and prealbumin. Although these serum protein concentrations have been used extensively as markers of nutritional status, they can be influenced by non-nutritional factors, such as infection or inflammation, hydration status, and peritoneal or urinary albumin losses [9–11].

Evaluation of somatic protein stores involves determining body composition by measuring the individual component of water, fat, bone, muscle and visceral organs. Muscle mass comprises the majority of somatic protein stores.

There are many techniques available to determine body composition, involving anthropometry, dual energy X-ray absorptiometry, bioelectrical impedance analysis (BIA), prompt neutron activation analysis and hydrodensitometry. Among them, BIA is now widely used for the evaluation of body composition in various fields, since it is relatively inexpensive to perform, non-invasive, requires minimal operator training, and provides data that correlates well with several aspects of body composition [12–16].

In the present study, we newly devised a body protein index (BPI) based on the measurement of multifrequency BIA and evaluated whole body somatic protein stores of maintenance hemodialysis (HD) patients.

Patients and Methods

Patients

We studied 448 consecutive ESRD patients, 394 on maintenance HD and 54 on continuous ambulatory peritoneal dialysis (PD). HD patients consisted of 282 men and 112 women, who were being treated three times a week in four centers in Japan. Their mean age was 58.5 ± 11.9 years old, mean dialysis history was 9.1 ± 7.3 years and cause of ESRF was diabetic nephropathy in 17, chronic glomerulonephritis in 16, nephrosclerosis in 4, polycystic kidney in 2 and chronic interstitial nephritis in 1. PD patients consisted of 33 men and 21 women, who were being treated in the Department of Dialysis, Tokyo Medical University Hospital. Their mean age was 51.9 ± 11.0 years old, mean history on PD was 2.9 ± 2.3 years and diseases causing renal failure were chronic glomerulonephritis in 42 and diabetic nephropathy in 12.

Controls were 88 subjects, 45 men and 43 women, mean age 51.6 ± 15.7 years old, who visited the Department of Nephrology, Tokyo Medical University Hospital, and whose creatinine clearance was more than 70 ml/min and urinary protein excretion was <1.0 g/day. No control subject had diabetes mellitus or definite diseases other than insignificant proteinuria or microscopic hematuria.

Measurement of Multifrequency BIA

The body composition was assessed by multifrequency BIA (in Body 3.0, Biospace Co. Ltd., Seoul, Korea). Bioimpedance measurement was conducted at 5, 50, 250 and 500 kHz. As the human body can be modeled as a cylindrical conductor with its length proportional to the subject's height, BIA measures the impedance by passing a low alternating current through the body. Based on the impedance measured, the volume of body water, fat and protein mass are calculated using formulae [13].

The measurements for HD patients were performed 10 min after finishing HD treatment by which excessive body fluids were removed, and the measurements for PD patients were performed after peritoneal dialysate drained completely. We ascertained the patients had no edema before all the measurements.

Then, BPI was calculated as body protein mass (kg) divided by the patients' height in meters (m^2) in the same manner as the calculation of body mass index (BMI), which is body weight (kg) divided by the square of the height in meters (m^2). Based on BPI, we defined

categories of nutritional status of the patients as normal if the value was within −10% of the mean value of control subjects, −10 to −14% as mild malnutrition, −15 to −19% as moderate malnutrition, and <−20% as severe malnutrition.

Statistical Analyses

All data were expressed as means ± SD. Mean group values were compared by ANOVA. Comparisons between groups were made using the χ^2 test and Student's t-test. Relationships between paired parameters were analyzed by Pearson product moment correlation coefficient. A p-value <0.05 was considered to indicate a statistically significant difference.

Results

The required time for measurement was 5.2 ± 1.3 min and the coefficient of variation of measurements was 0.8 ± 0.2%.

In HD patients, the mean BPI of men was 4.25 ± 0.37 kg/m^2 and that of women was 3.65 ± 0.34 kg/m^2. In PD patients, mean BPI of men was 4.38 ± 0.34 kg/m^2 and that of women was 3.83 ± 0.39 kg/m^2. In control subjects, the mean BPI of men was 4.72 ± 0.37 kg/m^2 and that of women was 4.00 ± 0.39 kg/m^2 (table 1). The mean BPI of men was significantly higher than those of women in all groups ($p < 0.001$). There were no significant differences in BPI values between diabetic and non-diabetic subjects either in men (4.26 ± 0.41 vs. 4.25 ± 0.36) or women (3.69 ± 0.36 vs. 3.65 ± 0.34). Among men, the mean BPI in both HD patients and PD patients was significantly lower than those of control subjects ($p < 0.001$). Among women it was significantly lower in HD patients than in control subjects ($p = 0.033$), whereas only a non-significantly lower value in BPI was found in PD patients compared to control subjects ($p = 0.067$). In comparing BPI between HD and PD patients, female PD patients had significantly higher BPI than female HD patients ($p = 0.033$), and male PD patients had a non-significantly higher BPI than male HD patients ($p = 0.054$).

Among all HD patients, 113 (28.7%) patients had mild malnutrition, 57 (14.5%) moderate malnutrition, 40 (10.1%) severe malnutrition, and 184 (46.7%) were considered normal, based on the BPI nutritional categories (fig. 1). The patients of longer dialysis history groups showed a tendency of lower BPI compared to those of shorter dialysis history groups, though ages of the patients were not significantly different in either group (fig. 2). Among the PD patients, 10 (18.5%) were classified as having mild malnutrition, 4 (7.4%) as moderate malnutrition, 3 (5.4%) as severe malnutrition, and 37 (68.5%) as normal. The frequency of malnutrition was significantly lower in PD patients than in HD patients ($p = 0.003$). However, among the patients receiving dialysis for less

Table 1. BPI in control subjects, HD patients and continuous ambulatory PD patients

Group	Gender	N	BPI (kg/m^2)
Control subjects	Men	45	4.72 ± 0.37
	Women	43	4.00 ± 0.34^{a}
HD patients	Men	282	$4.25 \pm 0.37^{b,c}$
	Women	112	$3.65 \pm 0.34^{a,d}$
PD patients	Men	45	4.38 ± 0.34^{b}
	Women	21	$3.83 \pm 0.39^{a,e}$

Data reported as mean ± SD.

$^{a}p < 0.0001$ vs. men in each group; $^{b}p < 0.0001$ vs. control men; $^{c}p < 0.0001$ vs. control women; $^{d}p = 0.033$ vs. PD women; $^{e}p = 0.067$ vs. control women.

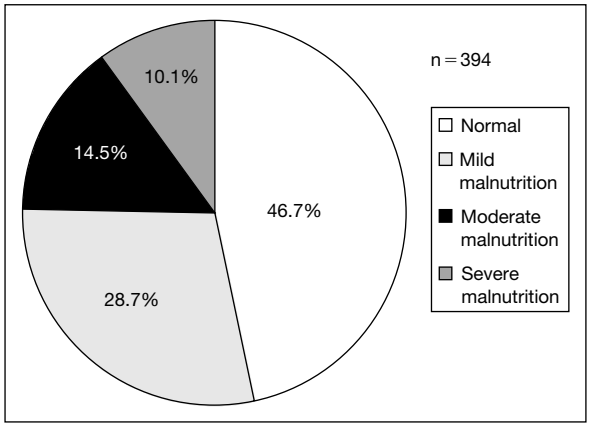

Fig. 1. Frequency of malnutrition in maintenance HD patients.

than 5 years, no significant differences were found in the frequency of malnutrition between HD and PD patients (table 2).

Correlations of BPI with other nutritional parameters in each group of patients are shown in table 3. No correlations were found between the BPI and serum albumin and transferrin concentrations, except for weak correlations with

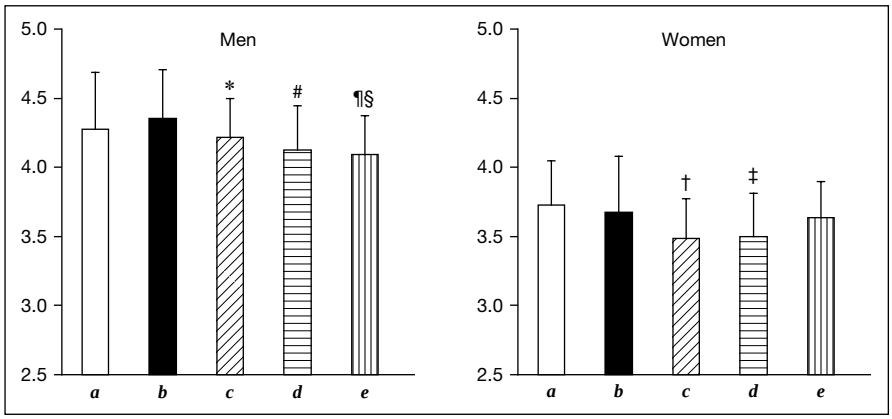

Fig. 2. Comparisons of BPI among HD patients treated for various durations. ***a*** <5 years, ***b*** 5–9 years, ***c*** 10–14 years, ***d*** 15–19 years, ***e*** over 20 years. * p = 0.029 vs. ***b***, # p = 0.013 vs. ***b***, ¶p = 0.014 vs. ***a***, §p = 0.001 vs. ***a***, †p=0.009 vs. ***a***, ‡p=0.043 vs. ***a***.

Table 2. Comparisons of the frequency of malnutrition diagnosed by BPI categories between HD patients and continuous ambulatory PD patients whose dialysis history was less than 5 years

Nutritional categories	HD patients (n = 167)	PD patients (n = 43)	Significance
Normal	97 (58.1%)	28 (65.1%)	NS
Mild malnutrition	36 (21.5%)	9 (20.9%)	NS
Moderate malnutrition	17 (10.2%)	3 (7.0%)	NS
Severe malnutrition	17 (10.2%)	3 (7.0%)	NS

Table 3. Correlation of BPI with other nutritional parameters

Parameters	HD-Men		HD-Women		PD-Men		PD-Women	
	r	p	r	p	r	p	r	p
Serum albumin	0.139	0.020	0.181	0.060	0.295	0.102	0.037	0.876
Serum transferrin	0.041	0.497	0.195	0.042	0.349	0.050	0.091	0.700
BMI	0.778	<0.0001	0.785	<0.0001	0.819	<0.0001	0.886	<0.0001

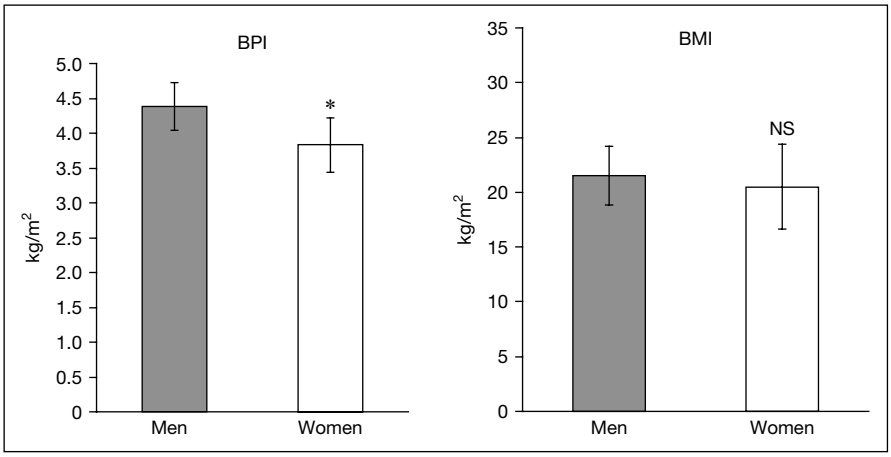

Fig. 3. Differences of BPI and BMI between men and women on continuous PD. * $p < 0.0001$ vs. men.

albumin in male HD patients and transferrin in female HD patients. There were strong relationships between the BPI and BMI in each patient group. Among PD patients, though the BPI was significantly different between men and women (4.38 ± 0.34 vs. $3.83 \pm 0.39\,kg/m^2$, $p < 0.0001$), the BMI was not significantly different between genders (21.5 ± 0.34 vs. $20.9 \pm 3.9\,kg/m^2$, $p = 0.465$) (fig. 3).

Discussion

Assessment of nutritional status in patients with ESRD is important because of its clear association with prognosis. Measurement of the stores of somatic protein is an essential component of the evaluation of nutritional status. To measure somatic protein stores in clinical practice, both accuracy and simplicity are needed. In this study, to assess whole body somatic protein stores, we devised the BPI based on multifrequency BIA and established normal values and categorized the malnutritional range. We then applied it to patients with chronic renal failure on maintenance dialysis.

Body composition parameters obtained by multifrequency BIA were reported to show good correlation with those by dual energy X-ray absorptiometry [17, 18]. It was reported that the phase angle (which is the difference between voltage and current and is determined from resistance and reactance by BIA) showed excellent correlation with arm muscle circumference measured

by the conventional anthropometric method [19]. In the present study, BIA measurements consumed only several minutes and required minimal operator training. Thus, assessment of somatic protein stores by multifrequency BIA appeared to be a convenient and accurate method. However, in the presence of overhydration or dehydration, potential errors could occur in the estimation of protein mass by BIA [20]. Thus, it is extremely important that dialysis patients are at their dry weight before a BIA measurement.

Many studies have documented that PEM is one of the most prevalent complications in patients with ESRD and is strongly associated with poor prognosis. A recent survey of 7,719 US adult hemodialysis patients enrolled in the international Dialysis Outcomes and Practice Pattern Study (DOPPS), in which the mean dialysis history was 2.1 $\pm$ 3.6 years, reported that 7.6% of the patients were found to have moderate malnutrition and 11.0% severe malnutrition by Subjective Global Assessment [1]. In the present results, the mean BPI of men and women among HD and PD patients were lower than those of control subjects and 53.3% of HD and 31.5% of PD patients were found to have malnutrition. Among HD patients, 14.5% was classified as moderate malnutrition, and 10.1% as severe malnutrition according to the nutrition category of the BPI. Present data regarding nutritional status assessed by the BPI was generally consistent with previous reports using other parameters [1, 21], and the BPI measurement could be considered a more simple method to evaluate somatic protein stores compared to other parameters.

Length of time on dialysis is reported to influence nutritional status in HD patients. Chertow et al. [22] showed body composition parameters by BIA tended to be lower after the second year of dialysis. Chazot et al. [23] reported that body weight tended to lower after 15 years of HD, and BMI, arm muscle circumference and arm muscle area were significantly lower in long-term HD patients. Our data also suggested the patients of longer dialysis history groups showed a tendency of lower BPI compared to those of shorter dialysis history groups. Several factors such as intercurrent illness, low energy intake and exposure to inflammatory mediators during extended dialysis history may contribute to body protein wasting [24, 25].

PD patients in this study tended to have a significantly higher BPI than HD patients. However, when we compared the BPI of HD and PD patients after matching dialysis history, no significant differences were found in the frequency of malnutrition. Compared to HD patients, PD patients may have an advantage in maintaining nutritional status because they are free from dialysis procedure-induced catabolic effects caused by inflammatory mediators due to extracorporeal blood circulation. However, it is uncertain from our data whether PD patients on lengthy dialysis can remain in better nutritional status than HD patients.

Visceral proteins such as serum albumin and transferrin are commonly used as nutritional markers. However, it is possible that their serum concentrations are affected by factors other than dietary protein and energy intake. For example, their serum concentrations would be lowered by dilution due to volume expansion, which is usually present before hemodialysis, and also by a decline in production due to acute phase response to underlying inflammatory processes [26, 27]. For this reason, discrepancies in markers between visceral protein stores and somatic protein stores have been recognized [23]. In the present study, no significant correlations were seen between BPI and serum albumin and transferrin in each group of dialysis patients. Slight but non-significant correlation was seen in albumin in men treated with HD and in transferrin in women treated with HD and men treated with PD. Though the reasons for the discrepancies are not apparent, one concern is that the amino acid metabolism may act to conserve plasma protein levels over somatic protein stores, breaking down muscle proteins to amino acids and reutilizing them for plasma protein synthesis [28].

BMI is the most easily available marker of lean body mass, even in the population of dialysis patients [29]. In our present study, the BPI correlated well with the BMI in all groups of patients. However, although the BMI of men and women was similar, the difference in BPI between men and women was significant in PD patients. Under the condition of normal body fluid volume, changes in the BMI mainly express the changes in sum of body fat and muscle mass, whereas changes in the BPI directly express muscle protein mass. Thus, a lower BPI in women than men with an equal BMI could indicate that fat mass is greater and muscle mass is smaller in women than men. Thus, the BPI could be considered a parameter that evaluates body protein stores, including mainly muscle mass, directly.

Conclusion

In conclusion, the BPI calculated from measurement of multifrequency BIA could evaluate whole body somatic protein stores, and is potentially a useful new marker assessing nutritional status in patients with chronic renal failure. Decreased body somatic protein stores, mainly due to muscle wasting, were prevalent in ESRF patients on maintenance dialysis.

Acknowledgments

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Toshiyuki Nakao
Department of Nephrology, Tokyo Medical University
6-7-1 Nishishinjuku Shinjuku ward
Tokyo 160-0023 (Japan)
Tel. +81 3 3342 6111, Fax. +81 3 3342 5027, E-Mail t-nakao@tokyo-med.ac.jp

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Nutritional Assessment by a New Method for Patients with Renal Disease

Yoshihiko Kanno[a], *Satoshi Sasaki*[b], *Hiromichi Suzuki*[a]

[a]Department of Nephrology, Saitama Medical University, Saitama,
and [b]National Institute of Health and Nutrition, Tokyo, Japan

Abstract

Evaluation of the amount of food intake is very important in the control of diet therapy. Previously 3-day food records have been used to examine the food intake of hemodialysis (HD) patients. However, these records are problematic with regard to calculation errors and food intake is not stable as the range is almost 3-fold. Especially in HD patients, food intake is different on HD and non-HD days. Thus, the food intake of HD patients must be studied over at least a week. A diet history questionnaire (DHQ) has recently been developed and may be useful for HD patients with unstable food intakes, and to examine or compare the mass examination. Our data, evaluated by DHQ, showed the shortage of many nutrients recommended for HD patients in the guidelines of the Japanese Society of Nephrology, and showed that grains are just as important as meat, fish, and milk products as a source of protein in Japanese patients.

It is known from experience in nephrology that the interval between the introduction of a restricted protein diet to the start of dialysis can be extended in patients with chronic renal failure before beginning dialysis therapy. Dietary counseling for a low protein diet for patients with end-stage renal failure has been established [1], but since it does not constitute a treatment for renal failure but only extends the time before the onset of uremia, it has been argued that dietary restrictions do not necessarily contribute to a longer life expectancy after starting dialysis [2]. Diets for dialysis patients might be decided, not on obtaining a prognosis for the longest period of activity, but rather on preventing abnormal lab test values from turning up in regular monthly blood tests. Dietary guidelines are empirically designed based on patients receiving dialysis therapy who are on low protein diets and on the efficiency of dialysis.

The number of patients who require dialysis therapy is rising steadily, with approximately 248,000 patients in Japan at the end of 2004. When dialysis therapy was first introduced in Japan in the middle 1960s, life expectancy was extended by only a few months. Now, however, with the exception of diabetic renal disease, patients can have an extended life expectancy of 10 years or more after starting dialysis [3]. While some patients may not strictly adhere to dietary restrictions in practice, many patients live for long periods at a high level of activity. Guidelines for dietary restrictions should be adjusted, taking into account individual lifestyles, pathophysiology, stage of disease, complications and dietary habits.

It is extremely difficult to perform epidemiological studies on diets, so much so in Japan because the field of nutritional epidemiology is still immature. In contrast, at Harvard University's School of Public Health, Willet et al. [4] in the Department of Nutrition and Epidemiology have established a new academic field, not just by simply applying epidemiological methods to traditional nutrition, but incorporating methods from psychiatry and psychology.

The very first step in the process is to precisely determine the patient's dietary intake. However, the traditional method of recording dietary intake used in dietary counseling up until now is inaccurate, for it relies on the patient's memory and the skill of the dietician [5]. It also has the problem of evaluating the whole from just a few days' data [6].

In a study which recorded dietary intake for 30 consecutive days, patients were found to show variations in protein and salt intake of double or more within the month (fig. 1). Figure 1 shows the changes in protein and phosphate intake in diets recorded for 30 days. The patient in figure 1a shows few changes, with a monthly average protein intake of 43 g/day and phosphate intake of 599 mg/day, with a variance of about 10%. The patient in figure 1b is of the same gender and approximately the same age, but shows greater variation. The average daily protein intake is 57 g, but the range went from 30 g (smallest intake) to 80 g (largest), representing an almost 3-fold change. To comprehend precise dietary intake in cases like this using the recording method is an extremely difficult task.

As can be seen in the graph of a 3-day recording of the type generally done in Japan (fig. 1b), the ten short lines show the calculated average value over 3 days, with a large difference between the smallest of 48 g and the largest of 70 g. In other words, depending on which 3 days are used for the recording of dietary intake, the evaluation of dietary intake can be entirely different. Similarly, averages over 7 days can be seen in the graph in the dotted line (4 longer lines). The averages are 67, 57, 56, and 52 g and since there is little variance over a 7-day period of recording, it is possible to get a reasonably accurate estimate of intake. However, aside from patients with high motivation, it is extremely difficult to record 7 days of food intake.

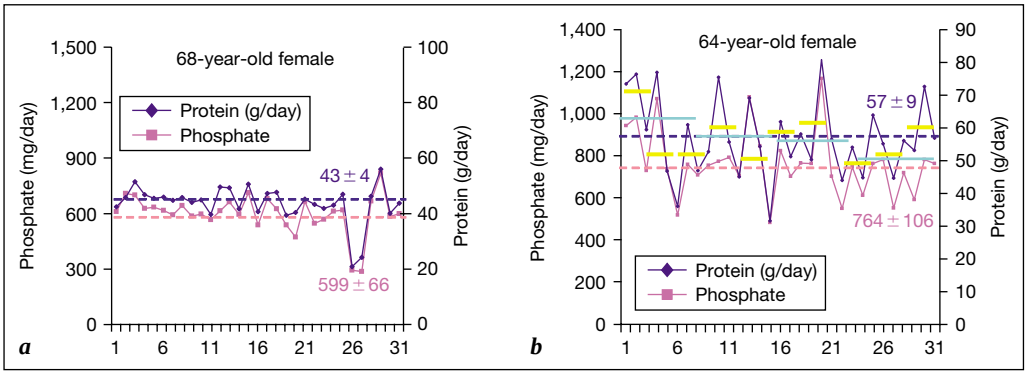

Fig. 1. Changes in protein and phosphorus intake in dialysis patients. ***a*** 68-year-old female patient receiving hemodialysis. ***b*** 64-year-old female patient receiving hemodialysis. Dashed lines express the average amount of daily intake of protein and phosphate. In (***b***), ten horizontal shorter lines (yellow) express 3 days average amount of protein intake, and four longer lines (blue) express 7 days average amount of protein intake.

Many methods have been tried to solve the problem, and Sasaki et al. [7] developed the self-administered Diet History Questionnaire (DHQ). The details of the DHQ have been reported, but besides simply learning about food intake, it may make it possible to quantify dietary habits of the participant and is a promising new tool for evaluating diet. Since dietary intake is an evaluation of the amount taken into the body, there is little chance that it will affect the calculations of DHQ in people with impaired renal function. However, since patients with renal disorders are on special diets, DHQ was studied to determine if it provided sufficiently accurate evaluations in cases of impaired renal function.

The results of 30-day food records from patients undergoing HD at Saitama Medical University Hospital were analyzed. The calculated DHQ value was compared with the average intake as measured by food records and expressed as a percentage for each patient in row 3 of table 1. DHQ values either underestimated or overestimated actual intake values, but no particular pattern was found by case or by item. While there were differences between calculated values and measured values, it was not possible to determine the closest value to actual intake, because it was not possible to determine the most accurate method.

Protein intake was compared with the two methods above, and in addition a third index, the calculated normalized protein catabolic rate (nPCR) from laboratory tests, was included. Table 2 shows protein intake as calculated by the three methods in four cases. The values obtained by food recording and nPCR

Table 1. The difference between the amount of daily intake of energy, protein, sodium, potassium, phosphate and vitamin B1 calculated using 30 straight day's diet record and DHQ

Patient		Energy (kcal/day)	Protein (g/day)	Sodium (mg/day)	Potassium (mg/day)	Phosphate (mg/day)	Vitamin B1 (mg/day)
1	DHQ	2,497	96	2,418	5,092	1,271	1.62
	30 day	1,778	43.7	1,384	1,372	599	0.42
	DHQ/30 day, %	140	220	175	371	212	386
2	DHQ	1,467	53.9	10,950	2,936	851	0.95
	30 day	1,568	57	2,906	2,089	764	0.71
	DHQ/30 day, %	94	95	377	141	111	134
3	DHQ	2,346	66.1	4,174	2,667	889	1.11
	30 day	1,685	52.1	2,797	1,768	708	0.7
	DHQ/30 day, %	139	127	149	151	126	159
4	DHQ	1,316	45.5	1,812	1,451	625	0.75
	30 day	1,545	60.4	3,554	1,927	829	0.78
	DHQ/30 day, %	85	75	51	75	75	96
5	DHQ	1,065	34.3	1,404	771	508	0.41
	30 day	1,349	53.6	3,034	1,991	758	0.58
	DHQ/30 day, %	79	64	46	39	67	71
6	DHQ	827	31.3	1,484	1,469	414	0.49
	30 day	1,341	50.7	3,032	1,936	744	0.64
	DHQ/30 day, %	62	62	49	76	56	77
7	DHQ	1,520	37	1,898	929	495	0.47
	30 day	2,066	52	2,953	1,485	746	0.75
	DHQ/30 day, %	74	71	64	63	66	63

The third row in each patient expresses the ratio of the intake amount calculated by DHQ/30 day's diet record.

are similar in cases 1 and 4, but with a big difference for all. This disparity was not seen in cases 2 and 3, in which the three methods all produced similar values for food recording. The columns on the right show a simple clinical profile of each case, but no particular pattern was seen for differences in dietary measures in terms of age, gender, or dialysis history. In other words, it can be expected that some cases are better measured by food recording and others by DHQ, but the evaluation would be better made by some other method than being determined by the physician actually in charge of each patient. The discrepancy in the calculated data between food recording and DHQ was investigated using normal subjects. Differences of more than 20% were seen in calcium and cholesterol, while the other nutrients showed differences of less

Table 2. The comparison of calculated daily protein intake (g/day) by three methods

Patient	DHQ	30 days	nPCR	Age	Sex	Urine (ml)	HD history (years)
1	96	43.7 219.7%	39.6 242.4%	68	F	800	1
2	54	57 94.7%	40.9 132.0%	64	F	800	3
3	45	40 112.5%	42.6 105.6%	64	M	0	13
4	22	47.5 46.3%	54.7 40.2%	55	M	0	6

DHQ: protein intake calculated by Diet History Questionnaire. 30 days: protein intake calculated by diet records for 30 straight days. nPCR: protein intake calculated by normalized protein catabolic rate. The second row in each patient expresses the rate of DHQ/30 days and DHQ/nPCR, respectively.

than 10% [7]. Although it is suggested that DHQ could be useful to examine the food intake in normal subjects from this investigation, only 3 days of food intake were recorded at the same time when DHQ was taken in this study. Concerning the dialysis patient, the discrepancies among the three methods were certainly not small, but whether these differences were due to the specific cookery and contents could not be determined. In our trial, there was a group of patients whose food intake was very unstable, and the 3-day recording did not exactly represent the real food intake because the 3 days might have involved 1 or 2 days of dialysis. Thus, DHQ could be objectively useful to evaluate the food intake of dialysis patients, especially in order to observe the changes in the long-term, or to compare the large patient group. The conditions of food intake were investigated in patients undergoing HD using DHQ. The participants were 89 patients on HD at Saitama Medical University Hospital and affiliated facilities. For comparing large numbers of cases like this, in order to minimize errors by dieticians during analysis, a standardized food questionnaire was utilized using DHQ. Dieticians and other medical staff provided assistance to minimize errors that occur when patients filled in the food questionnaires.

Table 3 shows the clinical profile of participating patients according to the time span for which they received HD treatment. The patients were divided into three groups. The short-group consisted of 23 patients who received HD less than 5 years. The intermediate-group included 25 patients treated for 5–10 years, and the long-group had 41 patients who received HD for more than 10 years.

Table 3. The clinical profiles of the patients receiving hemodialysis

	History of HD	Number of patients (M/F)	Age	BMI
Short-group (0–5 years)	3 ± 2	23 (14/9)	58 ± 13	20.0 ± 2.6
Intermediate-group (5–10 years)	8 ± 2	25 (15/10)	60 ± 14	21.3 ± 3.4
Long-group (>10 years)	16 ± 5	41 (26/15)	59 ± 13	19.7 ± 4.5

There is no significant difference among the three groups in age, male/female ratio, and BMI.

Table 4. The clinical data of the patients

	Short-group	Intermediate-group	Long-group
BUN (mg/dl)	72.3 ± 15.0	70.1 ± 12.4	77.5 ± 15.2
Creatinine (mg/dl)	9.9 ± 3.1*	12.3 ± 3.0	12.6 ± 2.5
Uric Acid (mg/dl)	7.8 ± 1.4	7.9 ± 1.2	7.8 ± 1.4
Total Protein (g/dl)	6.9 ± 0.5	6.8 ± 0.5	6.8 ± 0.5
Albumin (g/dl)	3.6 ± 0.4	3.9 ± 0.4	3.9 ± 0.4
Hemoglobin (g/dl)	9.8 ± 0.8	9.5 ± 1.7	9.9 ± 1.2
Fe (μg/dl)	46 ± 11*	72 ± 20	77 ± 29
Total Cholesterol (mg/dl)	178 ± 39	163 ± 32	146 ± 35*
Triglyceride (mg/dl)	137 ± 91	132 ± 123	131 ± 127
HDL cholesterol (mg/dl)	75 ± 12*	42 ± 14	38 ± 13
Sodium (mEq/l)	139 ± 4	138 ± 4	139 ± 3
Potassium (mEq/l)	5.3 ± 0.7	5.0 ± 0.7	5.1 ± 0.7
Calcium (mg/dl)	8.8 ± 0.7*	9.9 ± 0.8	9.7 ± 0.8
Inorganic phosphate (mg/dl)	5.9 ± 1.8	5.2 ± 1.2*	5.7 ± 1.2

*$p < 0.05$ vs. other two groups.

There was no significant difference among the three groups in age, male/female ratio, and BMI. Table 4 shows the clinical data measured at the beginning of the first dialysis session in the week (2 days interval). Figure 2 shows sufficiency rates of the amount of intake compared with the minimum daily requirements from the guidelines of the Japanese Society of Nephrology. Distinct deficiencies in energy and protein intake were observed in the short and intermediate

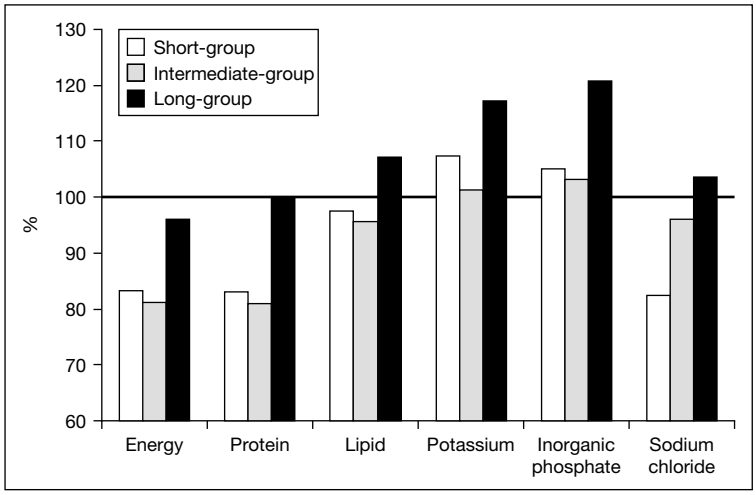

Fig. 2. Sufficiency rate of the amount of intake compared with the minimum daily requirements from the guidelines of the Japanese Society of Nephrology.

groups. On the other hand, the patients in the long-group did not show any deficiencies in protein, lipid, potassium, inorganic phosphate, and sodium chloride. From these results, it is suggested that it took a long time for the patients receiving HD to change their food habits. Moreover, the patients in the long-group showed over intake of potassium and inorganic phosphate. However, we could not conclude whether or not this over consumption was related to a longer prognosis. Further study will be needed to answer this question. Figure 3 shows percentages of each nutrient based on the origin by category of the list of food exchange determined by the Japanese Society of Nephrology. This data was very interesting. The proportion of grains (classified in category 1 of the list of food exchange), as a source of protein and phosphorus intake was higher than the proportion of meat, fish, and dairy products (category 4 of the list of food exchange) in all patients receiving HD in our research. It constituted almost 50% of protein intake and inorganic phosphate.

By adjusting intake of a certain category, an idea of what foods to be adjusted can be obtained. The results of our study showed that patients undergoing either HD or peritoneal dialysis [8] tended to have lower intake of nutrients than that recommended by the guidelines. No differences were found based on age or dialysis history, but in general, it was observed that the longer a patient was on dialysis the lower the food intake [9]. Increasing age is also thought to be a factor.

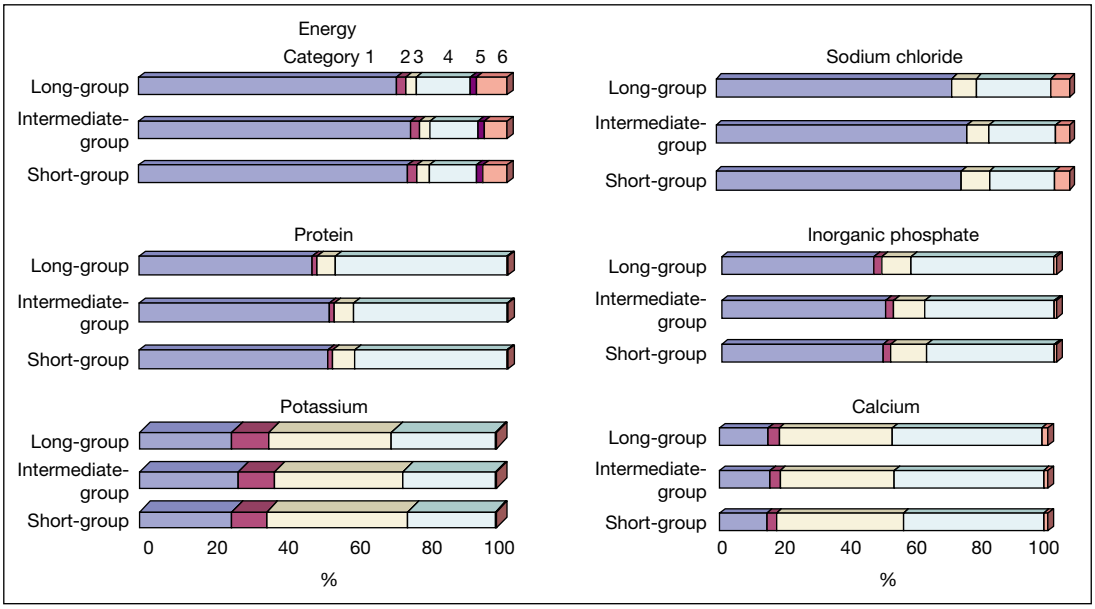

Fig. 3. The proportion of the categories in the amount of intake of the nutrients. Categories were decided by the Japanese Society of Nephrology. Category 1: Boiled rice, bread, noodles, rice, oatmeal. Category 2: Fruits, seeds, potato, a sweet potato, a taro, and potato. Category 3: Green vegetables, sweet corn, Japanese pumpkin. Category 4: Egg, meat, fish, beans, milk and its products, pork loin, ground chicken, hen, beef sirloin, beef tongue, pork liver, an egg, milk, cheese, cotton tofu, deep-fried tofu. Category 5: Sugar, starch, jam, juice. Category 6: Oil and fats.

Many studies have pointed out that patients on dialysis do not have sufficient nutritional intake [10–13]. There are differences by region and patients studied, but Morais et al. suggested that over 90% of patients do not satisfy minimal daily requirements. Poor nutrition [14] and decreased appetite [15] are factors in unfavorable outcomes for patients on dialysis, and quality of life decreases greatly due to dietary restrictions. It has been reported that overall quality of life decreases in Japanese patients who have poor appetite [16]. Thus, it is of great importance to have a good grasp of dietary intake to properly manage the long-term prognosis of patients on dialysis.

Quality of life was investigated by measuring SF 36 in some of the patients on HD in this trial and it was found that patients who had high scores for psychological health tended to have good appetites and significantly less physical pain (data not shown). SF 36 scores can be used as a prognostic tool for mortality

[17] and the use of such scoring to monitor the overall condition of patients on dialysis is of great importance. Thus, the importance of dieticians in a team approach to medicine is growing [18]. However, because of the less optimal conditions under which they work, the potential contribution of the dieticians has not been realized [19].

Many believe that supplements are needed to make up for insufficient intake [20, 21]. Many studies by Espinoza and others have shown that various supplements are effective in improving nutritional intake [22–26]. However, some studies show no effect in terms of supplementing caloric intake [27–29]. This, plus economic issues show that supplements are not useful for all patients. Furthermore, while the data show an increase in measured values, some believe that this does not reflect an improvement in nutritional status [30, 31]. There have been reports on the usefulness of supplements such as protein and amino acids in Japan [32, 33], but in order to expect an improvement in life expectancy, rather than just a temporary rise in measured values, it may be necessary to provide large amounts of supplements.

Aguilera et al. maintain that the eating behavior of uremic patients, particularly poor appetite, is affected by the disease itself, and is complicated by various other factors such as the efficacy of treatment, complications, as well as the culture and society to which the patient belongs [34, 35]. This means that it is difficult to predict the dietary habits of patients on dialysis, but our study using DHQ was able to analogize the characteristics of dietary habits of dialysis patients in Japan. As shown in figure 3, the proportion of grains, which are a source of protein and phosphorus, was very high. In general, meat, fish and dairy products are common protein sources, and patients with hyperphosphoremia are advised to restrict their intake of such products. However, if grains as a protein source are equivalent to that of meat and fish, such counseling will not be clearly effective. The Japanese, in particular, have rice as their main staple, with protein intake from rice being about 50% as shown in figure 3. This is an amount that cannot be ignored and should be included as part of their nutritional counseling [36].

By focusing our attention on food sources, we have obtained effective results by analyzing rice and using types with a small protein component and low protein absorption. There are large individual differences in terms of intake and absorption, which makes further studies necessary.

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Yoshihiko Kanno, MD, PhD
Department of Nephrology, Saitama Medical University
38 Morohongo, Moroyama, Iruma
Saitama 350-0495 (Japan)
Tel. +81 49276 1611, Fax +81 49295 7338, E-Mail kannoyh@saitama-med.ac.jp

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Protein Intake of More than 0.5 g/kg BW/Day Is not Effective in Suppressing the Progression of Chronic Renal Failure

T. Ideura, M. Shimazui, H. Morita, A. Yoshimura

Department of Internal Medicine, Showa University Fujigaoka Hospital, Yokohama City, Japan

Abstract

Background: Although it is well-known that the restriction of protein intake in chronic renal failure (CRF) is effective in slowing the progressive loss of renal function, recent randomized controlled trials have not consistently shown a beneficial effect on CRF. There is controversy regarding the amount of protein intake that results in this effect. In this study, various amounts of protein intake were compared in CRF patients due to chronic glomerulonephritis (CGN) in order to explore effective restriction of dietary protein. **Methods:** CGN patients (121 in total) with a serum creatinine level of 6 mg/dl were studied. They were subdivided into six groups depending on their protein intake: 0.3 g/kg BW/day (0.3 g), 0.4, 0.5, 0.6, 0.7, and ≥0.8 g (control group C). Deterioration of renal function was evaluated by the mean rate of decline in creatinine clearance, and the amount of protein intake was estimated on the basis of the urea nitrogen appearance rate in a 24-hour urine sample. **Results:** There was no significant difference in the suppression of the progression of renal dysfunction in the 0.6- and 0.7-g groups. However, significant suppression was observed in the 0.5-, 0.4-, and 0.3-g groups in comparison with those that received more than 0.6 g ($p < 0.05$). The renal survival rate in the groups that received less than 0.5 g was higher than that in the groups that received more than 0.6 g ($p < 0.05$). Malnutrition was not observed in all patients studied. **Conclusion:** We found that a protein intake of more than 0.5 g/kg BW/day is not effective in suppressing further deterioration of renal function in CRF resulting from CGN.

Although numerous experimental and clinical studies in the past have demonstrated the favorable effects of a low-protein diet (LPD), recent randomized controlled clinical trials (RCTs) have not consistently shown that dietary protein restriction is beneficial in slowing the progression of chronic

Table 1. Blood pressure and urinary protein excretion

Group	(n)	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)	Mean blood pressure (mm Hg)	Urinary protein excretion (g/day)
0.3-g	(21)	125.6 ± 2.1	75.8 ± 1.0	92.4 ± 1.1	0.9 ± 0.2
0.4-g	(43)	124.3 ± 1.2	73.8 ± 1.0	90.7 ± 0.9	1.2 ± 0.1
0.5-g	(24)	126.0 ± 2.1	76.3 ± 1.1	92.9 ± 1.3	1.0 ± 0.1
0.6-g	(11)	130.3 ± 2.5	76.0 ± 1.4	94.1 ± 1.4	1.2 ± 0.2
0.7-g	(7)	128.8 ± 2.1	73.2 ± 2.3	91.7 ± 1.9	1.3 ± 0.2
Control	(15)	129.9 ± 3.1	75.8 ± 1.5	93.9 ± 1.8	1.5 ± 0.5

Blood pressure and urinary protein excretion of each patient were measured once a month for 6 months at the out-patient department. Values are mean ± SE, (n): the number of patients.

renal failure (CRF) [1–9]. This disagreement prompted us to review the experimental designs of these RCTs. As a result, the following issues emerged: (1) different levels of protein intake (0.28–0.6 g/kg BW/day with supplementation of essential amino acids and ketoanalogs) were prescribed, (2) various levels of renal dysfunction were included, and (3) patients with various types of kidney diseases such as chronic glomerulonephritis (CGN), diabetic nephropathy, and polycystic kidney disease were included. In our opinion, the amount of protein intake in these RCTs mostly affected the results.

In this study, we tried to show the optimal level of protein intake that had a significant effect on retarding (or even halting) the progress of CRF without leading to malnutrition. In addition, the patients selected for this study were those who originally had CGN and in whom the kidney function at the start of the LPD was limited to a serum creatinine level of 6 mg/dl; this enabled observation of the decline in renal function over a period of several months.

Patients and Methods

CRF patients (121 in total) with a serum creatinine level of 6 mg/dl were divided into six groups according to their daily protein intake (table 1). Patients in the 0.3-g group (21 patients; age 51 ± 3 years) had a protein intake of 0.25–0.34 g/kg BW/day; the 0.4-g group (43 patients; age 58 ± 2 years), 0.35–0.44 g/kg BW/day; the 0.5-g group (24 patients; age 56 ± 2 years), 0.45–0.54 g/kg BW/day; the 0.6-g group (11 patients; age 59 ± 3 years), 0.55–0.64 g/kg BW/day; the 0.7-g group (7 patients; age 60 ± 4 years), 0.65–0.74 g/kg BW/day; and control group C (15 patients; age 52 ± 3 years), more than 0.75 g/kg BW/day.

Table 2. Effect of protein restriction on decline in creatinine clearance after reaching serum creatinine level of 6 mg/dl

Group	(n)	Ccr (ml/min/month) 10^{-1}
0.3-g	(13)	$-1.3 \pm 0.5^{a,b,c,d,e}$
0.4-g	(34)	$0.0 \pm 0.3^{c,d,e}$
0.5-g	(18)	$0.6 \pm 0.5^{c,d,e}$
0.6-g	(9)	7.1 ± 2.0
0.7-g	(4)	7.9 ± 1.8
Control	(8)	6.5 ± 1.5

Ccr = Decline in Ccr per month during 6 months.
$^{a}p < 0.05$ vs. 0.4-g; $^{b}p < 0.05$ vs. 0.5-g; $^{c}p < 0.001$ vs. 0.6-g; $^{d}p < 0.001$ vs. 0.7-g; $^{e}p < 0.001$ vs. Control.

All 121 patients were followed every month in the outpatient clinic of our hospital, for more than 6 months.

The LPD treatment in the present study was conducted without supplementation of either essential amino acids or ketoanalogs of amino acids. The average energy intake estimated by dietary records was 33.0 ± 1.0 kcal/kg BW/day; there were no differences between the groups in their daily energy intake.

The protein intake was calculated by the Maroni-Mitch formula [10], which is estimated on the basis of the urea nitrogen appearance rate in a 24-hour urine sample.

Blood pressure was controlled by antihypertensive drugs, except for angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists. Salt intake of all patients was ≤5 g/day throughout the study. As shown in table 1, the systolic and diastolic blood pressure and urinary protein excretion in each group did not differ significantly throughout the course of the study.

All patients originally had CGN. Patients who had been prescribed vitamin D, phosphate binders, erythropoietin, ion exchange resin and sodium bicarbonate were excluded from this study. The rate of decline in renal function was estimated by the decline in creatinine clearance per month. The renal survival rate was estimated using Kaplan-Meier curves. Values are expressed as mean ± SEM. Statistical analyses were performed using the unpaired Student's t test and the log-rank test. A p value <0.05 was considered to be statistically significant.

Results

The effect of different LPDs on the mean monthly rate of decline in the glomerular filtration rate is shown in table 2. The decline in creatinine clearance in the 0.6- and 0.7-g groups was not significantly different from that in the control group. In contrast, a significant effect was observed in the groups

receiving <0.54 g/kg BW/day (the 0.5-, 0.4-, and 0.3-g groups). The effect was most pronounced in the 0.3-g group.

Table 3 summarizes the blood chemistry data at 6 months after the diet. Although the serum creatinine level was significantly lower in the 0.5-g (6.8 ± 0.3 mg/dl), 0.4-g (6.5 ± 0.1 mg/dl), and 0.3-g (6.6 ± 0.2 mg/dl) groups than in the control group (10.0 ± 0.6 mg/dl, $p < 0.001$ in each), it was not decreased in the 0.7- and 0.6-g groups.

The change in the blood urea nitrogen (BUN) level was quite different from that of creatinine. The BUN level was significantly lower in the 0.6-g (67.5 ± 4.8 mg/dl) group than in the control (112.1 ± 6.6 mg/dl, $p < 0.05$) and 0.7-g (99.0 ± 10.9 mg/dl, $p < 0.05$) groups. The BUN level in the 0.5-g group was lowered to 40.2 ± 2.7 mg/dl; this is 35.9% of the value of the control group ($p < 0.001$). The BUN level in the 0.4-g (31.5 ± 1.1 mg/dl) group was less than that of the 0.5-g group ($p < 0.05$), while that of the 0.3-g group was significantly lower (22.6 ± 1.6 mg/dl) than that of the 0.4-g group ($p < 0.001$).

The serum bicarbonate level was in the normal range (21.0–25.0 mmol/l) only in the 0.5-g (21.2 ± 0.6 mmol/l), 0.4-g (22.6 ± 0.6 mmol/l), and 0.3-g (24.3 ± 0.8 mmol/l) groups. The serum potassium level was significantly lower in the 0.5-g (5.1 ± 0.2 mEq/l), 0.4-g (5.0 ± 0.1 mEq/l), and 0.3-g (4.4 ± 0.2 mEq/l) groups. The serum phosphate level was significantly lower in the 0.6-g (5.2 ± 0.1 mg/dl) group than in the control group (6.3 ± 0.3 mg/dl, $p < 0.05$). However, it was higher than the values of the normal range. In contrast, the serum phosphate levels in the 0.5-g (4.4 ± 0.2 mg/dl), 0.4-g (4.2 ± 0.1 mg/dl), and 0.3-g (3.7 ± 0.2 mg/dl) groups were significantly lower and were within the normal range. The serum calcium level was maintained within the normal range (8.3–10.2 mg/dl) in the 0.5-g (8.8 ± 0.1 mg/dl), 0.4-g (8.7 ± 0.1 mg/dl), and 0.3-g (8.8 ± 0.1 mg/dl) groups.

The nutritional indices at 6 months after initiation of the diet are listed in table 4. The body weight did not change with any change in the LPD. The total protein, albumin, and transferrin levels were within the normal range in all groups. However, after 6 months, the hemoglobin and hematocrit values were significantly lower in the 0.6-, 0.7-g, and control groups than those in the 0.5-, 0.4-, and 0.3-g groups.

The kidney survival rate is shown in figure 1. Dialysis was initiated in all patients of the control group within 2 years once their serum creatinine level reached 6 mg/dl. The Kaplan-Meier survival rate in the 0.7- and 0.6-g groups did not differ from that in the control group. The patients in these two groups were started dialysis within two years. In contrast, the initiation of dialysis was significantly delayed in patients in the 0.5-, 0.4-, and 0.3-g groups ($p < 0.0001$, compared with the control group). Furthermore, the LPD of the 0.3-g group was more effective than those of the 0.5-g ($p < 0.05$) and 0.4-g ($p < 0.05$) groups.

Table 3. Blood chemistry at 6 months after the diet (observed from serum creatinine level of 6 mg/dl)

Group	(n)	Cr (mg/dl)	(n)	BUN (mg/dl)	(n)	HCO_3 (mmol/l)	(n)	K (mEq/l)	(n)	P (mg/dl)	(n)	Ca (mg/dl)
0.3-g	(14)	$6.6 \pm 0.2^{e,j,m}$	(14)	$22.6 \pm 1.6^{b,d,g,j,m}$	(12)	$24.3 \pm 0.8^{c,f,i,m}$	(13)	$4.4 \pm 0.2^{b,c,g,h,m}$	(14)	$3.7 \pm 0.2^{a,c,g,j,m}$	(14)	$8.8 \pm 0.1^{e,i,k}$
0.4-g	(34)	$6.5 \pm 0.1^{f,j,m}$	(34)	$31.5 \pm 1.1^{c,g,j,m}$	(31)	$22.6 \pm 0.6^{e,h,m}$	(34)	5.0 ± 0.1^{g}	(34)	$4.2 \pm 0.1^{g,j,m}$	(34)	$8.7 \pm 0.1^{e,i,k}$
0.5-g	(19)	$6.8 \pm 0.3^{e,j,m}$	(19)	$40.2 \pm 2.7^{g,j,m}$	(18)	21.2 ± 0.6^{l}	(18)	5.1 ± 0.2^{e}	(19)	$4.4 \pm 0.2^{e,j,m}$	(19)	$8.8 \pm 0.1^{e,i,k}$
0.6-g	(10)	8.3 ± 0.8	(10)	$67.5 \pm 4.8^{i,m}$	(9)	20.0 ± 0.9	(10)	5.7 ± 0.1	(10)	$5.2 \pm 0.2^{i,k}$	(10)	8.2 ± 0.2
0.7-g	(5)	10.1 ± 1.0	(5)	99.0 ± 10.9	(5)	19.4 ± 1.5	(4)	5.2 ± 0.1	(5)	6.8 ± 0.4	(5)	7.9 ± 0.3
Control	(15)	10.0 ± 0.6	(15)	112.1 ± 6.6	(14)	17.5 ± 1.1	(15)	5.3 ± 0.1	(15)	6.3 ± 0.3	(15)	8.1 ± 0.3

BUN = Blood urea nitrogen; Cr = serum creatinine; HCO_3 = bicarbonate.

$^{a}p < 0.01$ vs. 0.4-g; $^{b}p < 0.001$ vs. 0.4-g; $^{c}p < 0.01$ vs. 0.5-g; $^{d}p < 0.001$ vs. 0.5-g; $^{e}p < 0.05$ vs. 0.6-g; $^{f}p < 0.01$ vs. 0.6-g; $^{g}p < 0.001$ vs. 0.6-g; $^{h}p < 0.05$ vs. 0.7-g; $^{i}p < 0.01$ vs. 0.7-g; $^{j}p < 0.001$ vs. 0.7-g; $^{k}p < 0.05$ vs. Control; $^{l}p < 0.01$ vs. Control; $^{m}p < 0.001$ vs. Control.

Table 4. Nutritional indices at 6 months after the diet (observed from serum creatinine level of 6 mg/dl)

Group	(n)	Change in body weight (%)	(n)	TP (g/dl)	(n)	Alb (g/dl)	(n)	Tf (mg/dl)	(n)	Hb (g/dl)	(n)	Ht (%)
0.3-g	(14)	99.8 ± 0.4	(14)	6.9 ± 0.1	(14)	4.1 ± 0.1	(14)	215.5 ± 10.1	(13)	10.0 ± 0.4[c,e,f]	(13)	30.7 ± 1.3[c,e,g]
0.4-g	(32)	100.5 ± 0.7	(34)	6.7 ± 0.1	(34)	4.0 ± 0.1[a]	(34)	210.6 ± 7.7	(31)	9.3 ± 0.2[c,e,f]	(31)	28.9 ± 0.8[c,e,g]
0.5-g	(15)	101.1 ± 1.1	(19)	6.8 ± 0.1	(19)	4.2 ± 0.1[f]	(19)	225.5 ± 8.1	(17)	9.3 ± 0.4[b,d]	(17)	28.9 ± 1.2[b,d,f]
0.6-g	(10)	99.4 ± 0.6	(10)	6.9 ± 0.2	(10)	4.0 ± 0.1	(10)	201.0 ± 14.2	(9)	7.8 ± 0.5	(9)	23.9 ± 1.5
0.7-g	(4)	98.2 ± 1.7	(5)	6.6 ± 0.2	(5)	4.0 ± 0.1	(4)	232.2 ± 36.2	(4)	6.5 ± 0.5	(4)	19.9 ± 1.5
Control	(8)	100.1 ± 1.0	(14)	6.7 ± 0.1	(14)	4.0 ± 0.1	(7)	218.4 ± 8.9	(14)	8.0 ± 0.6	(14)	24.3 ± 1.7

Alb = Serum albumin; Hb = hemoglobin; Ht = hematocrit; Tf = serum transferrin; TP = serum total protein.
[a]$p < 0.01$ vs. 0.5-g; [b]$p < 0.05$ vs. 0.6-g; [c]$p < 0.01$ vs. 0.6-g; [d]$p < 0.01$ vs. 0.7-g; [e]$p < 0.001$ vs. 0.7-g; [f]$p < 0.05$ vs. Control; [g]$p < 0.01$ vs. Control.

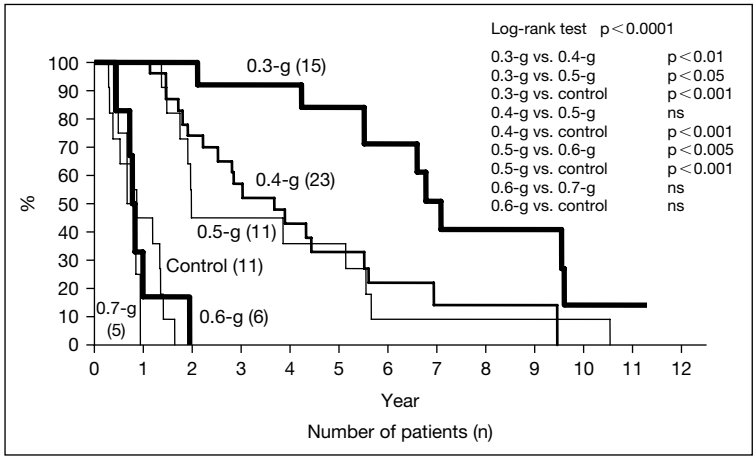

Fig. 1. Effect of protein restriction on renal survival rate after reaching serum creatinine level of 6 mg/dl.

Discussion

In this study, we assessed the optimal protein intake required to retard the progression of CRF, alleviate uremic symptoms, and maintain a good nutritional state.

The progression of advanced CRF usually exhibits an irreversible course. However, slight or moderate renal insufficiency does not always exhibit a linear decline in glomerular filtration rate in a limited period of follow-up [11]. Thus, we tried to observe the effect of LPDs in patients with a serum creatinine level of 6 mg/dl in whom the kidney function declines without fluctuations. It is known that underlying renal disease influences the rate of progression in CRF [11, 12]; we dealt with only CGN in this study. The effect of a LPD on slowing the progression of CRF was observed when the protein intake was $\leq$0.5 g/kg BW/day. Interestingly, a protein intake of $\geq$0.6 g/kg BW/day was of no therapeutic value.

The influence of the diet on blood chemistry abnormalities, uremic symptoms, and related complications is well-known [13, 14]. In this study, blood chemistry abnormalities were suppressed significantly in groups where the protein intake was $\leq$0.5 g/kg BW/day. In contrast, a protein intake of $>$0.5 g/kg BW/day had no favorable effect on blood chemistry, with the exception of the BUN and serum phosphate levels. Furthermore, the values of BUN and phosphate did not decrease to within the normal range. The effect on the serum calcium level is interesting. In spite of a low-calcium content in the LPD, the serum calcium level in the LPD groups receiving $\leq$0.5 g/kg BW/day remained

within the normal range. The suppression of hyperphosphatemia to some extent might play a role in this effect. Conversely, a protein intake of >0.5 g/kg BW/day did not improve hypocalcemia.

Based on these results, we concluded that the effective protein intake for slowing the progression of CRF and blood chemistry abnormalities was ≤0.5 g/kg BW/day.

This study showed that severe protein restriction ≤0.5 g/kg BW/day without supplementation of essential amino acids or ketoanalogs enabled the patients to maintain a good nutritional state as well as a good clinical condition. In general, the level of malnutrition directly correlates with the glomerular filtration rate in all subgroup patients in cases with moderate renal failure, those in the predialysis end stages, and in dialysis patients [15, 16]. This may be due to the reduced nutritional intake associated with renal insufficiency or because of hypercatabolism in end-stage renal disease. In addition, some reports state that LPD will lead to malnutrition [17]. This is incorrect [16]. Our patients were on a strict LPD, i.e., 0.3 g/kg BW/day; they maintained a normal nutritional state even in the absence of supplementation. Subanalysis of the Modification of Diet in Renal Disease (MDRD) study revealed that chronic kidney disease patients treated with LPD for 2.2 years had a small but significant increase in serum albumin levels [18]. Another study found that long-term LPD treatment is associated with higher serum protein concentrations when dialysis therapy is initiated [13]. Walser and Hill [19] evaluated 76 chronic kidney disease patients who were on LPD. Their body weight did not decline, and their serum albumin level was maintained within a normal range (4.1 g/dl). Aparicio et al. [20] reported data from 239 chronic kidney disease patients who had been followed for an average of 29.6 months. There was no decline in their weight or body mass index, and their serum albumin level was 3.9 g/dl. We reported that an LPD of 0.39 g/kg BW/day without supplementation in very late stage (creatinine level > 10.0 mg/dl) CRF patients did not result in nutritional disturbance [21]. In another study, we reported that plasma amino acid profiles did not change in CRF patients who had a serum creatinine level of 6 mg/dl and were on an LPD (0.5 and 0.3 g/kg BW/day) for 2 years without any supplementation [22].

Progressive renal anemia was suppressed in patients on a LPD of ≤0.5 g/kg BW/day. On the other hand, the anemia progressed when the protein intake was >0.6 g/kg BW/day. This result indicated that severe LPD has a beneficial effect on renal anemia. Although the mechanism remains unclear, improvement in blood biochemistry abnormalities might have an effect. The higher BUN levels in patients on LPDs of 0.6 and 0.7 g/kg BW/day might lead to greater suppression of bone marrow function than in those maintained at 0.5, 0.4, and 0.3 g/kg BW/day whose BUN level was significantly lower.

Why did malnutrition not occur when the protein intake was ≤0.5 mg/kg BW/day in the absence of essential amino acid or ketoanalog supplementation? In our study, more than 73% of cereals that had a very low amino acid score (e.g., the amino acid score of rice is 64 and that of wheat is 46) were replaced with starch products such as starch rice, starch noodle, starch flour, and starch rice cake, which contain <0.2% protein. The excluded protein from cereals was then replaced by animal proteins such as egg, meat, fish, and milk. Because the amino acid score of animal protein is 100, the average amino acid score of our patients' diets was more than 90 [22]. These results suggest that nitrogen balance was maintained in the very low-protein group without supplementation, although a nitrogen balance study was not performed.

Conclusion

In conclusion, we claim that the optimal level of protein intake that is required to slow the progression of renal failure, ameliorate uremic symptoms by suppressing serum biochemical abnormalities, and maintain a good nutritional state ranges from 0.5 to 0.3 g/kg BW/day.

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T. Ideura
Department of Internal Medicine
Showa University Fujigaoka Hospital
1-30 Fujigaoka, Aoba-Ku
Yokohama City, Kanagawa 227 0043 (Japan)
Tel. +81-45-973-3025, Fax +81-45-973-3010, E-Mail ideura@showa-university-fujigaoka.gr.jp

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Diet Therapy in Diabetic Nephropathy

Yoshitaka Maeda, Tatsuo Shiigai

Nephrology Section, Department of Internal Medicine, Toride Kyodo General Hospital, Ibaraki, Japan

Abstract

Although protein restriction has been suggested as a mainstay of therapy for patients with diabetic nephropathy, controversy exists regarding the exact dietary prescription and stage of disease for implementation. This chapter reviews the pathophysiology and stages of diabetic nephropathy, clinical studies of dietary therapy in diabetic nephropathy, and provides a framework for using diet in the treatment of diabetic renal disease.

Calorie-restriction diet is an essential part of the treatment of diabetes mellitus (DM) unaccompanied by nephropathy, but optimal nutritional patterns should crucially be changed in the case of overt nephropathy after its development [1–3]. Protein-restriction, rather than calorie-restriction becomes a major concern in treating diabetic nephropathy, since strict plasma glucose control alone never ameliorates advanced nephropathy (>stage 3 on table 1). Hence most recommendations in guidelines suggest the importance of protein-restriction for treatment of diabetic nephropathy [2], even based on insufficient evidence. Such issues and limitations, along with outlines of nutritional support for diabetic nephropathy are clarified in the following description.

Medical Aspects of Diabetic Nephropathy

DM itself is never a life-threatening disease after insulin and its derivatives had been introduced to regulate plasma glucose levels in its appropriate range. However, DM still causes cardio- or cerebro-vascular diseases and three major complications: nephropathy, retinopathy, and neuropathy after long-term exposure

Table 1. Clinical stages of diabetic nephropathy

Stage	Urinary protein (albumin)	GFR (Ccr)	Pathological findings	Recommended treatment
1	Negative	WNL or increased	No-mild diffuse lesions	Regulating PG level
2	Microalbuminuria (20–200 μg/min or 30–300 mg/day)	WNL–increased	Mild–moderate diffuse lesions and/or nodular lesions	Regulating PG/BP levels
3-A	Persistent proteinuria (>0.5 g/day)	Almost WNL	Moderate diffuse lesions and nodular lesions	Regulating PG/BP levels, and protein-restriction and plasma glucose regulation
3-B	Persistent proteinuria (>1 g/day)	Decreased (GFR < 60 ml/min)	Severe diffuse lesions and nodular lesions	Regulating BP levels, and protein-restriction and plasma glucose regulation
4	Persistent proteinuria	Remarkedly decreased (Elevated serum Cr)	End-stage kidney lesions	Regulating BP levels, protein-restriction, and dialysis
5		Under dialysis therapy		Dialysis and transplantation

BP = Blood pressure; Ccr = creatinine clearance; GFR = glomerular filtration rate; PG = plasma glucose; WNL = within normal limit.

to high plasma glucose levels. The number of patients with DM has increased worldwide, and DM has consequently become a major cause of renal diseases requiring renal replacement therapies, which has subsequently increased the medical burden [1]. Hence, it is a serious and urgent issue to prevent and to treat diabetic nephropathy all around the world by any possible means including medical and nutritional management.

As figure 1 shows, diabetic nephropathy may develop through hemodynamic and metabolic processes [3]. As a hemodynamic process, glomerular hyperfiltration or hypertension was first proposed by Brenner et al. [4]. Glomerular hyperfiltration phase was detected in patients with type 1 DM, but not apparent, or variable in type 2 DM, since features of the latter were more heterogeneous. The evoked glomerular hyperfiltration causes glomerular damage and subsequently increases glomerular permeability to plasma proteins. The filtered protein itself impairs tubular and interstitial structure and function through the mechanism called ‘protein-overload proteinuria’, in a vicious cycle

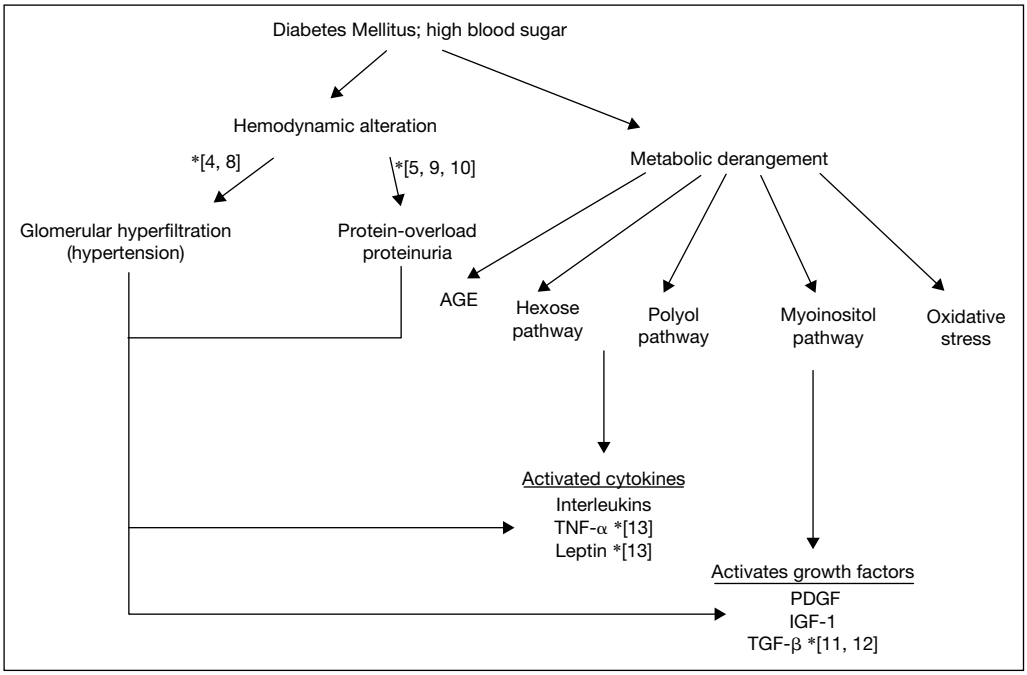

Fig. 1. Progressive mechanism and expected target points (an expected target point of PRD and the number of related reference) of PRD against diabetic nephropathy.

[5]. Metabolic alterations include the polyol pathway, activated protein kinase C/mitogen activated protein kinase, hexosamine pathway, advanced glycation end products (AGE), and oxidative processes. These derangements, along with hemodynamic changes, may activate various cytokines and growth factors such as TNF-α, interleukins, PDGF, TGF-β, and IGF-1 [3].

Clinical stage of diabetic nephropathy is generally divided into five grades in most guidelines (table 1) mainly based on the proposal by Mogensen et al. [6]. Since the renal damage in DM is reversible before overt proteinuria manifests, it is important to keep plasma glucose levels in the appropriate range at stages 1 and 2. Hence it is a main concern at that stage to restrict calorie supply to avoid obesity and poorly controlled plasma glucose levels. Meanwhile, nephropathy with overt proteinuria (>stage 3) is not improved only by regulating plasma glucose levels. Hence protein-restriction plays a role in nutritional management, unless an extreme replacement therapy, pancreas transplantation is performed to treat DM [7].

Table 2. Clinical studies of PRD in diabetic nephropathy

References	Type of DM (stage)	Study design	Patients	Effect of PRD
Ciavarella et al. [16]	Type 1 (3-A–4)	RCT	16	Reduced albuminuria
Barsotti et al. [17]	Type 1 (3-B–4)	TCT	8	Reduced decline of Ccr and proteinuria
Walker et al. [18]	Type 1 (3-B–4)	TCT	19	Reduced decline of GFR and albuminuria
Evanoff et al. [19]	Type 1 (3-B)	TCT	11	Reduced decline of GFR and proteinuria
Brouhard and LaGrone [20]	Type 1 (2)	CCT	15	Reduced decline of GFR and albuminuria
Zeller et al. [21]	Type 1 (3-A–4)	RCT	35	Reduced decline of GFR
Dullaart et al. [22]	Type 1 (2)	RCT	30	Reduced albuminuria
Pomerrleau et al. [23]	Type 2 (2)	RCOT	12	Reduced albuminuria and GFR
Raal et al. [24]	Type 1 (3-A–4)	RCT	22	Reduced decline of GFR and proteinuria
Pijls et al. [25]	Type 2 (1–2)	RCT	121	Reduced albuminuria
Hansen et al. [26]	Type 1 (3-A–4)	RCT	82	Reduced ESRD and death

CCT = Case-control trial; RCOT = randomized cross-over trial; RCT = randomized controlled study; TCT = time-control trial.

Nutritional Management of Diabetic Nephropathy

Figure 1 also shows the targeted points of protein-restriction diet (PRD) on the progression of diabetic nephropathy. Protein intake itself is known to increase renal plasma flow and glomerular filtration [8], and protein-restriction inversely reduces glomerular filtration [4, 8]. Moreover, reduced glomerular hyperfiltration subsequently suppresses proteinuria [9, 10]. PRD may also diminish activated cytokines and growth factors through unknown mechanisms [11–13].

Consequently, apparent effects of protein-restriction on diabetic nephropathy were obtained either by animal experiments [14, 15], or by clinical studies [16–26]. Table 2 summarizes these clinical trials. A meta-analysis also suggested the benefit of protein-restriction [27]. However, sample sizes of these clinical trials were small, and performed among the patients restricted to type 1 DM except for two trials [23, 25] dealing with type 2 DM. Moreover, effects of angiotensin I converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), prominent treatments for diabetic nephropathy, were not clearly distinct from those of diet therapies in these reported studies. Hence, a nutritional standard for the treatment of diabetic nephropathy has not been established yet. It will be crucial to observe the effects of PRD under administration of ACEI or ARB.

Table 3. Nutritional guidelines for diabetic nephropathy

Stage	Total energy (kcal/kg*/day)	Protein (g/kg*/day)	Salt (g/day)	Potassium (g/day)
1	25–30	NR	NR**	NR
2	25–30	1.0–1.2	NR**	NR
3-A	25–30	0.8–1.0	7–8	NR
3-B	30–35	0.8–1.0	7–8	MR
4	30–35	0.6–0.8	5–7	1.5
5	30–35	1.0–1.2	0.15 g/kg***/day	1.5

The recommendation of stage 5 is restricted to hemodialysis patients, and not for peritoneal dialysis patients or patients receiving transplantation therapies.

MR = mildly restricted; NR = not restricted.

* = Ideal body weight: (Height in meter)^2 × 22; ** = 7–8 g/day in patients with hypertension; *** = actual body weight after a dialysis session.

Nutritional Management of Diabetic Nephropathy in Japan

As in other countries, PRD for the treatment of diabetic nephropathy is not fully accepted even by Japanese physicians, since, in addition to the above reasons, a physician alone cannot fully help patients to learn how to cook foods according to the ordered amounts of protein and other nutritional factors, unless skillful dietitians and nurses can take part in the training system.

As a favorable aspect of Japan, cereals comprise more than 40% of the total calories in Japan, contrary to Western developed countries where <30% of energy supply was by cereals [28], which may facilitate PRD by accomodating rice and other foods more easily than in other developed countries [29]. For instance, more than ten kinds of low-protein rice produced by mechanical (over-polished), chemical (enzyme-digested), or genetic engineering methods are all commercially available in Japan.

The Japanese Society of Nephrology proposed nutritional guidelines for diabetic nephropathy in 1997 [30]. As table 3 shows, the grade of protein restriction is stepped up in accordance with the level of renal damage. For the convenience of patients, several guidebooks are also available, which show protein units; 3 g of protein defined as a single unit, along with calorie units; 80 kcal defined as a single unit, in each food to calculate the amount of protein and calories more easily.

Nutritional support for CKD patients, the so-called ‘Toride Project’ began at Toride Kyodo General Hospital in 1987. More than 1,400 patients were

Table 4. Effect of PRD on non-insulin dependent diabetic nephropathy treated with an ARB

	PRD		MRD	
M/F	14/10		17/7	
Age	62.6 ± 2.4		61.9 ± 1.5	
	Baseline	After 6 months	Baseline	After 6 months
Estimated protein intake (g/kg/day)	0.79 ± 0.05	0.70 ± 0.03	0.92 ± 0.04	0.88 ± 0.04
Serum Cr	2.25 ± 0.26	2.72 ± 0.40*	2.41 ± 0.26	3.39 ± 0.42**
Ccr (ml/min)	45.0 ± 7.7	36.7 ± 4.6	40.9 ± 5.0	27.2 ± 3.4*
Urinary protein excretion (g/day)	4.31 ± 0.69	2.88 ± 0.45*	4.97 ± 0.50	4.24 ± 0.44
Patients requiring dialysis within a year	1		4	

The data are shown as mean ± SEM.

MRD = Mildly restricted diet (target protein intake, 1.0–1.2 g/kg/day); PRD = protein-restricted diet (target protein intake, 0.5–0.7 g/kg/day).

* $p < 0.05$ compared with baseline values; ** $p < 0.01$ compared with baseline values.

involved in this project, and many hospital-based studies have been performed and are on-going [29].

Now we are investigating effects of PRD on progression of diabetic nephropathy with type 2 DM patients treated with ARB. As table 4 shows, the patients receiving 8 mg/day of candesartan were randomly assigned either to PRD (0.5–0.6 g/kg/day with supplemented essential amino acid) or to a mildly restricted diet (1.0–1.1 g/kg/day). Even though the results are still preliminary, PRD may reduce decline in creatinine clearance, urinary protein excretion, and may consequently decrease the number of patients requiring dialysis within a year.

Future Problems

As described before, most investigations related to diet therapy in DM have been performed among patients with type 1 DM. Type 2 DM is actually a more heterogeneous clinical entity than type 1 DM, which may affect results and conclusions of clinical trials. However, it is also true that the number of type 2 DM patients is increasing around the world. Overcoming type 2 DM and its complications is now an issue in every country. The most appropriate diet for diabetic nephropathies, not restricted to type 1 DM, should be established by continuing research efforts.

Substantial benefits of ACEI and ARB therapy for diabetic nephropathy have been established. Since PRD also suppress renin activity [31], the effects of PRD during the administration of ACEI or ARB should be evaluated. Our results, even though on-going and preliminary, suggest additive effects of PRD on diabetic nephropathy during treatment with an ARB, consistent with previous basic experiments [12] and clinical observations [9].

Foods with high-protein scores are usually recommended for patients requiring protein-restriction to avoid malnutrition. However, some benefits of plant protein in kidney diseases have been reported [32, 33], even though such effects are still controversial [2, 3, 34].

In the nutritional management of diabetic nephropathy, possible roles of dietary factors other than protein such as homocysteine and its related vitamins [3], iron, and polyphenol were also reported [35]. However, actual functions of these nutrients are still unclear and controversial.

PRD certainly lacks sufficient evidence to be accepted by all physicians. However medical personnel have to make appropriate recommendations for foods to patients with diabetic nephropathy. It is the responsibility of medical personnel to continue to work at establishing the optimal nutritional goal for the treatment of diabetic nephropathy.

Conclusions

PRD should be prescribed for patients with diabetic nephropathy, as far as calorie intake is sufficient and the prescribed protein intake dose not cause malnutrition. More detailed guidelines should be established by continuing efforts at research in this field.

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Tatsuo Shiigai, MD, PhD
Nephrology Division, Department of Internal Medicine
Toride Kyodo General Hospital
2-1-1 Hongoh, Toride
Ibaraki 302-0022 (Japan)
Tel. +81 297 74 5551, Fax +81 297 74 2721, E-Mail pv2t-sigi@asahi-net.or.jp

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Nutritional Therapy for Patients Undergoing Hemodialysis

Hiromichi Kumagai

Department of Clinical Nutrition, School of Food and Nutritional Sciences,
University of Shizuoka, Shizuoka, Japan

Abstract

Protein energy malnutrition (PEM) frequently appears in hemodialysis (HD) patients, and it has been established as a risk factor for morbidity and mortality. Recent studies have shown that inflammation might be a key mediator between PEM and cardiovascular events. On the other hand, it remains unknown whether over-nutrition has an implication as a risk factor for cardiovascular diseases and mortality. Although many studies have indicated that obesity seemed not to be directly associated with mortality, metabolic abnormalities including hypertriglyceridemia, a low level of high-density lipoprotein cholesterol, glucose intolerance and visceral fat accumulation are common in HD patients with over-nutrition. Furthermore, the plasma adiponectin concentration has been reported to show an inverse correlation with the visceral fat mass, and low plasma adiponectin was associated with a high susceptibility to cardiovascular events and mortality in HD patients. These results suggest that nutritional therapy for HD patients may be necessary to consider in patients with either PEM or over-nutrition.

Nutritional disturbances are serious complications in hemodialysis (HD) patients. Although protein energy malnutrition (PEM) is already well-known to be a risk factor for morbidity and mortality, it remains controversial as to whether over-nutrition would be associated with atherosclerotic cardiovascular diseases and poor prognosis. This review presents part of the pathogenesis of these nutritional disturbances and the strategies for nutritional intervention in HD patients.

Protein Energy Malnutrition

PEM has been established as a death risk since the association between hypoalbuminemia and high-mortality was reported in the early nineties by

Table 1. Pathogenesis of protein–energy malnutrition

Predialysis factors
Uremic toxicity
Diet restriction
Anorexia
Uremic toxicity (under dialysis)
Taste abnormality
Gastroenteropathy
Physical inactivity
Psychiatric factors
Medications
Catabolic factors
Nutrient loss in dialysate
Metabolic acidosis
Inflammation
Co-morbidity

Lowrie et al. [1] and Iseki et al. [2]. Such other indices of malnutrition as hypoprealbuminemia [3], low body mass index (BMI) [4] and hypocholesterolemia [5] have also been reported to be risk factors for short-term and long-term survival. Major studies in US and Japan have indicated that one-third to one-fourth of HD patients suffered from PEM, and that 5% of these patients had an extremely low serum albumin concentration (<3.0 g/dl) and low BMI (<16 kg/m^2) [6, 7].

The pathogenesis of PEM in HD patients involves many factors that have a complex association with each other (table 1).

Predialysis Factors

Predialysis factors that induce PEM in HD patients include uremic conditions [8] and dietary restrictions [9]. PEM has been reported to progressively worsen in conjunction with declining renal function. Furthermore, the low-protein diet that is prescribed to prevent the progression of chronic renal failure would induce PEM if a sufficient amount of energy is not provided. As a result, most patients initiating HD lose weight and show hypoalbuminemia. After starting dialysis, however, these components of PEM may possibly be improved by relieving the uremic milieu and supplementing a sufficient amount of protein and energy.

Anorexia

A diminished appetite is one of the important factors in the decreased nutritional intake and inducting of PEM seen in HD patients. Anorexia is caused by uremic toxicity, uremic gastrointestinal disturbances, physical inactivity,

psychiatric factors, side effects of medications, co-morbidity, and inflammation with high levels of circulating CRP and cytokines [10, 11]. Some of these factors can be alleviated by increasing the frequency of dialysis. In fact, it has been reported that short daily HD significantly improved appetite, food intake and nutritional indices, including serum albumin, prealbumin and lean body mass [12]. In spite of significant developments in dialysis technology, under-dialysis is still an important issue in elderly, diabetic and other patients who demonstrate circulatory instability during HD.

Catabolic Factors

Catabolic factors are the most important cause of PEM in HD patients. These factors can be classified into those directly related to the HD procedure and those associated with the complications of dialysis. About 6–10 g of amino acids is lost into the dialysate during one session of HD with a low-flux membrane, and a loss of 1–2 g of albumin can be added if a high-flux membrane is used [13]. If the dialysate does not contain glucose, 20–30 g of glucose is also lost into the dialysate. A bio-incompatible dialysis membrane and endotoxin-contaminated dialysate may cause an inflammatory reaction with monocyte activation and increasing cytokine production [14, 15]. These inflammatory responses have been reported to induce net catabolism of muscle protein with enhanced oxidation of branched-chain amino acids [16].

Inflammation might be a key factor for developing malnutrition in HD patients [17]. While PEM is not usually caused by inadequate nutritional intake alone, inflammation can easily induce PEM solely or through inflammation-mediated anorexia [18]. Inflammation stimulates activation of the ubiquitin-proteasome pathway, leading to muscle protein catabolism [19], and diminishes albumin synthesis [20]. In addition, the marked effect of inflammation in the pathogenesis of PEM is that it impairs the adaptive response that protects muscle and albumin breakdown [21].

Metabolic Syndrome in HD Patients

Some HD patients may possibly have another type of nutritional disturbance: the metabolic syndrome. Glucose intolerance, hypertriglyceridemia, low high-density lipoprotein (HDL)-cholesterol and hypertension are frequent complications in HD patients [22]. These laboratory findings led us to suspect that HD patients with these abnormalities might have visceral obesity, and we attempted to examine this by abdominal computed tomography [23]. The results showed that the intra-abdominal fat mass in HD patients was significantly higher than that in healthy subjects with comparable BMI (fig. 1),

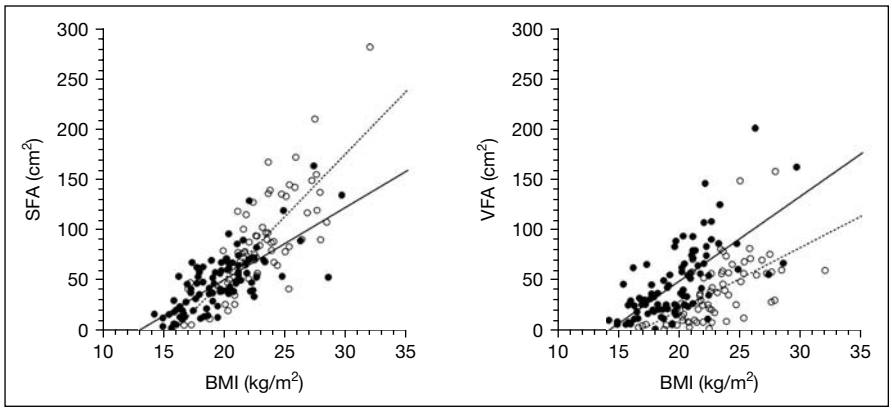

Fig. 1. Association between BMI and SFA or VFA in HD patients (●) and healthy subjects (○). The viseral fat mass in HD patients was significantly higher than that in healthy subjects with comparable BMI, while there was no difference in the subcutaneous fat mass between HD patients and healthy subjects [23]. SFA = Subcutaneous fat area; VFA = Visceral fat area.

while there was no difference in the subcutaneous fat mass between HD patients and healthy subjects. These results indicate that HD patients might tend to develop symptoms resembling the metabolic syndrome if they continued to ingest an excessive diet.

In contrast to PEM, however, the effect of obesity, visceral obesity or the metabolic syndrome on morbidity and mortality is uncertain in HD patients. Fleischmann et al. [24] and Kopple et al. [25] have demonstrated that obesity was not associated with increased mortality over 1 year in HD patients. Similar findings of an inverse association between BMI and mortality have been shown in other large cohort studies in US and Europe [26–28]. This phenomenon is in contrast to the general population, in which there is a significantly positive association between obesity and increased mortality [29]. Such a dialysis-related change in the relationship between obesity and mortality is referred to as 'reverse epidemiology' [30].

Although the exact reason for the occurrence of this reverse epidemiology has not yet been determined, Kalantar-Zadeh et al. [31] have proposed some possible explanations in their critical review article. These include a more stable hemodynamic status, alterations in circulating cytokines, unique neurohormonal constellations, endotoxin–lipoprotein interaction, reverse causation, survival bias, time discrepancies among competitive risk factors, and the malnutrition–inflammation complex syndrome. In contrast, there are some cohorts of HD patients showing conventional epidemiology in the relationship between

obesity and mortality. Wong et al. [32] and Johansen et al. [33] have independently demonstrated that obesity was associated with increased mortality in Asian-American HD patients, whereas the inverse association between BMI and mortality was shown in Caucasian and African-American patients. These studies simply suggested a racial difference in the effect of obesity for an unknown reason. Kaizu et al. [34] have indicated a U-shaped relationship between BMI and mortality when Japanese HD patients were followed for 12 years. A remarkable finding of this study is that the higher mortality rate in obese patients became apparent after a follow-up of 5 years. Indeed, the 1-year survival rate of obese patients did not become higher even with the Japanese HD patients [35]. As reported by Kalantar-Zadeh, such traditional risk factors as obesity and hyperlipidemia may be overwhelmed by such short-term risk factors as malnutrition and inflammation if the patients have a shorter life expectancy. Obesity might become a serious risk factor for cardiovascular diseases and mortality in HD patients who survive for a longer time. The change from reverse epidemiology to traditional epidemiology during a long-term follow-up study has also been suggested in the relationship between hypercholesterolemia and mortality [31].

Adiponectin (ADPN), one of the secretory proteins from adipocytes, has been reported to play a protective role against atherosclerotic vascular injuries and consequent cardiovascular events [36]. A recent study has demonstrated that a low plasma ADPN concentration was associated with a high incidence of cardiovascular events and high-mortality in HD patients [37], similar to the case of healthy subjects. Furthermore, the plasma ADPN value showed an inverse association with abdominal adipose tissue and, especially, with the visceral fat mass in HD patients [38]. Considering the fact that HD patients are liable to accumulate visceral fat [23], obese HD patients have the potential to induce cardiovascular diseases through visceral fat accumulation and decreased ADPN concentration. In fact, it has been reported that HD patients with visceral fat accumulation had a high prevalence of carotid atherosclerosis [39].

This evidence suggests that obesity cannot be ignored as a risk factor for cardiovascular diseases in HD patients. The effect of visceral fat accumulation and hypoadiponectinemia on long-term mortality remains to be investigated by future epidemiologic studies.

Nutritional Intervention in HD Patients

Protein and Energy

The current nutritional guidelines of the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) recommend

1.2 g/kg/day of dietary protein and 35 kcal/kg/day (<60 years old) or 30–35 kcal/kg/day (≥60 years old) for HD patients [40]. The Japanese Society of Nephrology (JSN) has also proposed similar guidelines that recommend 1.0–1.2 g/kg/day of protein and 35 kcal/kg/day for maintenance HD patients [41]. However, since the recommended protein intake of 1.2/kg/day was set at the safe level for approximately 95% of HD patients, this level might exceed the physiological requirement of most HD patients. Furthermore, this recommendation was based on relatively old nitrogen-balance studies performed when low-flux, bio-incompatible cellulose membranes and acetate dialysate were used [42]. It has recently been proposed that the protein requirement for dialysis patients should be modified to a lower level. There are several reasons for this proposal. Firstly, no evidence for the acceleration of dialysis-related protein breakdown was found by a study based on the leucine turnover [43]. Secondly, the introduction of a biocompatible synthetic membrane, bicarbonate dialysate and pyrogen-free dialysate in recent HD protocols might have resulted in the additional suppression of catabolism. Thirdly, even if the amino acid and protein losses into the dialysate reach 6–12 g/HD session, the estimated additional protein needed would be only 0.04–0.08 g/kg/day [44]. Fourthly, high-protein loading might lead to some adverse effects in HD patients; e.g., hyperphosphatemia, hyperkalemia, metabolic acidosis and an accumulation of uremic metabolites. Among these metabolic disorders, hyperphosphatemia is still the most important issue with contemporary HD, because it can induce hyperparathyroidism or metastatic calcification in concert with abnormal calcium metabolism, and it is difficult to control by pharmacological intervention. Fifthly, patients with a high protein intake often also have a high-energy intake, and this might induce hyperlipidemia and visceral obesity. We have recently investigated the association between the dietary protein intake measured by the protein catabolic rate and the muscle mass or visceral fat mass measured by X-ray computed tomography in HD outpatients [45]. The results indicated that the thigh muscle area increased with increasing dietary protein intake from <0.7 to 0.9–1.1 g/kg/day, and reached a plateau at >0.9–1.1 g/kg/day (fig. 2). On the other hand, the subcutaneous and visceral fat area increased with increasing protein intake and no plateau was reached. Those patients with a protein intake >1.3 g/kg/day satisfied the criterion for visceral obesity with >100 cm^2 of visceral fat area. We concluded from this evidence that the optimal dietary protein requirement for patients undergoing maintenance HD in a stable condition seems to be less than the level recommended by the NKF-KDOQI and JSN nutritional guidelines.

Dietary energy intake is important for HD patients not only to balance their energy expenditure, but also to protect against protein catabolism. There has been no additional evidence presented against the recommendation of

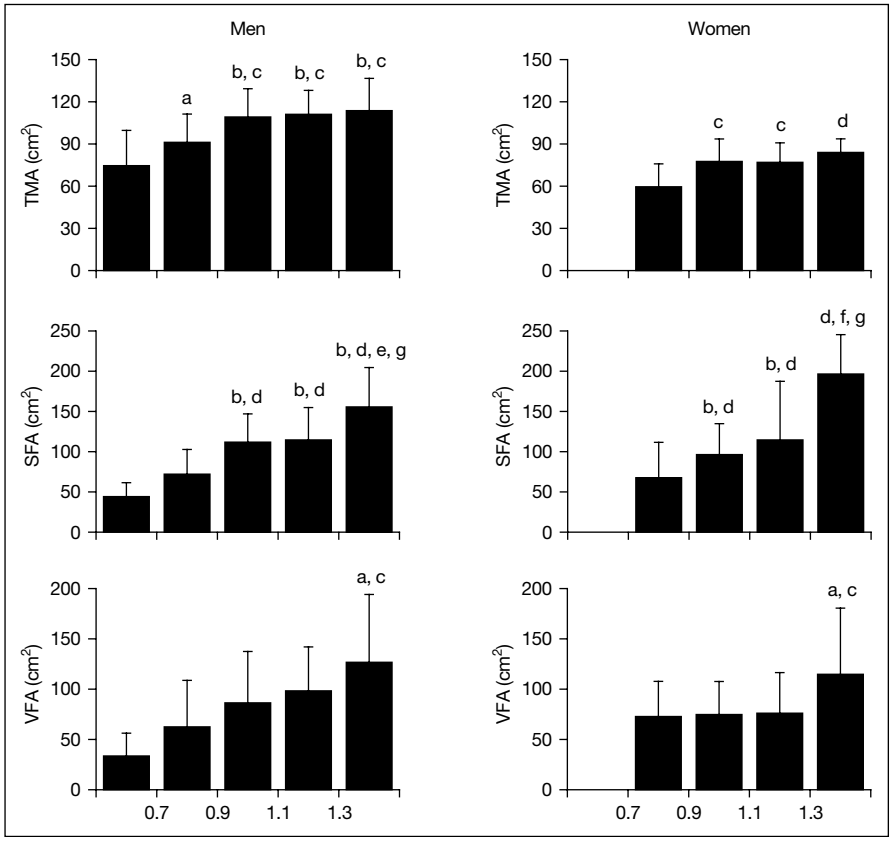

Fig. 2. Association between protein intake and the TMA, abdominal SFA or VFA between the men (left panels) and women (right panels) [45]. TMA = Thigh muscle area. [a,b]$p < 0.05$, <0.01 vs. protein intake of <0.7 g/kg/day; [c,d]$p < 0.05$, <0.01 vs. protein intake of 0.7–0.9 g/kg/day; [e,f]$p < 0.05$, <0.01 vs. protein intake of 0.9–1.1 g/kg/day; [g]$p <0.01$ vs. protein intake of 1.1–1.3 g/kg/day.

35 kcal/kg/day by the NKF-KDOQI and JSN nutritional guidelines. However, those patients with obesity, visceral obesity or metabolic syndrome may need to limit their energy intake to reduce unnecessary fat mass which should have a favorable effect on glucose tolerance and lipid abnormalities.

Nutritional Supplements

Nutritional intervention may be necessary for HD patients suffering from malnutrition, together with the treatment of non-dietary factors. Non-dietary intervention includes increasing the dose of HD, eliminating any catabolic

factors and medical therapy to improve the patient's condition. Dietary counseling is important for dietary intervention, and is sometimes effective for improving nutritional status. However, oral or parenteral nutritional supplements are necessary in many cases of severe malnutrition.

There have been many studies that reported the effect of oral nutritional support for HD patients [46], although reliable data such as those from a randomized controlled study are scarce. These studies have shown that oral nutritional supplements can increase total nutritional intake by 20–50% and result in anthropometric and biochemical improvements in nutritional status. The weight gain was in the 0–12% range, and the increase in serum albumin concentration was 0.05–0.5 g/dl. Caglar et al. [47] evaluated the impact of oral nutritional supplementation on the nutritional status of 85 malnourished HD patients and found that serum albumin had been significantly increased (0.29 g/dl) within 1 month of starting the supplement. A distinctive point of this study was that a supplement with 475 kcal and 16.6 g of protein was administered during HD when the catabolism was considered to be highest. This approach is supported by Veeneman et al. [48] who examined the effect of an oral nutritional supplement during HD on whole body protein balance by means of the stable isotope tracer method. Their acute experiment demonstrated that whole body protein balance was changed from negative to positive during HD by the ingestion of a drink containing proteins with high biological value.

Another interesting approach is a supplement of amino acids three times daily with meals. Eustace et al. [49] examined the effect of essential amino acids (10.6 g/day of Rose formula), and Hiroshige et al. [50] examined the effect of branched-chain amino acids (12 g/day) on the nutritional status of malnourished HD patients. Both studies identified a significant increase in the serum albumin concentration by such supplementation when compared to a placebo. This effect might have been dependent on not only the simple quantitative effect of added amino acids, but also on the specific effect of some amino acids on appetite stimulation and protein anabolism [51].

Oral nutrient supplementation has the advantages of its cost effectiveness and physiological administration route. In contrast, the disadvantage might be poor compliance over a long period. It has been reported that more than 50% of patients dropped out from the Caglar study, even though they received the supplement during HD in order to maintain better compliance [47].

Intradialytic parenteral nutrition (IDPN) may be another choice for nutritional supplementation for malnourished HD patients. The advantages of IDPN are that a solution with high osmolality can be given without central catheter insertion and that it can be performed regardless of a patient's appetite. There are many formulations for IDPN supplementation, from a minimal amount of

nutrients to a large dose with 50 g of amino acids and 1,000 kcal of energy [52]. Pupim et al. [53] have provided evidence for the beneficial effects of IDPN on the protein metabolism of HD patients by using the stable isotope infusion technique. They infused 45 g of amino acids and 650 kcal of energy to patients for 3.5 h from 30 min after starting HD to the end of the dialysis session. The results showed that the fractional albumin synthetic rate was significantly improved in parallel with a significant improvement in whole-body protein synthesis. When IDPN is performed during an HD session, a substantial amount of infused amino acids and dextrose would be lost to the dialysate. Therefore, a relatively large dose of a supplement might be necessary to maintain a positive nitrogen balance. The high cost and non-physiological route for nutritional supplementation are disadvantages of IDPN. Furthermore, such metabolic abnormalities as hyperglycemia, hyperlipidemia, and mineral electrolyte imbalance may occur during IDPN. IDPN is therefore considered as the second choice for the nutritional treatment of a patient who cannot tolerate or cannot be successfully treated by enteral feeding.

Lipids

Dyslipidemia is more prevalent in HD patients than in the general population. The characteristics of dyslipidemia in HD patients are hypertriglyceridemia, a high serum concentration of very low-density lipoprotein and a low-serum concentration of high-density lipoprotein [22]. Intermediate-density lipoprotein may be increased [54], but the low-density lipoprotein and total cholesterol levels are usually within the normal range. Hypertriglyceridemia and low high-density lipoprotein-cholesterol may be associated with visceral fat accumulation and metabolic syndrome in HD patients, as has been similarly shown for the general population [55]. Such dyslipidemia may also have close association with the development of atherosclerosis and cardiovascular diseases, which are the leading causes of death in HD patients, although the exact cause and resulting relationship remain to be proven. On the other hand, a low-serum cholesterol level has been shown to be associated with a poor outcome in HD patients [31]. Such lipid abnormalities are frequently seen in malnourished HD patients.

There are no definite guidelines for treating dyslipidemia in HD patients. Although JSN has recommended that dietary fat should be limited to within 25% of the total energy intake and that the ratio of saturated fat, mono-unsaturated fat and poly-unsaturated fat (the PMS ratio) should be 1:1.5:1 [41], these recommendations are only derived from those for the general population. Saltissi et al. [56] evaluated the effect of a lipid-lowering diet whose formula was based on recommendations by the Australian National Heart Foundation and modified for HD patients with hyperlipidemia [56]. The formula consisted of

dietary fat representing <40% of the total energy intake and a PMS ratio of 1:1:1. The results indicated a reduction of total cholesterol from 232 ± 8 to 209 ± 4 and of triglycerides from 248 ± 35 to 195 ± 9 in patients who had strictly adhered to this dietary prescription. The recommendation for patients with low cholesterol has not yet been published.

Sodium and Water

The interdialytic weight gain of an HD patient is always of major concern to the staff of a dialysis unit, because an excessive increase of fluid volume may be a strong risk for heart failure and rapid removal of the gained fluid in a short time during HD might induce severe hypotension, angina and muscle cramps. When a doctor, nurse and dietitian engage in dialysis counseling of patients not to gain weight, they may sometimes confuse the role of sodium and water intake on the overall weight gain [57].

The plasma sodium concentration is usually maintained within a narrow range of 135–140 mEq/l, even in an HD patient, and this concentration is principally regulated by thirst and consequent water drinking by the patient who has lost renal regulatory mechanisms. A patient taking sodium feels thirsty and wants to drink. Even if the patient has been educated not to drink too much, it is natural to drink until the feeling of thirst has been relieved, since the driving force for drinking according to thirst is very strong. In contrast, a patient with a restricted sodium intake would not drink, even with free access to water. Therefore, a HD patient should first be educated to restrict sodium intake and then to avoid unnecessary drinking. The restricted intake of sodium chloride is recommended to be <5 g/day [58] or 0.15 g/kg/day (JSN) [41].

It is noteworthy that a low-interdialytic weight gain has been proven to be a higher risk for mortality than a moderate-interdialytic weight gain. The plausible explanation for this phenomenon is that a low-interdialytic weight gain is associated with poor nutritional intake and malnutrition, which is a serious risk factor for morbidity and mortality [59]. Unexpectedly, a very high-interdialytic weight gain only represents a modestly increased risk for mortality.

Conclusion

The prevention of nutritional disturbances is one of the most important factors in prolonging the survival of an HD patient. In addition to PEM, the aspect of over-nutrition needs to be extensively debated to prevent resulting atherosclerosis and cardiovascular diseases. The preferable nutritional status and the objectives for nutritional intervention remain to be determined for HD

patients, and the nutritional recommendations need to be considered from the results of further studies.

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Hiromichi Kumagai, MD, PhD
Department of Clinical Nutrition, School of Food and Nutritional Sciences
University of Shizuoka
52-1 Yada, Suruga-ku, Shizuoka-city
Shizuoka 422-8526 (Japan)
Tel. +81 54 264 5567, Fax +81 54 264 5567, E-Mail kumagai@u-shizuoka-ken.ac.jp

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Diet Therapy in Patients Receiving Peritoneal Dialysis

Yoshihiko Kanno

Department of Nephrology, Saitama Medical University, Saitama, Japan

Abstract

The guidelines in US and Japan recommend CAPD patients to have protein intake twice that of CKD patients before the start of dialysis therapy. However, it is very difficult for patients, and may encourage the deterioration of residual renal function (RRF). We propose 0.8 g/kg body weight/day of protein intake for CAPD patients who still urinate, because it maintained RRF significantly in our study of 24 Japanese patients. Also in our investigation in 93 patients, almost all patients did not satisfy their recommended amount in energy (92.4%), protein (91.3%), and calcium (90.3%) intake. For the patients, it is hard to change their life-style, especially dietary habits. We have to consider the improvement of dietary guidelines which are suitable for individual patients, and the adaptation of behavior science to nutrition counseling.

The NKF K/DOQI Guidelines for Nutrition advocate certain dietary allowances for patients on peritoneal dialysis (PD) [1]. They recommend a dietary protein intake of 1.2–1.3 g/kg body weight/day in clinically stable chronic PD patients. This is the core of their nutritional guidelines for patients on PD. The 1997 guidelines in Japan also recommend a similar amount of protein intake of 1.1–1.3 g/kg body weight/day [2].

Protein intake recommendations in both guidelines are set high in comparison to diets before the introduction of dialysis at an early stage of renal insufficiency. There is ongoing discussion regarding the appropriate amount of protein intake at the early stages of renal insufficiency, but the K/DOQI guidelines are 0.6–0.75 g protein/kg body weight/day and the Japanese guidelines are 0.6 g protein/kg body weight/day. The amount of protein recommended after dialysis begins is set at almost twice that of the pre-dialysis standards. This is because protein losses into peritoneal dialysate are almost always higher than protein

losses into hemodialysate. A state of protein deficiency can easily result from peritoneal protein losses that can reach an average of 5–15 g/24 h [3] or from anorexia due to glucose absorption from dialysate that can reduce dietary intake. The resulting malnutrition stemming from these factors is associated with poor outcomes in PD patients [4]. It has been shown that malnutrition is a factor contributing to poor outcomes for patients on hemodialysis [5]. The DOPPS Study [6], designed to investigate the usefulness of K/DOQI, and the Euro-DOPPS Study [7], showed that malnutrition is a factor contributing to poor outcome, and noted that body mass index and serum albumin were among the predictive factors.

However, changing daily habits, including what is eaten at meals, is a challenge [8, 9]. It is almost impossible for people who complied with dietary restrictions for an extended period in the early stages of renal insufficiency to suddenly double their protein intake upon the initiation of renal dialysis, and it is even harder for those who closely adhered to a low-protein diet.

The actual protein intake of adults in Japan is about 1.6 g/kg/day, but this figure includes young people. There are many healthy elderly people whose intake is $<$1.2 g/kg/day. Also, since PD is essentially a therapy that depends on residual renal function (RRF) [10], the maintenance of RRF is beneficial for patients' quality of life [11]. In order to maintain RRF, it may be just as important to follow a low-protein diet after dialysis begins, as it is before the start of dialysis therapy.

For the two reasons stated above, we believe that it may be necessary to reconsider the advisability of following a high-protein diet of 1.2 g protein/kg/body weight/day for a certain period of time following the initiation of dialysis, at least for the period in which RRF contributes to weekly total clearance. A recent report noted that only 39% of patients actually comply with a protein intake diet of 1.2 g protein/kg body weight [12]. But since continuing on a low-protein diet may result in malnutrition, we considered it worthwhile to study a protein intake of about 0.8–1.0 g protein/kg body weight/day.

At our institution, we implemented nutrition counseling for CAPD patients that started on a protein intake of 0.8 g/kg body weight/day instead of the usual 1.3 g/kg body weight/day, as practiced previously (fig. 1). We compared the course of disease of two groups of 12 patients after discharge. The protein-restricted group received the new nutrition counseling (9 males, 3 females, 3 diabetic nephropathy; average age 55.8 years (SD = 12.5)) and the conventional group received traditional counseling for a CAPD diet (7 males, 5 females, 2 diabetic nephropathy; average age 55.1 years (SD = 10.5)).

As shown in table 1, 6 months after the start of dialysis and nutrition counseling, we measured RRF and dialysis efficacy and found that urine output increased in the protein-restricted group, but was unchanged in the conventional

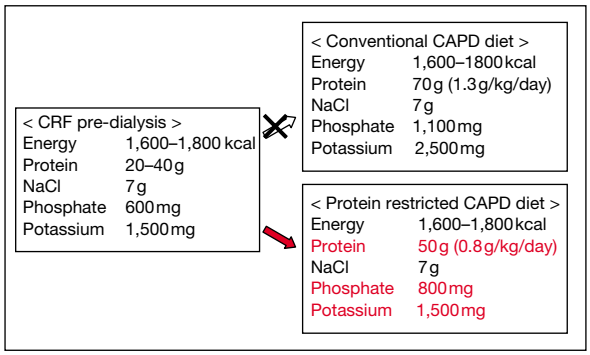

Fig. 1. Detailed ingredients of each dietary menu for the PD patients.

Table 1. Changes in indicators of the patients receiving PD

		0 month	6 month
BUN (mg/dl)	Conventional	55.0 ± 5.0	55.7 ± 7.4
	Protein restricted	52.7 ± 3.4	60.3 ± 1.9
Serum creatinine (mg/dl)	Conventional	8.0 ± 0.7	7.6 ± 0.9
	Protein restricted	7.6 ± 0.7	9.8 ± 1.1
Serum albumin (g/dl)	Conventional	3.7 ± 0.6	3.4 ± 1.1
	Protein restricted	3.8 ± 0.8	3.6 ± 0.6
Plasma potassium (mEq/l)	Conventional	4.4 ± 0.9	4.3 ± 0.6
	Protein restricted	5.0 ± 0.9	4.6 ± 0.9
Serum phosphate (mg/dl)	Conventional	6.1 ± 1.4	4.8 ± 1.0
	Protein restricted	5.6 ± 1.2	4.7 ± 0.8
Hemoglobin (g/dl)	Conventional	8.2 ± 2.2	9.8 ± 2.3
	Protein restricted	8.8 ± 1.6	9.4 ± 1.4
Urine volume (ml/day)	Conventional	1,160 ± 254	810 ± 243
	Protein restricted	1,050 ± 110	1,009 ±113

Data are expressed in mean ± SD.

group. There was no statistically significant difference in Kt/V or total clearance between groups, but RRF (ml/min) was maintained in the protein-restricted group and was significantly different than the conventional protein intake group (fig. 2). There was little difference between the actual protein intake as calculated from protein catabolic rate and the amount recommended in counseling as measured by diet records, a diet history questionnaire, and clinical data (fig. 3).

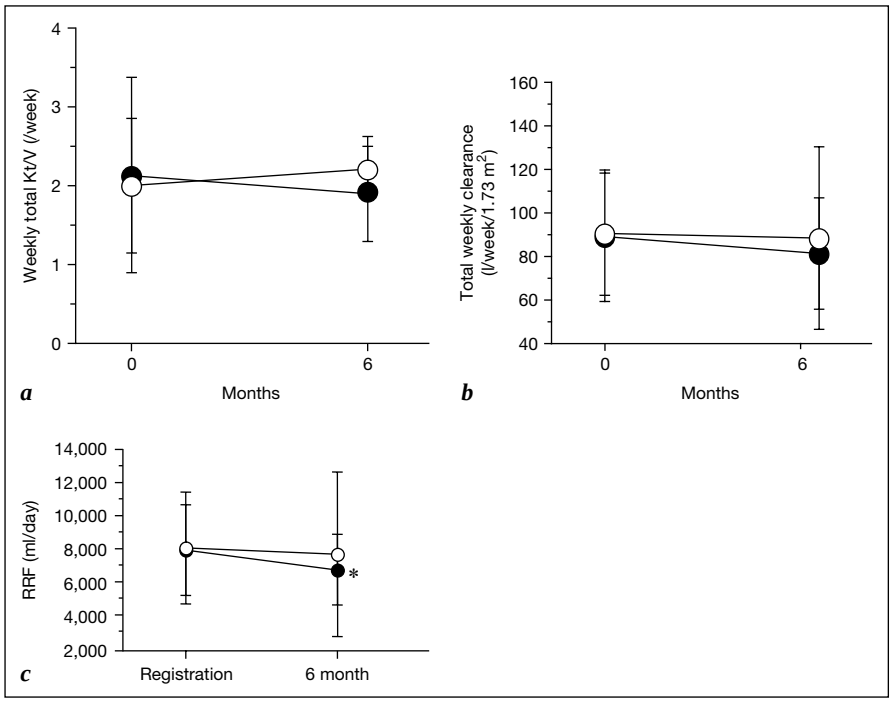

Fig. 2. Changes in the indicators of the patients with conventional and protein restricted diets. Closed and open circles denote conventional PD and protein restricted PD diets, respectively. Data are expressed as mean with standard deviation (SD). *Mean $p < 0.05$ vs. at registration (paired t-test). (***a***) Changes in total Kt/V. (***b***) Changes in total weekly clearance. (***c***) Changes in RRF.

To summarize these findings:

1. After 6 months, RRF was preserved in the group that received nutrition counseling for a protein restricted diet and was significantly different compared to the group that received conventional nutrition counseling.
2. Hypoproteinemia, which we feared might result from reduced protein intake, was not found.
3. No significant difference was found between groups for weekly total clearance, which included peritoneal clearance.
4. There was little resistance to moving from a low-protein diet introduced from before dialysis began to a CAPD diet, with small divergence between the recommended and actual intake.

We believe, however, that a longer period of observation is needed to determine differences in clinical courses between different dietary regimens.

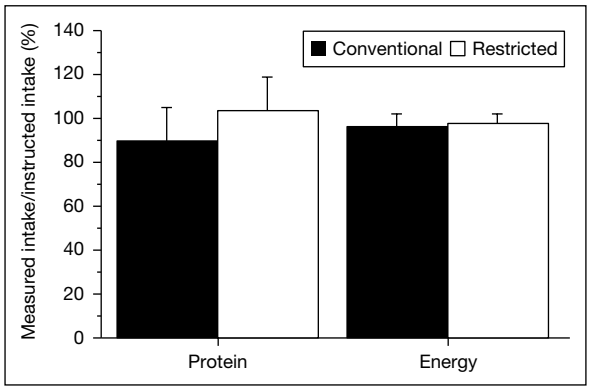

Fig. 3. Actual intake of protein and energy as a percentage of the recommended amounts in the patients receiving PD.

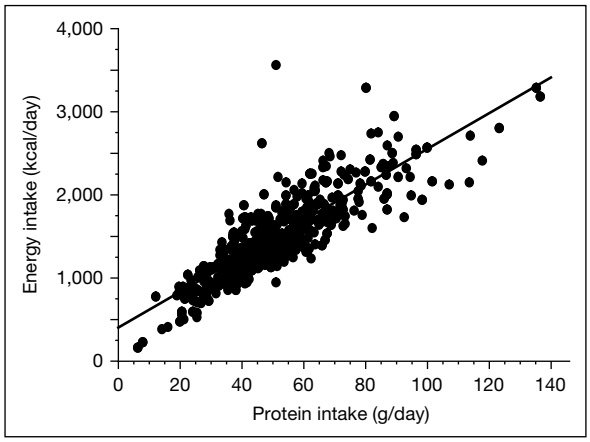

Fig. 4. Correlation between calories and protein intake in the dialysis patients. Energy intake = 21.487 × protein intake + 408.407; $r^2 = 0.703$.

The DOQI guidelines recommend a calorie intake of 35 kcal/kg/day (below age 60) and 30–35 kcal/kg/day (above age 60). The Japanese guidelines call for 35–40 kcal/kg standard weight/day for people at or above elementary school age [2]. Energy requirements for patients on dialysis are believed to be the same as those for healthy people, but restrictions for patients with diabetes should be made as appropriate. Adequate energy consumption is a basic feature of dietary therapy for patients with chronic renal failure in the pre-dialysis stage. However, it is very difficult to take in a sufficient number of calories when on a diet that restricts protein intake (fig. 4).

Table 2. The daily intake amount of each nutritional factor in 93 Japanese patients receiving PD

	Amount actual intake	Sufficient rate (%)
Energy (kcal)	1,473 ± 377	
(kcal/kg SBW)	26.3 ± 6.3	84.8
Protein (g)	47.9 ± 15.3	
(g/kg Bw)	0.85 ± 0.27	77.3
Lipid (g)	42.8 ± 18.9	
Carbohydrate (g)	218.4 ± 56.4	
Calcium	341 ± 155	56.8
Salt (g)	7.2 ± 2.7	102.9
Pottasium (mg)	1,581 ± 596	71.8
Phosphate (mg)	708 ± 240	101.1

The actual intake is calculated by DHQ (Dietary h Questionnaires). Sufficient rate expresses the rate of actual intake for the recommended amount by the Japanese Society of Nephrology. Data are expressed in mean ± SD. BW = Body weight; SBW = standard body weight.

We summarized the results of a dietary study of 93 patients on PD at Saitama Medical School Hospital. The clinical profile of the 93 patients is as follows (mean [SD]): 54 males (58%), 39 females (42%), average age (59.6 years [14]), history of dialysis (3.6 years [3.6]), height (159.5 [8.65]), weight (57 kg [9.3]), body mass index (23 [3]), blood pressure (134 [17]/79 [15]).

Table 2 shows the nutritional intake of the patients. Calorie intake was low (at 84.8% of the amount stated in the guidelines) which likely reflected the low-protein intake as a result of counseling. Compliance with the other major nutritional recommendations was also low, with only salt and phosphorus intake meeting the amounts recommended in the guideline (fig. 5). This does not mean that there is adequate intake. Rather, for these two items, it seems to show the technical obstacles of adequate nutrition on a restricted diet. We reported separately on the comparison with hemodialysis patients in another chapter in this book.

A typical dialysate for PD contains a certain percentage of dextrose, which can be said to have a calculated calorie intake equivalent, but in recent years there have been reports challenging this suggestion [13]. Some have recommended non-oral nutritional compensation, such as the intravenous administration of amino acids or dextrose [14] or provision of supplements [15]. More recently, the use of dialysis fluid with amino acids [16] has been recommended. However, some question the usefulness of such supplements. From the point of

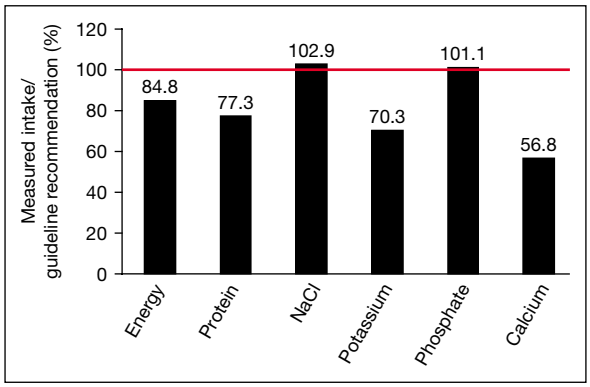

Fig. 5. Measured actual intake of several nutritional factors as a percentage of the amount recommended by guideline of Japanese Society of Nephrology in patients receiving PD.

view of cost performance as well, it is necessary to look at this with caution. In general, when dietary restrictions are lax, there is not much decrease in appetite, and compared to hemodialysis, a smaller incidence of poor nutrition may be expected [17]. However, since there have been reports of gastrointestinal disorders due to abnormalities in digestive tract hormones [18], caution is advisable at all times. Especially in regard to protein, there are reports showing that over 40% of patients have inadequate intake, mainly the elderly who have complications or decreased RRF. However, unwitting high protein intake can cause uremia, so adequate dialysis, specifically a weekly Kt/V of 2.0 or more, is required [19].

There are many reports on how RRF is involved in calorie intake, not just protein intake [20, 21], and it is thought that this is involved in the decrease of appetite and taste. If so, it can be seen how maintenance of RRF becomes very important for the maintenance of nutritional status. Johnson et al. carried out a prospective cohort study of 146 patients on PD. The average follow-up period was 20.5 months (SD = 14.8) with a decrease in RRF over that period of an average of only 0.5 ml/min/month. Johnson et al. [22], using a multivariate Cox proportional hazards model analysis, showed that time from commencement of PD to development of anuria was independently predicted by baseline RRF [adjusted hazard ratio (HR) = 0.81, 95% CI = 0.60–0.81], dialysate/ plasma creatinine ratio at 4 h (HR = 2.87, 95% CI = 2.06–82.3), body surface area (HR = 6.23, 95% CI = 1.53–25.5), dietary protein intake (HR = 2.87, 95% CI = 1.06–7.78), and diabetes mellitus (HR = 1.65, 95% CI = 1.00–2.72). Decline of RRF was independent of age, gender, dialysis modality, urgency of

initiation of dialysis, smoking, vascular disease, blood pressure, medications (including angiotensin-converting enzyme inhibitors), duration of follow-up, and peritonitis rate.

RRF was predicted by protein intake in the study of Johnson et al. as well, but RRF at the time of initiation of PD was more strongly involved than anything else. Thus, in order to preserve RRF over the long-term, introducing PD at an early stage may be useful before deterioration sets in. Clinical findings on patients with chronic renal insufficiency in the early stages show that excessive protein intake at this stage is a stress on RRF [23, 24]. Taking our findings into account as well, we believe that an appropriate level of protein intake, especially at the beginning of dialysis, should be 0.9–1.0 g protein/kg body weight/day [25]. These studies should result in improved levels of nutrition and less mortality [26].

As discussed, there are many guidelines regarding dietary intake for patients on PD, but there is no consensus on whether or not they are appropriate. In reality, we deal with patients on an individual basis, and since there is no standard for evaluating dietary intake precisely, not much effort is put into nutrition counseling for patients. There are reports on the use of computer programs, but there is a high rate of misdiagnosis of malnutrition [27] and it will be some time before standardization is achieved. Also, there is no method of compensation based on such evaluations.

In order to reform the dietary habits of patients, it is necessary to introduce ideas from behavioral therapy and follow a process that tailors a program for each individual. It may be necessary to involve personnel other than the physician and the dietician to provide psychological education. For example, attempts to use social behavior science to correct daily habits, including dietary habits, have been made overseas, using nurses in a central role to treat diabetic patients. Improving dietary habits is of great importance for the prevention of lifestyle related diseases in advanced countries, not just for patients on PD. However, medical approaches that have been used so far are unlikely to result in success [28]. Team medicine is essential for the management of PD. As with other fields of medicine, communication between physicians and other healthcare professionals in nephrology is desirable. New approaches like those outlined above can be adapted without difficulty ahead of other fields because of the nature of this area.

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Yoshihiko Kanno, MD, PhD
Department of Nephrology, Saitama Medical University
38 Morohongo, Moroyama, Iruma
Saitama 350-0495 (Japan)
Tel. +81 49276 1611, Fax +81 49295 7338, E-Mail kannoyh@saitama-med.ac.jp

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Diet Therapy after Kidney Transplantation

A Comparative Debate between Japan and Western Countries

Shinichi Nishi[a], *Fumitake Gejyo*[a], *Kazuhide Saito*[b], *Yuki Nakagawa*[b], *Kota Takahashi*[b]

[a]Blood Purification Center, Medical and Dental Hospital, [b]Division of Urology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata City, Japan

Abstract

Kidney transplantation has a powerful influence on the nutritional status of patients with end-stage renal disease. How to control diet varies in different races and periods after kidney transplantation. In general, malnutrition in patients with end-stage renal disease slowly recovers after kidney transplantation; however, several dietary interventions are required throughout the post transplant course. While hyperalimentation is warranted to control the hypercatabolic state immediately following the transplant operation, dietary restriction of protein, salt and calories is recommended to prevent life-style related diseases, which affect patient and graft survival. No consensus on dietary control in kidney transplant recipients has been reached yet. Herein, we present the nutritional status of Japanese kidney allograft recipients, discuss some unresolved nutritional problems and review the recent literature.

Compared to healthy subjects, patients undergoing maintenance hemodialysis are usually malnourished. They have lower muscle volume and/or body mass index (BMI) due to uremic catabolism, diabetes [1] and higher leptin levels [2]. Malnutrition that exists prior to transplantation may lead to an increased risk of infection, delayed wound healing, and muscle weakness [3].

Because of the improved appetite, many transplant recipients become overweight or even obese [4]. Transplant recipients are at particular risk of obesity-related diseases, such as type 2 diabetes, hypertension, hyperlipidemia and hyperuricemia, which play a crucial role in the pathogenesis of atherosclerotic

heart disease and of chronic allograft nephropathy [5]. Therefore, an appropriate diet is important not only to prevent cardiovascular events but also to maintain normal graft function.

Diet Control in the Early Phase after Kidney Transplantation

Catabolic Conditions after Kidney Transplantation

The immediate post-transplant period is characterized by a hypercatabolic state. Beside the operation, other factors and events inflict a considerable catabolic effect on the recipient's body, such as acute tubular necrosis, acute graft rejection, as well as the effect of high doses of antirejection treatment [6].

The intensive catabolic condition continues at least for a few months after kidney transplantation. During this time, the various parameters of nutrition, such as body components, biochemical indexes and immunological markers show signs of deterioration. The body weight falls below the dry body weight of the recipient before the operation. The body fat mass drops accordingly [7]. Anthropometric markers, such as triceps, biceps and subscapular skin folds and midarm circumference reveal a decrement after transplantation [7, 8]. The absolute blood lymphocyte count drops significantly because of the use of immunosuppressive drugs, particularly steroids. Figure 1 reveals the sharp decline of body weight, albumin and lymphocyte count among Japanese recipients (n = 32) during the first three post-transplant months at a rate of 7.6, 21.3 and 61.1%, respectively.

The DOPPS study has shown that the mean BMI of European and American dialysis populations is 25.2 kg/m^2 [9]. In contrast, the BMI of Japanese hemodialysis patients ranges from 19.0 to 20.0 kg/m^2 [10]. Consequently, since Japanese transplant patients are more vulnerable to developing emaciation after kidney transplantation, we must pay close attention to diet control in order to prevent malnutrition and its related complications, such as infection and delayed wound healing.

Diet in the Early Phase after Kidney Transplantation

To control the rapid catabolic state following kidney transplantation, an appropriate intake of dietary protein and calories is warranted. Table 1 shows the typical target of diet control in Western countries and Japan. In Western countries, the daily requirement of protein throughout the early post-transplant period generally ranges from 1.3 to 2.0 g/kg body weight, with a recommended

Table 1. Targets of diet control in kidney transplantation (cited from [6])

	Early phase	Late phase
Western countries		
Calorie, kcal/kg body weight	30–35	35
protein, g/day	1.3–2.0	0.8–1.0
NaCl, g/day	<6.0–7.0	<6.0–7.0
Japan		
Calorie, kcal/kg body weight	35	35
Protein, g/day	1.0–1.3	0.8–1.0
NaCl, g/day	<6.0–7.0	<6.0–7.0

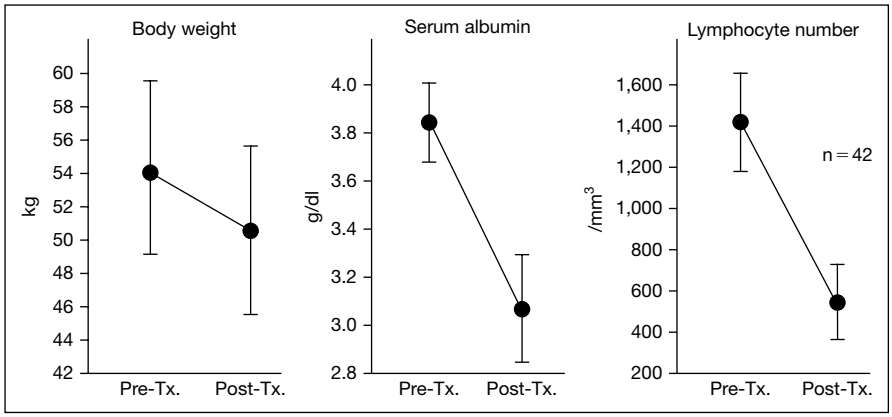

Fig. 1. The changes of body weight, serum albumin and lymphocyte number during the 3 months after transplantation. Each parameter significantly drops 7.6, 21.3 and 61.1%, respectively from pre- to post-transplantation level (n = 42 mean ± SD). Tx = transplantation.

daily calorie intake of 30–35 kcal/kg body weight [6]. However, this amount of protein intake is usually accompanied by a relentless rise of blood urea nitrogen and uric acid. In Japan, protein intake of about 1.0–1.3 g/kg body weight and a total calorie intake of 35 kcal/kg body weight per day are the standard levels agreed upon by many transplant institutions.

Figure 1 shows the body weight changes of 42 living kidney transplant recipients during the first 3 months. The reduction of body weight was restricted to <5% from the dry weight before the operation. During this period, there were no apparent infections and/or delay of wound healing. Therefore, a protein intake level of 1.0–1.3 kg/body weight per day seems reasonable enough even in the

very early post-transplant period. At its best, creatinine clearance of the recipients is usually below 60–70 ml/min during the early phase after the transplantation. As in any patient with renal dysfunction, mild restriction of protein, <0.8 g/kg body weight, is recommended to avoid glomerular hyperfiltration secondary to an excess load of protein. In a patient with a single-functioning kidney, glomerular hyperfiltration is an inevitable complication [11]. Therefore, nephrologists in Japan have adopted a rather lower dietary protein level for renal transplant recipients as compared to Western countries.

Post-transplant hypertension (PTHT) and post-transplant diabetes mellitus (PTDM) are well-known complications. PTHT in cyclosporine-treated renal transplant recipients is known to be sodium dependent [12]. Since a renal allograft is naturally vulnerable to the excess load of salt, a salt intake of <6 or 7 g/day is recommended for the prevention of PTHT. PTDM is frequently induced by the adverse effects of immunosuppressive agents, including steroids and calcinuerin inhibitors. Additionally, older age, greater BMI, presence of hepatitis C virus infection, and smoking have all been reported to be significant risk factors for PTDM [13]. A restricted calorie intake of <30 kcal/kg body weight seems rational from the perspective of blood sugar control in patients requiring rest after transplantation. On the other hand, preventing catabolism is thought to be a priority in the early phase after kidney transplantation; thus, a calorie intake of 35 kcal/kg body weight is generally recommended, even if the recipient has PTDM requiring insulin injection. This is especially applicable for Japanese recipients who generally have low BMI of <22 at the time of surgery.

Nutrition in the Late Phase after Kidney Transplantation

The Change in Body Weight after Kidney Transplantation

When the early hypercatabolic state following kidney transplantation is terminated, the nutritional balance of many recipients gradually improves, as is reflected by a gradual rise of their body weight. Figure 2 demonstrates the rate of body weight change of recipients (n = 32) at our institution throughout a 5-year period after kidney transplantation. At first, the mean body weight dropped less than that of dry weight, but it subsequently recovered to the level of dry weight at 3 years after the operation, and finally exceeded the dry weight by 5% at 5 years after the operation. Compared to the situation in Western countries, where body weight recovery occurs within 1 year of the operation [14, 15], the change of body weight among Japanese recipients seems relatively slow.

The etiology of obesity in renal transplant recipients is multifactorial [16]. The sustained administration of oral steroid agents is a key factor. In addition,

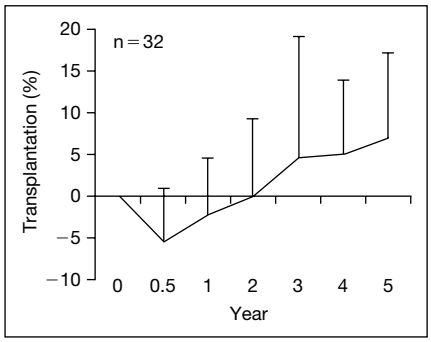

Fig. 2. The rate of body weight change during 5 years after kidney transplantation in our institution. Pre-transplantation weight is dry weight of each case (n = 32, mean ± SD).

the withdrawal from the catabolic and psychological burden of dialysis treatment is considered to be a potent stimulant for appetite. The lack of active exercise by many recipients, who usually tend to be restricted in their physical activity because of the fear of harming their transplants by excessive exercise, may be a contributing factor. Finally, obesity may be iatrogenically induced as doctors sometimes encourage recipients to gain excess body weight.

Leptin, an adipocytokine that has an inhibitory effect on the satiety center of the brain, rises in serum of dialysis patients to levels higher than healthy subjects. Serum leptin level decreases after kidney transplantation according to the recovery of glomerular filtration rate, thereby stimulating appetite. Nonetheless, the relationship between leptin level and post-operative nutritional condition or dietary intake is still unclear [17, 18].

Life-Style Related Diseases and Diet Therapy

Obesity

Obesity itself is recognized as an important life-style related disease which produces other life-style related diseases, such as hypertension, hyperlipidemia, hyperuricemia and diabetes mellitus [19]. These comorbid conditions are frequently observed in post-operative transplant recipients. Post-transplant obesity is considered to be a significant risk factor for cardiovascular diseases [20]. It also produces glomerular hyperfiltration in the graft, leading to an earlier deterioration of its function [21].

Metabolic syndrome (MS), a constellation of hypertension, hyperlipidemia and hyperglycemia along with visceral obesity, is particularly common among renal transplant recipients. It has a potent synergistic adverse effect on the development of cardiovascular disease, greater than that of its individual components

[22]. De Vries et al. [23] reported a high prevalence of MS (63%) in a cohort of 606 patients 6 years after transplantation. They emphasized that the presence of MS was related to the impaired renal allograft function beyond 1 year post-transplantation. However, not all individual components of the MS contributed equally to the impaired renal function. Only systolic blood pressure and hypertriglyceridemia were independent risk factors in the multivariate analyses.

So far, no ideal remedy to reduce the prevalence of post-transplant obesity has been adopted. Active interventions, such as appropriate diet, physical exercise, withdrawal of steroid agents and psychological education, are expected to be effective [24].

Hypertension

Salt restriction is generally advisable for the prevention of hypertension. Because a patient with a kidney transplant has only one functioning kidney, his/her ability to excrete sodium is theoretically halved compared to a healthy subject. Therefore, a more stringent restriction of salt is thought to be favorable. However, this matter remains somewhat controversial. Moeller et al. [25] and Prasad et al. [26] found no direct relationship between urinary salt excretion and blood pressure in renal transplant recipients.

There is evidence that increasing potassium intake to more than 90 mEq/day is a useful dietary strategy for the prevention of hypertension [27]. However, high potassium intake is not without risk in patients with decreased graft function.

Hyperlipidemia

The control of hypercholestrolemia is relatively easy with low cholesterol diet and statins. Hypertriglyceridemia though is more difficult to control, because diet and statin administration are usually ineffective. There is evidence that hypertriglyceridemia, rather than hypercholesterolemia, exerts the deleterious effect on graft and patient survival [28]. Restriction of calorie intake and avoiding alcohol are the generally recommended measures in patients with hypertriglycemia. The administration of fibrate agents excluding gemfibrozil is relatively contraindicated in patients with renal dysfunction [29]. Note that in Japan, the use of gemfibrozil is not covered by insurance for medical care. The administration of agents containing omega-3 fatty acids or the intake of foods rich in fish oil is considered safe [30, 31].

Hyperuricemia

The basic preventive strategy for hyperuricemia is the restriction of dietary purine intake. Dietary restriction of foods rich in purines, such as protein, is desirable in patients with hyperuricemia. Other risk factors for hyperuricemia include

smoking, alcohol intake and dehydration [32]. Alcohol decreases renal excretion of uric acid; thus, excess alcohol intake should be avoided. Sustained hyperuricemia causes graft dysfunction. Gerhardt et al. [33] reported that transplant survival in hyperuricemic patients (male: >8.0 mg/dl, female: >6.2 mg/dl) 2, 4, and 5 years post-transplantation was significantly reduced (92.2, 70.6, and 68.8% vs. 98.1, 85.6, and 83.3%), compared to normouricemic recipients [33].

Conclusion

After reviewing the nutritional problems following kidney transplantation, we conclude that although diet is the basic treatment for comorbid conditions after transplantation, various nutritional problems need further interventions and are yet to be resolved by future clinical trials.

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Shinichi Nishi
Blood Purification Center Niigata University Medical and Dental Hospital
Asahimachi-dori 1-754
Niigata City 951-8520 (Japan)
Tel. +81 25 227 2770, Fax +81 025 227 0775, E-Mail snishi@med.niigata-u.ac.jp

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Sodium and Kidney Disease

Hiromichi Suzuki[a], *Tsuneo Takenaka*[a], *Yoshihiko Kanno*[a], *Yoichi Ohno*[a], *Takao Saruta*[b]

[a]Department of Nephrology, Saitama Medical University, Saitama,
[b]Emeritus Professor of Keio University, School of Medicine, Tokyo, Japan

Abstract

Salt is essential and important for maintaining life. Excess salt intake produces an increase in blood pressure. In several subpopulations of patients with hypertension, such as those with obesity, post-menopausal women, and patients with chronic kidney diseases, for example, salt sensitivity is based on a pressure-natriuresis mechanism. In this mechanism, neuro-humoral regulation is mainly responsible for sodium handling. In addition, NO has a powerful effect on the pressure-natriuresis mechanism. Based on this mechanism, progression of chronic kidney disease is governed by salt uptake. Moreover, a genetic component for salt sensitivity is important in normotensive subjects with a family history of hypertension. In these regards, modulation of salt is of utmost importance in the fields of hypertension and nephrology.

Salt is essential for life, however, it is an important candidate dietary substance that needs to be evaluated as a potential factor contributing to the development of hypertension and progression of chronic kidney disease. In normotensive subjects, the effects of salt intake on blood pressure appear to be relatively small; however, increased salt intake may increase intraglomerular pressure, which can exacerbate chronic renal damage and increase the risk for progressive kidney disease. The mechanism underlying salt-induced blood pressure elevation and progression of chronic kidney diseases is based on the concept that patients with a salt-sensitive increase in blood pressure may have diminished nephron mass and an overall reduction in glomerular ultrafiltration capacity, in addition to enhanced sodium reabsorption, which changes the slope of the pressure–natriuresis curve. In addition to this, there are a number of mechanisms by which excess salt intake induces an increase in blood pressure. These include the suppression of the activity of the renin–angiotensin

system and sympathetic nervous system during salt loading, increased activity of Na-K ATPase, and changes in nitric oxide (NO) activity contributing to increased oxidative stress. Such effects are observed in patients with essential hypertension [1–4]. In this article, we will discuss the relation between salt and the kidney, mainly based on work from our group. We, however, acknowledge that many investigators in this field have made important contributions to understanding the mechanism of blood pressure regulation by the kidney.

Role of Salt in Pressure–Natriuresis Relationship

The kidney–blood volume–pressure control system works by shifting the balance between sodium intake and output. A shift in favor of sodium intake causes accumulation of fluid and leads to blood pressure elevation. On the other hand, a shift in favor of sodium output induces the opposite effect, resulting in a fall in blood pressure. Abnormality in the pressure–natriuresis response has been induced by various humoral and neural factors in the kidney, as well as elsewhere in the body. In Dahl salt-sensitive (DS) rats, elevation of blood pressure has been shown to result from salt loading, and renal transplantation from DS rats to Dahl salt-resistant (DR) rats can elevate the recipient's blood pressure [5, 6]. These results indicate that the intrinsic defects in the kidney of DS rats might be associated with elevation of blood pressure in this hypertensive rat model. Takenaka et al. [7] characterized the pressure–natriuresis curve of DS rats using in vivo renal perfusion [8]. When untreated, in the DS rats the pressure–natriuresis curve was blunted and excretion of prostaglandin E2 was decreased in comparison to DR rats. With the cyclooxygenase inhibitor, indomethacin, the pressure–natriuresis curve in the DR rat was blunted, while no significant changes were observed in the DS rat. Prostaglandin E2 synthesis was reported to be diminished [9] and prostaglandin E2 receptor was up-regulated [10]. Combining these observations with our findings, the decreased activity of renal prostaglandins, at least PGE2, appeared to be responsible for the blunted pressure–natriuresis relationship in DS rats. These results have some clinical implications. Patients with salt-sensitivity taking medicines containing a cycloxygenase inhibitor may experience elevation of blood pressure and edema.

Several subpopulations of patients with hypertension are classified as salt sensitive based on pressure–natriuresis. These include obese patients, those with chronic kidney diseases, the elderly, and post-menopausal women. However, there are no easy and simple tools in clinical practice to identify those individuals who are sensitive to dietary salt and those who are not. With these

data in mind, our group performed further studies utilizing this system in rat models.

Insulin resistance is a characteristic feature of obesity, as is hypertension [11]. Insulin resistance can elevate blood pressure by several mechanisms in patients with obesity by causing sodium retention, activating the sympathetic nervous system, or stimulating vascular smooth muscle growth and hypertrophy [11]. In a dog model, Rocchini [12] demonstrated that chronic insulin infusion caused a progressive rise in blood pressure associated with sodium retention. Suzuki et al. [13] characterized the pressure–natriuresis curve of Wistar fatty rats (WFR), developed as a new model of obesity-related non-insulin-dependent diabetes mellitus (NIDDM). This rat strain was derived from crosses between the obese Zucker (13 m strain, fa/fa) and Wistar-Kyoto rats [14]. In WFR, the pressure–natriuresis curve was shifted to the right and its slope was flattened compared to control Wistar lean rats, indicating an underlying abnormality in renal excretory function. Moreover, salt loading produced an elevation of blood pressure in the WFR. The shift of the pressure–natriuresis curve to the right before the development of hypertension suggests that the response is not a result of impairment of the pressure–natriuresis relationship produced by hypertension, but rather is related to a pre-existing alteration of this relationship in WFR. An association between hyperinsulinemia and blood pressure sensitivity to salt has been shown in young normotensive black subjects [15]. Higher dietary intake of sodium causes a significant decline in insulin sensitivity. Overall, the findings suggest that an excess of salt intake may elevate blood pressure in obese subjects with hyperinsulinemia through alterations in the pressure–natriuresis responses.

Staessen et al. [16] reported that the prevalence of hypertension is 2.2 times higher in post-menopausal women than in pre-menopausal women. These authors suggested that increased sodium reabsorption by the kidney may play an important role in the blood pressure elevation after menopause. However, the underlying mechanisms of the sexual differences in hypertension are not completely understood. Our group previously reported that decreases in sex hormones and increases in sodium sensitivity are important factors in the genesis of post-menopausal hypertension [17]. Dahl's genetically selected salt-sensitive rat strain shows the effects of gonadal hormones on salt-induced hypertension, as do other hypertensive rats. Blood pressure increased in ovariectomized DS rats fed a high sodium diet, but it did not differ as a function of hormonal treatment [18]. Again, utilizing Roman's method, Otsuka et al. [19] demonstrated that the pressure–natriuresis relationship was blunted in DS rats compared with DR rats. The impaired pressure–natriuresis response of DS rats was further blunted by ovariectomy, while that of DR rats was not. The ovariectomized DS rats developed hypertension earlier than sham-operated DS

rats by salt loading, indicating that ovariectomy enhances genetic salt sensitivity by blunting the pressure–natriuresis relationship, which precedes the development of overt hypertension in female DS rats.

Alterations in the renin–angiotensin system, along with other hormonal and autocrine factors, likely have roles in the mediation of salt sensitivity in patients with hypertension. Investigations have shown that renin levels are inappropriately suppressed in patients with salt-sensitive hypertension, and blockade of the renin–angiotensin system in salt-sensitive patients has a tendency to restore renal hemodynamics to a state favorable to salt excretion [20]. Therefore, manipulations that alter the renin–angiotensin system greatly influence the pressure–natriuresis relationship. In this regard, since administration of estrogen alters plasma angiotensinogen levels, ovariectomy may also affect the renin–angiotensin system, and thus, alter the pressure–natriuresis relationship through mechanisms associated with the renin–angiotensin system.

Since increasing evidence suggests an intimate relationship between the renin–angiotensin system and NO, it is possible that the renin–angiotensin system modulates the pressure–natriuresis response through the NO pathway. Further, the vascular endothelium is also able to generate vasoactive substances like endothelin, and its interaction with NO has been recognized [21–23]. Together, the findings suggest that in the kidney, complex interactions among NO and the renin–angiotensin system exist, affecting the pressure–natriuresis response [24].

Role of Neuro-Humoral Regulation in Salt-Induced Hypertension

Although the mechanisms of salt-induced hypertension still remain unclear, the kidney is responsible for sodium balance by regulating fluid and electrolyte reabsorption and excretion through modulation of renal hemodynamics. Increased salt intake may increase intraglomerular pressure, which can induce or exacerbate chronic renal damage and increase the risk for progressive kidney disease. Excess salt intake produces inappropriate suppression of the renin–angiotensin system; however, the interplay between salt ingestion, the renin–angiotensin system, and oxidative stress is interesting to consider [25]. Both a high-salt diet and angiotensin II stimulate oxidative stress and consequent production of reactive oxygen species. Reactive oxygen species have been implicated in various pathways that can injure blood vessels, including growth factor signaling, mitogenic responses, apoptosis, and oxygen sensing [26]. Thus, increased salt intake might lead to elevation of blood pressure and produce vascular and renal injury by stimulating production of reactive oxygen

species. In addition to these factors, neurocirculatory regulation might play an important role [27]. When the arterial baroreceptor reflex is impaired, blood pressure increases more rapidly because of the increases in blood volume [28]. Ryuzaki et al. [29] demonstrated that in sinoaortic denervated animals with intact kidneys, blood pressure did not increase during the administration of hypertonic saline, in spite of elevation of plasma catecholamines. This indicates that the inability of the kidneys to excrete sodium contributes to the development of hypertension in sinoaortic-denervated animals with salt loading, and that the activation of the sympathetic nervous system at the initiation of salt loading cannot induce hypertension without sodium retention. In sinoaortic-denervated animals with uninephrectomy, salt loading induced more prominent sodium retention compared with sinoaortic-denervated or uninephrectomized animals.

Arginine vasopressin is known to exert various cardiovascular effects through peripheral and central mechanisms, in addition to its peripheral direct vasoconstrictor action [30–33]. In sinoaortic-denervated animals, salt loading did not induce any increase in plasma levels of vasopressin, whereas in sinoaortic-denervated animals with uninephrectomy, plasma levels of vasopressin significantly increased. By contrast, during the intravenous infusion of a vasopressin receptor antagonist in sinoaortic-denervated animals with uninephrectomy, sodium retention was not found. These data suggest that subtle sodium retention induces release of vasopressin, and that elevated vasopressin activates the sympathetic nervous system and vascular responses. In the same study described previously, Ryuzaki et al. [29] reported an interesting observation that salt-induced changes in ionic environment were involved in reduction of blood pressure lability under the sensitization of cardiopulmonary baroreceptor reflex, indicating that excess salt intake might contribute to fluctuations of daily blood pressure.

It is known that both the efferent and afferent renal nerves play a significant role in the pathogenesis of salt-induced hypertension [34]. Ryuzaki et al. [35] demonstrated that renal nerve denervation prevented salt-induced hypertension in sinoaortic-denervated uninephrecomized animals, and counteracted the retention of sodium, activation of the sympathetic nervous system, and elevation of plasma vasopressin. Together, the data strongly suggest that secretion of vasopressin is related to intact renal nerves and that the contribution of vasopressin to the development of salt-induced hypertension needs activation of the sympathetic nervous system and retention of sodium. The activation of the afferent renal nerves may be enhanced through activation of intrarenal receptors by salt loading. This notion of a close relationship between the renal nerves and vasopressin is also verified by the demonstration of Kumagai et al. [36] that the interaction of central and peripheral vasopressin with the renin–angiotensin

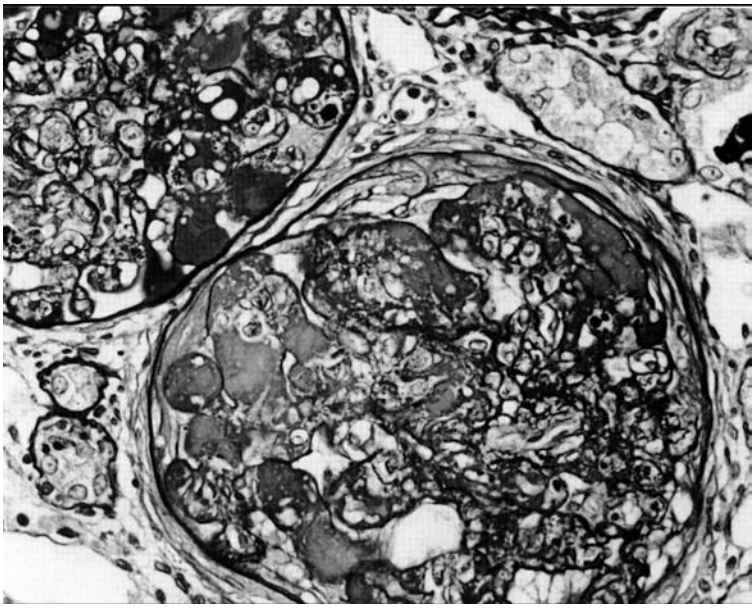

Fig. 1. Glomeruli were noticeably enlarged with mesangial expansion and densely eosin-stained fibrinoid substances. PAS × 400 (reproduced from [38]).

system and the sympathetic nervous system through the renal nerves in renal hypertension plays an important role in blood pressure regulation.

Effect of Salt Intake on Progression of Chronic Kidney Disease

About a half century ago, Meneely et al. [37] found that an increase in dietary salt shortened the life span of rats. Salt-loading produced an increase in the incidence of arteriosclerosis and renal failure. Katsumata et al. [38] demonstrated that a high salt diet produced a marked elevation in blood pressure and prominent renal damage in 5 of 6 nephrectomized spontaneously hypertensive rats. Enlarged glomeruli, dilated tubules containing massive hyaline casts, and laminated hypertrophied vessels were found in these rats (fig. 1). The glomeruli were enlarged with mesangial expansion and contained densely eosin-stained fibrinoid substances. In spite of these changes in the glomeruli, there was no hypercellularity. The majority of small arteries and arterioles showed segmental thickening of the vessel walls by deposition of plasma components and

fibrinoid changes of the outer wall of interlobular arteries, similar to the histological changes seen in patients with malignant hypertension. In the above study, elevated systolic blood pressure was significantly reduced by administration of a thiazide diuretic, trichlormethiazide, but not by administration of either an angiotensin-converting enzyme inhibitor, captopril, or a calcium antagonist, nicardipine. However, in contrast to changes in blood pressure, marked glomerular changes were ameliorated by treatment with captopril or nicardipine, but not with trichlormethiazide, indicating that captopril and nicardipine might have renoprotective actions regardless of the level of blood pressure in salt loading hypertension. Recently, Sanders [39] emphasized the importance of salt intake in the progression of chronic kidney disease independent of blood pressure, and provided cogent suggestions for clinicians who care for patients who have chronic kidney disease. A mainstay of therapy continues to be angiotensin-converting enzyme inhibitor or angiotensin receptor antagonists, both of which appear to slow progression of kidney failure, which is in part related to inhibition of stimulation of transforming growth factor-β production by angiotensin II. In addition to this strategy, reduction of salt intake is important for the management of intrarenal transforming growth factor-β production, which works through a mechanism that is independent of angiotensin II. Moreover, administration of a diuretic might not reduce intrarenal production of transforming growth factor-β under continuing salt loading [40, 41]. This might explain our previous experiments in which a diuretic did not ameliorate renal damage in spite of reduction of blood pressure.

In addition to the data from the animal studies, Cianciaruso et al. [42] analyzed prospectively the progression of chronic kidney disease in hypertensive patients with baseline creatinine clearances between 10 and 40 ml/min who were divided into two groups based on consistent urine sodium excretion rates of either <100 mEq/day or >200 mEq/day. Mean blood pressures of the groups did not differ, and both glomerular and tubulointerstitial diseases were present in both groups. The rate of decline in creatinine clearance was greater in the high-salt group compared with the low-salt group. Proteinuria increased in the high-salt group and decreased in the low-salt group. Also, reduction of salt intake enhances the anti-proteinuric effect of angiotensin-converting enzyme inhibitors [43]. Together, the data support the notion that efforts to monitor and reduce salt intake through dietary restriction produce beneficial effects that might be independent of blood pressure.

In addition, in patients on hemodialysis, a salt-restricted diet is the most important factor in the reduction of thirst and interdialytic weight gain. Despite the clear benefits of dietary sodium restriction in patients with kidney diseases, the main clinical dilemma is the compliance of the patient with such a diet. This might be expected in view of the frequent addition of salt to

manufactured food products and drugs. Success of dietary sodium restriction depends on meticulous and repetitive efforts by a motivated team composed of physicians, dieticians, and nurses [44].

Does Salt Loading Induce Development of Hypertension in Normotensive Offspring of Hypertensive Patients?

Salt loading produces elevation of blood pressure in subjects with the loss of functioning nephrons. In addition to this direct effect on blood pressure, sodium may have an effect on the vasculature and the glomerulus. Familial clustering and a high frequency of hypertension and renal diseases in first-degree relatives of patients point to a strong independent genetic component [45, 46]. These findings raise the issue of whether blood pressure response to salt loading is a risk factor for high blood pressure in subjects who are offspring of patients with hypertension and/or chronic kidney disease. Recently, Strojek et al. [47] demonstrated that the blood pressure sensitivity to salt might be an intermediate phenotype in individuals with a high risk of future diabetic nephropathy. Similar findings reported by Nelson et al. [48] suggested that pre-diabetic blood pressure determines the risk of onset of type 2 diabetes, at least in Pima Indians. This would also be consistent with the observation that blood pressure values and frequency of hypertension are higher in families where there is at least one affected member with diabetic or non-diabetic glomerular disease [49]. In this context, it is interesting to note the hypothesis of Brenner and Chertow [50] that individuals pre-disposed to hypertension and renal disease have lower number of nephrons. Yamakawa et al. [51] assessed the possible heritability of a disturbance in calcium metabolism in relation to blood pressure regulation in 28 young normotensive offspring of either hypertensive or normotensive parents receiving a defined diet with daily sodium chloride content of 6 and 20 g for 7 days (fig. 2). On exposure to a high salt diet, the mean blood pressure in offspring of hypertensive patients who had higher cytosolic calcium concentration in platelets began to elevate. In the article, they proposed that disturbed intraplatelet and systemic calcium metabolism may be of predictive value in the development of hypertension. This hypothesis is now further developed by Ohno et al., stating that genetic abnormalities in platelets may contribute to hypertension via platelet hyperactivity, independent of blood pressure elevation [52–55]. Regarding the disturbance in calcium metabolism in salt-sensitive hypertension, Iwamoto et al. [55] reported that salt-sensitive hypertension is triggered by Ca^{2+} entry through Na^{+}/Ca^{2+} exchanger type 1 in arterial smooth muscle.

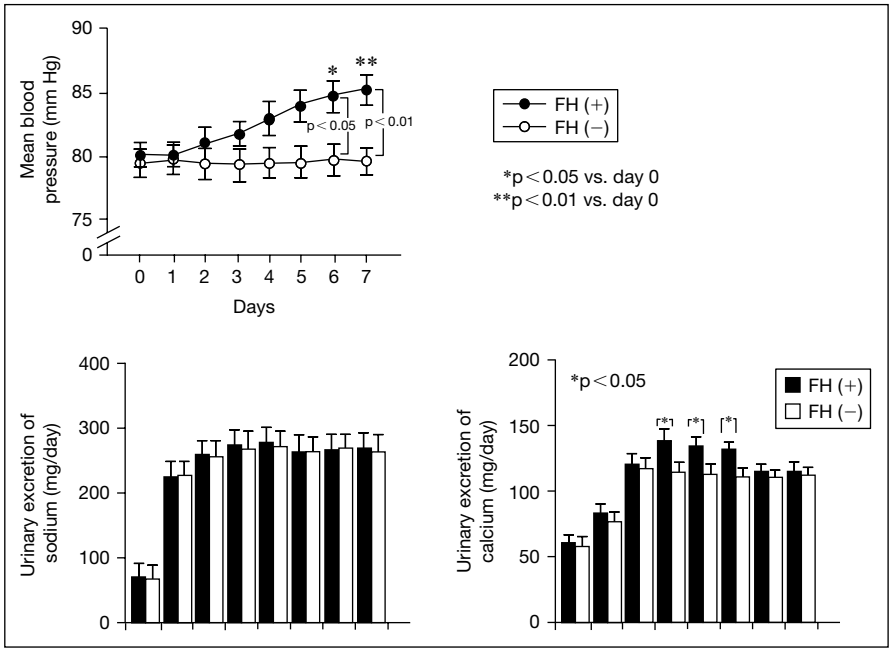

Fig. 2. Line plot shows serial changes in mean blood pressure of each group during 20 g/day sodium chloride intake in negative and positive FH group (*p < 0.05 compared with FH negative group). Bar groups show effects of 20 g/day sodium chloride intake on urinary sodium and calcium excretion in negative and positive FH group (*p < 0.05 compared with FH negative group). Reproduced from [51]. FH = Family history.

Conclusion

In the kidney, there is a close interplay between salt intake and blood pressure regulation, producing loss of renal function in the long-term. The reduced nephron mass is associated with disruption of normal intrarenal hemodynamic vascular responses, with elevation of systemic and intraglomerular pressure. As a result, increases in salt intake cause blood pressure elevation and progressive renal dysfunction. This holds even in the offspring of subjects with renal diseases and hypertension.

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Hiromichi Suzuki, MD
Department of Nephrology, School of Medicine
Faculty of Medicine, Saitama Medical University
38 Morohongo, Moroyama, Iruma
Saitama 350-0495 (Japan)
Tel. +81 49276 1620, Fax +81 49295 7338, E-Mail iromichi@saitama-med.ac.jp

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Dietary Protein Intake and Kidney Disease in Western Diet

Roberto Pecoits-Filho

Centro de Ciências Biológicas e da Saúde, Pontifícia Universidade Católica do Paraná, Curitiba, Brazil

Abstract

Components of the diet related to changes in eating habits that characterize the modern Western world are important factors in the increasingly high prevalence of chronic disease, including obesity, diabetes, hypertension and as a consequence, chronic kidney disease. The healthy diets recommended for the general population to promote longevity (such as the Mediterranean diet), are defined based on epidemiological and intervention studies and are usually characterized by a relatively higher amount of protein than the usual Western diet. Unfortunately, very few clinical studies focused on diet-based strategies of prevention of kidney disorders. Furthermore, this review will propose that the concept that protein restricted diets decrease the risk of developing kidney disease in the general population is not supported by the scientific literature. Indeed, preliminary studies showing a positive effect of relatively high protein diets on risk factors for chronic kidney disease (particularly on obesity, hypertension and diabetes) point to the need for future studies addressing diets that could prevent the increasingly high prevalence of kidney disease in the Western world. On the other hand, there is a potential role for protein restriction in patients with established kidney disease, particularly in patients with significant decrease in glomerular filtration rate. The exact protective action of protein restriction in patients with established renal disease needs further analysis, taking into account the more broad effects of protein restriction (lower phosphate, acidosis, uric acid) and a more current definition of malnutrition.

In the Western world, diet-related chronic diseases represent the largest cause of morbidity and mortality. Although it has been suggested in the past that a single dietary element can be involved in chronic disease (i.e., saturated fat causing heart disease and salt causing high blood pressure), evidence now indicates that virtually all diseases of civilization have multifactorial dietary elements that underlie their etiology and physiopathology, along with other

environmental and genetic factors. Many of these chronic diseases do not arise simply from one single element in the diet but rather from a complex interaction of multiple nutritional factors, which are potentially linked to the excessive consumption of novel Industrial era foods [1]. These foods, in turn, adversely influence nutritional factors, which contribute to or exacerbate virtually all chronic diseases of civilization. In addition, recent advances in the understanding of the physiopathology of diseases such as diabetes, hypertension, atherosclerosis, obesity (which are all closely linked to the development of chronic kidney disease [CKD]) play a pivotal role in nutrition, particularly through pathways such as glycemic load, fatty acid composition, micronutrient density, acid–base balance, sodium–potassium ratio, fiber content and macronutrient composition (carbohydrate, fat and protein). This chapter will mainly focus on the latter, with a particular emphasis on how protein intake can affect kidney function and disease.

Protein Intake in the Western Diet and Its Health-Related Consequences

Western culture usually associates protein intake with muscle, vitality, strength, power, energy, and liveliness. In fact, protein serves as raw material to build tissues and without sufficient protein intake, there would be important organic consequences, such as growth failure, loss of muscle mass, decreased immunity, and impairment of cardiac and respiratory function. Lately there has been an explosion of interest in the area of protein intake, largely triggered by high-protein diets proposed for weight loss and metabolic control. On the other hand, there has been intense debate on the role of high-protein diets increasing the risk of development and progression of CKD.

Currently, in the diet observed in most Western countries, the vast majority of the total food energy derives from three major macronutrients: carbohydrate, fat, and protein. While the optimal ratio of macronutrient intake for adults to maintain morbidity and mortality at low levels has typically focused on fat and carbohydrate, contemporary discussions include the role of dietary protein [2]. Although the macronutrient compositions of human diets during the Paleolithic period cannot be directly determined, skeletal analyses support the notion that protein consumption may have been substantially higher than current values [1]. On the other hand, the main characteristic of the modern Western diet has been the introduction of dairy products, cereals, refined cereals, refined sugars, refined vegetable oils, fatty meats, and salt, leading to a significant decrease in the contribution of protein to the total intake. Most likely, not a single component change, but combinations of these foods have played an important role in

the increasing prevalence of obesity, diabetes, hypertension and atherosclerosis. Although all these pathological conditions are linked to the development of CKD, the impact of dietary changes over time on the prevalence of kidney disease has not been properly studied.

Current advice for reducing the risk of chronic diseases has been to limit the fat intake to 30% of total energy, to maintain protein at 15% of total energy, and to increase complex carbohydrates to 55–60% of total energy [3]. Both the actual macronutrient intakes and suggested healthy levels differ considerably from average levels obtained from studies of hunter gatherers in which dietary protein is characteristically elevated (19–35% of energy) at the expense of carbohydrate (22–40% of energy) [4]. In addition, the Mediterranean diet, which is consistently associated with longevity and quality of life, is also characterized by a relatively high (up to 25%) protein content, mainly from seafood sources. It is important to highlight, however, that many other components of this healthy diet, such as fibers, omega-3 fatty acids, fat intake (mostly in monounsaturated and polyunsaturated forms), olive oil, wine, garlic and herbs may also play a role in the benefits [5].

Relatively little evidence has been gathered regarding the effect of protein intake on the development of chronic diseases. A prospective observational study (the Nurses' Health Study) has investigated the association between dietary protein intake and vascular complications, showing that women who ate the most protein were less likely to have had a stroke [6]. Although this is not a settled issue, an increasing body of evidence indicates that high-protein diets may improve blood lipid profiles and reduce the risk of cardiovascular disease [7]. Similar beneficial blood lipid changes have been observed in type 2 diabetic patients in conjunction with improvements in glucose and insulin metabolism [8]. In obese women, hypocaloric, high-protein diets improved insulin sensitivity and prevented muscle loss, while hypocaloric, high-carbohydrate diets worsened insulin sensitivity and caused reductions in fat-free mass [9]. Interestingly, epidemiologic evidence supports the clinical data, showing a cardiovascular protective effect of dietary protein. Protein intake has been shown to be inversely related to cardiovascular disease in a cohort of over 80,000 women [7]. In numerous population studies, higher blood pressure has been associated with lower protein intake [10]. Because protein has three times the thermic effect of either fat or carbohydrate, and because it has a greater satiety value than do fat or carbohydrate, increased dietary protein may represent an effective weight-loss strategy for the overweight or obese [11]. Indeed, recent clinical trials have shown that calorie-restricted, high-protein diets are more effective than that are calorie-restricted, high-carbohydrate diets in promoting and maintaining weight loss in overweight subjects, while producing less hunger and more satisfaction [2].

Chronic Kidney Disease and Its Risk Factors

CKD is defined as kidney damage or a decline in renal function as determined by decreased glomerular filtration rate (GFR). It is estimated that almost 10% adults in the United States meet this criteria, while an additional 10% are at increased risk for CKD, particularly due to the high prevalence of hypertension and diabetes [12]. Moreover, blood pressure and glycemic control are important strategies to avoid progression of CKD [13]. Recent findings suggest that modifiable lifestyle risk factors, particularly obesity and physical inactivity are also associated with CKD [14].

Protein Intake and Risk Factors for Chronic Kidney Disease

Limited data exist regarding the role of dietary protein intake as an independent risk factor for either the initiation or progression of renal disease, but population studies have consistently demonstrated an inverse relationship between dietary protein intake and systemic blood pressure, obesity and diabetes [2], all risk factors for the development of CKD [12]. While these findings suggest that high-protein diets may be beneficial to hypertensive, obese and diabetic individuals (and potentially to prevent kidney disease), further studies will need to clarify the exact characteristics of this beneficial diet in terms of glycemic load, fatty acid composition, micronutrient density, acid–base balance, sodium–potassium ratio and fiber content. Interestingly, there are no published studies showing the effect of different diets on the risk of developing CKD, although an ongoing study analyzing the cardiovascular effects of the Mediterranean diet includes renal outcome as a secondary endpoint [15]. Results of this study will shed light on the issue of the impact of a healthy diet on kidney disease.

Protein Intake and Kidney Function: History and Insights from Animal Studies

The relationship between dietary protein and renal function has been studied for many years, and there is a historical concern that high-protein intake may promote renal damage by chronically increasing glomerular pressure and hyperfiltration [16]. The fact that a high-protein intake may harm the kidneys is even frequently advertised in the media. Although there is limited research regarding the long-term effects of high-protein intakes on renal function in humans, animal models have provided important insight into this question in

the past. The relationship between levels of dietary protein and rates of urea excretion have been observed for many years, and it is well-established that increased protein intake elevated rates of creatinine and urea excretion [17]. The common mechanism underlying increased excretion rates was attributed to changes in GFR since renal blood flow was the basis for GFR mediated changes in clearance rates in response to increased protein intake.

In concert, these observations led to the hypothesis that high-protein intake is associated with progressive renal dysfunction, through increased glomerular filtration and glomerular pressure [16]. Indeed, early and seminal studies in a canine model showed that increased dietary protein induced renal hypertrophy and led to speculation that dietary protein intake may have deleterious effects on the normal kidney [18]. Research in the rat model produced evidence supporting previous observations from canine research [19]. Recently, another study demonstrated an independent effect of increased protein intake on renal hypertrophy and function in a mouse model [20]. On the other hand, other animal studies failed to demonstrate the adverse effect of protein overload on renal function and histology [21, 22].

Protein Load and Kidney Disease: Clinical Observational Studies

To date, scientific data linking protein-induced renal hypertrophy or hyperfiltration to the initiation or progression of renal disease in healthy individuals is lacking. Few clinical studies that provide important insight on the issue of protein load and renal disease are available. Firstly, the observation of individuals with unilateral nephrectomy shows that, despite prolonged hyperfiltration, remnant kidney function remained normal and did not deteriorate after more than 20 years of follow-up [23]. The possibility that protein-induced changes in renal function are a normal physiological adaptation to nitrogen load and increased demands for renal clearance is supported by changes noted in renal structure and function during pregnancy [24]. GFR increases by as much as 65% in healthy women during pregnancy, typically returning to nonpregnant levels by 3 months postpartum [24]. Despite these changes in renal function, pregnancy is not a risk factor for developing CKD. Athletes, particularly in sports requiring strength and power, consume high levels of dietary protein. In fact, many athletes habitually consume protein in excess of 2.0 g/kg/day. Supplementation with amino acids will further increase dietary protein levels in these individuals, yet there is no evidence that this population is at greater risk for kidney disease or losses in renal function [25]. Similarly, protein intakes in the range of ~1.4–1.9 g/kg/day (170–243% of the recommended dietary allowance) did not impair renal function in athletes [26]. Actually, there are no

data in the scientific literature to link high-protein intakes to increased risk for impaired kidney function in healthy, physically active men and women. The most important clinical evidence in this regard comes from the Nurses' Health Study [27], which clearly shows that high-protein intake was not associated with renal functional decline in women with normal renal function. On the other hand, in the same study, high total protein intake, particularly high intake of nondairy animal protein, accelerated a decline in renal function in women with mild renal insufficiency [27]. Thus, compensatory hyperfiltration appears to be a biological adaptation to a variety of renal challenges that is not associated with increased risk of CKD in healthy individuals. In summary, while a deleterious effect of hyperfiltration on renal function in animal models and in those individuals with pre-existing renal disease may possibly occur, the application of these observations to healthy persons with normal renal function remains does not appear to hold true.

Protein Load and Kidney Disease: Clinical Interventional Studies

The Modification of Diet in Renal Disease (MDRD) study was the largest randomized multicenter, controlled trial undertaken to evaluate the effect of dietary protein restriction on the progression of renal disease [28]. Patients were included in the study if their GFR was 25–55 ml/min (Study A) or 13–24 ml/min (Study B) and their dietary protein intake was ≥0.9 g/kg body weight/day (Study A only). Study A patients were randomly assigned to a usual protein diet (1.3 g protein/kg/day) or a low-protein diet (0.58 g/kg/day), while Study B patients were randomized to a low-protein diet (0.58 g/kg/day) or a very low-protein diet (0.28 g/kg/day). Mean follow-up was 2.2 years. No significant differences in GFR decline, measured by ^{125}I-iothalamate clearance were found between the diet groups. In Study A, a biphasic response of GFR to the low-protein diet was noted, with a greater decline in the first 4 months, followed by a significantly slower rate of decline, which only resulted in a small absolute benefit of 1.1 ml/min/year. A sub-analysis of Study B showed that each 0.2 g/kg/day decrease in achieved dietary protein intake was associated with a slower mean GFR decline and an approximate halving of the risk of renal failure or death.

Fourteen other randomized controlled trials in this area were published, and of those 11 studies were negative, while only three investigations demonstrated a significant benefit of dietary protein restriction on the progression of renal failure. Also, a systematic review of seven randomized controlled trials concluded that low-protein diets were associated with a significantly lower incidence of renal death compared with higher protein diets [29]. An important

confusing factor in all of these studies was that they did not control for the use of anti-proteinuric drugs, which are at present important tools for the prevention of the progression of renal disease.

Although the efficacy of high-protein diets for weight loss has been evaluated [2], there have been scarce reports of protein-induced diminutions in renal function despite subject populations that are generally at risk for kidney disease, such as those with dyslipidemia, obesity and hypertension. A small randomized comparison of the effects of high- and low-protein diets on renal function in obese individuals suggested that high-protein diets did not present a health concern with regard to renal function [30]. In this study, the overweight subjects who adhered to a high-protein diet for 6 months showed an increase in kidney size and GFR in comparison to the baseline. No changes in albumin excretion were noted for either group. The authors concluded that, despite acute changes in renal function and size, high-protein intake did not have detrimental effects on renal function in healthy individuals. Similar findings were recently reported in a study of 10 diabetic patients who consumed their typical diet for 7 days, followed by strict adherence to a high-protein diet for 14 days [31]. No significant changes were noted in serum or urinary creatinine and albumin excretion, suggesting no negative effects of a high-protein diet on renal function.

In summary, although excessive protein intake remains a health concern in individuals with pre-existing renal disease, the literature lacks significant research demonstrating a link between protein intake and the initiation or progression of renal disease in healthy individuals. More importantly, evidence suggests that protein-induced changes in renal function are likely a normal adaptative mechanism, well within the functional limits of a healthy kidney. At present, there is no sufficient proof to warrant public health directives aimed at restricting dietary protein intake in healthy adults for the purpose of preserving renal function.

Potential But Still Unexplored Advantages of Low-Protein Diets in Kidney Diseases

Aside from the classical decrease in urea and creatinine clearance, patients with reduced GFR accumulate sodium, acids, phosphates, uric acid, oxalate and many other compounds. The indirect advantage of protein restriction in avoiding the accumulation of these compounds is an interesting concept that deserves discussion. Even in the early stages of CKD, reduced kidney function leads to hyperparathyroidism and bone disease, reduced insulin sensitivity, increased breakdown of protein and amino acids, and increase in proteinuria [32]. Protein-rich foods are rich in salt, uric acid and phosphates, and these ions

and compounds are deeply involved in the complications of uremia described above. For example, even a mild increase in the serum phosphorus of CKD patients is associated with an increase in mortality [33]. Moreover, evidence of hyperparathyroidism can be found in patients with mildly reduced creatinine clearance values unless phosphate accumulation is prevented by restricting dietary phosphates. Likewise, even a mild increase in serum uric acid can cause vascular and kidney damage [34], and it is well-established that a high-protein diet leads to an increase in uric acid levels [35]. Likewise, there is a potential activation of proteolytic processes as a result of metabolic acidosis or insulin resistance [36], and restriction of dietary protein intake ameliorates or eliminates these problems, suppressing protein breakdown and muscle catabolism. Finally, reducing the intake of protein-rich foods (which are also rich in salt) may be an important strategy in the control of fluid status and hypertension, which are clinical problems even in the early stages of CKD [37]. Further studies will need to address the impact of low-protein diets on reducing complications of uremia related to those substances.

Compliance and Potential Side-Effect Issues in Protein Restriction

Compliance with protein restriction has been an important point of discussion. Many authors consider the rate of noncompliance extremely high. In the MDRD study [28], the achieved dietary protein intakes were considerably higher than targets in both Study A (0.73 rather than 0.58 g/kg/day) and Study B (0.66 rather than 0.38 g/kg/day). Also, in a meta-analysis of 13 randomized controlled trials, the mean dietary protein intake in the restricted group was 0.68 g/kg/day, which is only marginally below the lower limit of the normal daily protein intake recommended by the World Health Organization (0.75 g/kg/day). On the other hand, other authors [32] believe that, with assessment of 24 h urine urea nitrogen excretion and knowledge of a patient's protein intake, a skilled dietician can design and implement an acceptable diet for most patients. There may be regional issues related to compliance, since about two-thirds of French CKD patients comply satisfactorily with low-protein diets [38]. Whether this degree of compliance will be found in other areas of the world is still unknown.

Another reason why dietary protein restriction may be underutilized is fear of inducing malnutrition. Malnutrition is common in CKD, and dietary protein intake spontaneously falls with declining GFR [39]. Also, in Study A of the MDRD trial [28], the low-protein diet group had significantly lower energy intakes, body weight and biochemical nutritional markers than the control group, although only two patients left the MDRD study because of concerns about malnutrition.

However, there have been significant changes in the way malnutrition is defined at the present time, particularly due to the description of the close relationship between malnutrition and inflammation markers, and the relationship between the state of chronic inflammation and outcomes in CKD patients [40]. The term malnutrition traditionally refers to abnormalities caused by an insufficient or imbalanced diet and, hence, should be cured simply by increasing dietary protein intake. The metabolic problems attributed to malnutrition in CKD patients are, in fact, caused by complications of CKD rather than an inadequate diet [41]. For example, a low-serum albumin concentration in patients with kidney failure is generally due to inflammation rather than decreased dietary protein intake [40]. Future studies in this area should take these new definitions into account when analyzing the impact of protein restriction on malnutrition in CKD patients.

Summary and Conclusions

In the Western world, aspects of the diet are important factors in the increasingly high prevalence of chronic disease, including CKD, although few studies focused on diet-based strategies of prevention of kidney disorders. The concept that protein-restricted diets decrease the risk of developing kidney disease in the general population is not supported by the scientific literature, and preliminary studies showing a positive effect of relatively high-protein diets on risk factors for CKD (particularly obesity, hypertension and diabetes) point to the need for future studies of diets that could prevent the increasingly high prevalence of kidney disease in the Western world. Finally, the role of protein restriction in patients with established renal disease, particularly when GFR is significantly reduced, needs to be further studied, taking into account the more broad effects of protein restriction (lower phosphate, acidosis, uric acid) and more current definitions of malnutrition.

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Roberto Pecoits-Filho, MD, PhD
Center for Health and Biological Sciences
Rua Imaculada Conceição, 1155
Curitiba, PR 80215-901 (Brazil)
Tel./Fax +55 41 3301657, E-Mail r.pecoits@pucpr.br

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Phosphate Restriction in Diet Therapy

Eiji Takeda, Hironori Yamamoto, Yuka Nishida, Tadatoshi Sato, Naoki Sawada, Yutaka Taketani

Department of Clinical Nutrition, Institute of Health Biosciences, University of Tokushima Graduate School, Tokushima, Japan

Abstract

Hyperphosphatemia and hyperparathyroidism, frequently observed in patients with end-stage renal disease, are associated with renal osteodystrophy, organ calcification, cardiovascular disease and sudden death. Restriction of dietary protein and phosphorus is beneficial in slowing the progression of renal failure. Dietary phosphorus restriction must be prescribed at all stages of renal failure in adults. It may be achieved by decreasing protein intake and avoiding foods rich in phosphorus. An average of 60–80% of the phosphorus intake is absorbed in the gut in dialysis patients. If phosphate binders are employed, the phosphorus absorbed from the diet may be reduced to 40%. Conventional hemodialysis with a high-flux, high-efficiency dialyzer removes approximately 30 mmol (900 mg) phosphorus during each dialysis performed three times weekly. Therefore, 750 mg of phosphorus intake should be the critical value above which a positive balance of phosphorus may occur. This value corresponds to a protein diet of 45–50 g/day or 0.8 g/kg body weight/day for a 60 kg patient. Target levels should become 9.2–9.6 mg/dl for calcium, 2.5–5.5 mg/dl for phosphorus, <55 mg^2/dl^2 for the calcium–phosphorus product, and 100–200 pg/ml for intact parathyroid hormone.

Phosphorus is essential for multiple and diverse biological functions, including cellular signal transduction, mineral metabolism, and energy exchange. Although >80% of total body phosphorus is stored in bone and teeth, intracellular phosphorus exists in the form of organic compounds such as adenosine triphosphate and as free anions such as $H_2PO_4^-$, which are commonly referred to as phosphate. Serum phosphorus primarily occurs in the form of inorganic phosphate, which is maintained within the physiological range by regulation of dietary absorption, bone formation, and renal excretion, as well as equilibration with intracellular stores.

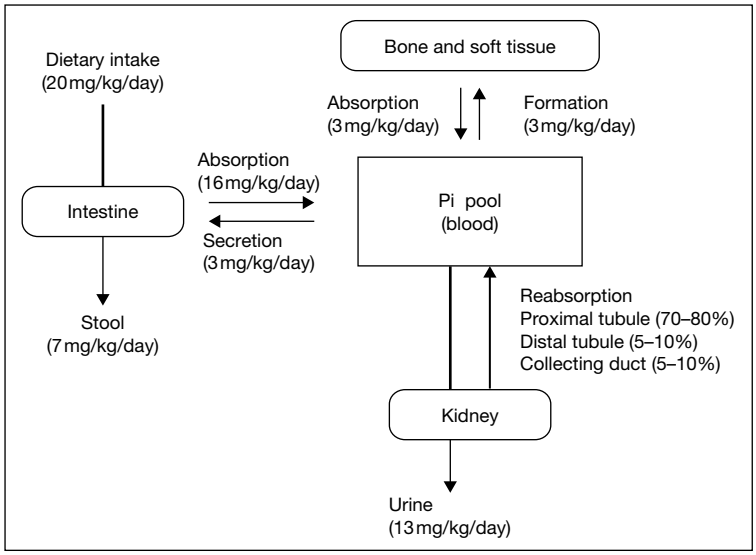

Fig. 1. Phosphate metabolism in humans.

Phosphate is abundant in the diet, and intestinal absorption of phosphate is efficient and minimally regulated. The kidney is a major regulator of phosphate homeostasis and can increase or decrease its phosphate reabsorptive capacity to accommodate phosphate need (fig. 1). Plasma phosphate is almost completely filtered by the glomerulus. Over 80% of the filtered load of phosphate is reabsorbed. The bulk of filtered phosphate is reabsorbed in the proximal tubule where sodium-dependent phosphate (Na/Pi) transport systems in the brush-border membrane mediate the rate-limiting step in the overall phosphate reabsorptive process [1]. Renal phosphate transport is mainly regulated by parathyroid hormone (PTH) and by changes in the dietary intake of phosphorus. In the presence of excess PTH, phosphate excretion is increased. This is reflected by inhibition of Na/Pi transport at the brush-border membrane.

Hyperphosphatemia in Kidney Disease

Phosphate retention and hyperphosphatemia are extremely common in patients with end-stage renal disease. A mean phosphorus concentration in hemodialysis patients was 6.2 mg/dl. In the study, 39% of patients had a phosphorus level >6.5 mg/dl, 30% <7 mg/dl, and 10% >9 mg/dl [2]. Sixty percent of patients had phosphorus levels >5.5 mg/dl, the usual upper limit of normal.

Phosphorus retention plays a primary role in the genesis of the secondary hyperparathyroidism of uremia.

In mild-to-moderate renal failure, intraepithelial phosphorus retention induces a decrease in 1α-hydroxylase activity and consequently decreases plasma calcitriol levels [3], which may lead to a negative balance of calcium when the decrease of dietary calcium due to protein restriction is not corrected. Thus, the deficiency of calcitriol synthesis favored by phosphate retention leads to hyperparathyroidism by two mechanisms: an indirect mechanism through this negative calcium balance and a direct mechanism by favoring parathyroid cell hyperplasia and the synthesis of PTH. Indeed, PTH levels begin to rise when creatinine clearance falls below 60 ml/min [4]. A major mediator of increased phosphate excretion per nephron is a rising level of PTH. PTH levels are elevated with moderate reductions of glomerular filtration rate and rise progressively with worsening renal function. The maximal rate for Na/Pi transport was reduced in renal brush border membrane from uremic rats [5].

Fibroblast growth factor 23 (FGF23) is a member of the fibroblast growth factor superfamily which displays a strong phosphaturic action and an inhibition of vitamin D α-hydroxylase activity in the proximal tubule [6, 7]. The serum FGF23 levels were distributed within a quite wide range in dialysis patients, and in most cases the levels were elevated [8–10]. Patients with advanced secondary hyperparathyroidism demonstrated extremely elevated levels of serum FGF23, and some of those patients showed levels approximately two thousand times greater than those of healthy volunteers.

Complications of Hyperphosphatemia

Renal Osteodystrophy

Hypocalcemia, hyperphosphatemia and impaired renal 1,25-dihydroxyvitamin D synthesis with attendant reductions in serum calcitriol concentrations and decreases in vitamin D receptor expression in the parathyroid glands each contribute to excess PTH secretion in patients with chronic renal failure. Changes in mineral metabolism and bone structure begin early in chronic kidney disease. These changes include osteitis fibrosa cystica because of secondary hyperparathyroidism, less commonly osteomalacia because of defective mineralization and adynamic bone disease because of the absence of both osteoblast and osteoclast activities. Bone disease can result in pain and an increased risk of fracture.

Organ Calcification

Phosphorus is unique because it enhances vascular calcification directly through its participation in the calcium–phosphorus product (Ca × P), and indirectly

through its role in the pathogenesis and progression of secondary hyperparathyroidism. A growing body of evidence implicates hyperphosphatemia and elevated Ca × P as contributors to the excess cardiovascular disease risk in kidney failure [11]. Potential pathways include increased large vessel calcification with its associated effects on arterial stiffening, increased pulse pressure, decreased coronary perfusion, and left ventricular hypertrophy. There are limited data evaluating the relationships of serum levels of phosphorus and Ca × P with cardiovascular disease in earlier stages of chronic kidney disease. However, the process of vascular calcification in patients with chronic renal failure occurs 10–20 years earlier than in the general population [12] and it has greater repercussions in terms of mortality [13]. Borle and Uchikawa [14] have shown that the PTH-induced increase in cell calcium level is greatly enhanced when phosphate is present in extracellular buffers. This may explain the in vivo studies that demonstrate the occurrence of secondary hyperparathyroidism and soft-tissue calcifications after oral phosphate supplements [15].

Increased Mortality

Pooling two random samples of prevalent US hemodialysis patients evaluated during the early 1990s, US Renal Data System investigators showed a 27% increase in the relative risks of death associated with a serum phosphorus >6.5 mg/dl and a 34% increase associated with Ca × P >72 mg^2/dl^2 [16]. Using the same data source, serum phosphorus >6.5 mg/dl was found to be significantly associated with sudden death and death as a result of coronary artery disease. Moderate to severe hyperparathyroidism (PTH > 495 pg/ml) was weakly associated with sudden death [17]. A recent analysis of a cohort of United States veterans with stage 3 chronic kidney disease also demonstrated that serum phosphorus levels >3.5 mg/dl were independent predictors of all-cause mortality [18].

Role of Phosphate in the Progression of Renal Failure

Management of Predialysis Adult Patients

The importance of the early management of diet in the control of hyperphosphatemia was demonstrated in a study of 157 patients with different levels of chronic renal failure not yet receiving dialysis. Moderate restriction of phosphorus in the diet, associated with the administration of calcium supplements, reduced the occurrence of secondary hyperparathyroidism in these patients [19]. If patients learn to manage their phosphorus and calcium intake in the predialysis phase, it will be beneficial when they start dialysis treatment. In addition, they will need fewer phosphate-binding agents, and will know when they need to take them and how to do so much more effectively.

The slopes of the reciprocal of serum creatinine level against time were lower in patients receiving protein and phosphorus-restricted diets when compared with controls (serum creatinine level of 2.28 mg/dl) who were not undergoing dietary restriction [20]. Barsotti et al. [21] studied 39 patients with a mean creatinine clearance of 22.5 ml/min who had been placed on either a low nitrogen diet (controls) or a low-phosphorus–low-nitrogen diet. In the phosphorus-restricted (7.0 mg/kg) group, the creatinine clearance decreased by 0.59 ml/min/month before the dietary restriction, compared with an increase of 0.1 ml/min/month during the study. Furthermore, the rate of decline of creatinine clearance was slower in the patients after both nitrogen and phosphorus-restricted diets, when compared with those on nitrogen restriction alone. A positive correlation was found between the rate of decline in renal function and the urinary phosphate excretion [22]. In the study of Ciardella et al. [23], patients were observed during 1 year on a conventional low-protein diet, then switched to a low-protein–low-phosphorus diet supplemented with essential amino acids and ketoanalogs for an additional year. The mean creatinine clearance decreased from approximately 18 to 9.1 ml/min during the control period, but remained unchanged during the experimental period. Similar results were obtained in another study involving 10 predialysis patients observed for 4 months with a comparable dietary restriction [24]. From these studies, it can be surmised that restriction of dietary protein and phosphorus is beneficial in slowing the progression of renal failure, especially in mild-to-moderate renal insufficiency.

Management of Pediatric Predialysis Patients

In a study of four children placed on a low-protein diet (50% reduction compared with control period), serum creatinine level rose 0.2 mg/dl during the 6 months on the restricted diet, compared with 0.4 mg/dl during a similar period on a nonrestricted diet [25]. Furthermore, growth velocity increased significantly on the low-protein diet compared with the control period. In infants and children, it is not possible to restrict protein intake below 0.8 g/kg/day because of the risk of severe malnutrition. Because of the difficulty following a protein-restricted diet below 0.6 g/kg/day and because of the contraindication in children to restriction of protein intake below 0.8 g/kg/day, it is almost always necessary to use a phosphate binder for the control of phosphate retention.

Management of Hemodialysis Patients

In hemodialysis patients, the daily intake of protein must be maintained at 1 g/kg, and in adults receiving continuous ambulatory peritoneal dialysis, at 1.2 g/kg [26]. Several studies have reported beneficial effects of dietary protein and phosphorus restriction on the correction of phosphate retention and acidosis, which led to improvement of hyperparathyroidism [3, 27, 28]. Lafage et al. [27]

used a very low-protein diet (0.3 g/kg/day) supplemented with amino acids and ketoanalogs and with only 1 g of calcium carbonate and 1,000 IU of vitamin D_2 in 17 patients with advanced renal failure (glomerular filtration rate <15 ml/min). They have shown not only a beneficial effect related to the control of hyperphosphatemia on the biologic and histologic parameters of hyperparathyroidism, but also a correction of acidosis, which resulted in the disappearance of the osteomalacic component.

In conclusion, dietary phosphorus restriction must be instituted at all stages of renal failure in adults. It may be achieved by decreasing protein intake and avoiding foods rich in phosphorus, such as dairy products and certain animal proteins and cereals.

Treatment of Chronic Renal Failure

Parameters of Treatment

Using the treatment strategies now in place, 60% of dialysis patients have phosphorus levels >5.5 mg/dl and Ca $\times$ P >50 mg^2/dl^2. A Ca $\times$ P >72 mg^2/dl^2 is associated with a significant increase in the relative risk (RR) of mortality (RR = 1.34) compared with Ca $\times$ P <50 mg^2/dl^2 [29]. In a study of patients on hemodialysis, those who did not experience valvular calcification had maintained Ca $\times$ P at an average of 51 mg^2/dl^2 in the 6 months prior to the study, while those who did experience valvular calcification had an average Ca $\times$ P of 60 mg^2/dl^2 [30]. The upper limit for the Ca $\times$ P of 70 or 75 no longer appears acceptable. A cut-off of 60 discriminated those with visceral calcification vs. those without [31]. This is supported by Riberio et a1. [30] and Hulting [32] who found cardiac calcification occurring at levels of 60 and 55, respectively. Therefore, it has been recommended that target levels should become 9.2–9.6 mg/dl for calcium, 2.5–5.5 mg/dl for phosphorus, <55 mg^2/dl^2 for Ca $\times$ P product, and 100–200 pg/ml for intact PTH.

Treatment with Low Phosphate Diet

The objectives of nutritional support in patients with renal failure are to provide optimal nutrition and at the same time to minimize the load of metabolites presented for handling by the compromised kidney. The latter objective is particularly important in patients with seriously impaired renal function in whom an effort is made to avoid dialysis and complications. Therefore, the prevention and treatment of secondary hyperparathyroidism must be regarded as a major goal in the conservative management of chronic renal failure. In view of these pathophysiologic considerations, strict control of phosphate retention at all stages of renal failure is the major objective in the prevention and treatment of

hyperparathyroidism. Diet, adequate use of phosphate-binding agents, and dialysis can be used to modify the levels of serum phosphate in patients with chronic renal failure. The development of hyperparathyroidism may be prevented by restricting dietary phosphate intake (e.g., colas, nuts, peas, beans, dairy products), using a calcium-based phosphate binder with meals, and administering vitamin D to suppress PTH secretion. Vitamin D supplementation is safe and effective for lowering PTH secretion in patients with elevated PTH levels or hypocalcemia despite adequate correction of hyperphosphatemia [33].

A highly significant correlation was observed between protein and phosphorus intake in 60 stable chronic uremic patients (mean age: 55 ± 15 years, 25% diabetics, 68% males) on standard 4 h hemodialysis. For patients in the range of 50–70 kg body weight and below the adequate 1 g/kg body weight of protein intake, the mean derived phosphorus intake is 792–1,093 mg/day. These figures are not substantially different from those reported by others, which are considered to be the standard in industrialized countries [34, 35]. An average of 60–80% of the phosphorus intake is absorbed in the gut in dialysis patients, a figure slightly lower than for normal individuals [36]. If phosphate binders are employed, the phosphorus absorbed from the diet may be reduced to 40% [37, 38]. Conventional hemodialysis with a high-flux, high-efficiency dialyzer removes approximately 30 mmol (900 mg) of phosphorus each time it is performed three times weekly. Treatment with erythropoietin may further reduce phosphorus clearance [39]. In these circumstances, 750 mg of phosphorus intake should be the critical value above which a positive balance of phosphorus may occur (fig. 2). This value corresponds to a protein diet of 45–50 g/day. Thus, a neutral balance of phosphate may be difficult to achieve when protein intake is >50 g/day (>0.8 g/kg body weight/day for a 60 kg patient).

Even with optimal dialysis and compliance with binders, many patients have a net positive phosphorus balance [40]. Menus that nutritionally support predialysis and dialysis patients should be provided by clinical dietitians (table 1). In addition, some formulas designed for patients with renal failure are available (table 2). In those formulas, the energy content is increased to be 1.6–2.0 kcal/ml with a decrease in protein and phosphorus.

Treatment with Calcium, Vitamin D and Phosphate-Binding Medications

Oral calcium alone, without 1α-hydroxyvitamin D_3 derivatives, can prevent hyperphosphatemia and hyperparathyroidism in most patients with renal failure before dialysis and in about half of the patients dialyzed with a dialysate calcium of 1.5–1.65 mmol/l. 1α-Hydroxyvitamin D_3 derivatives, which increase intestinal absorption of phosphate, should be used only when hyperphosphatemia has been prevented by oral calcium and diet and when plasma PTH levels increase above three times the upper limit of normal. Given the limitations

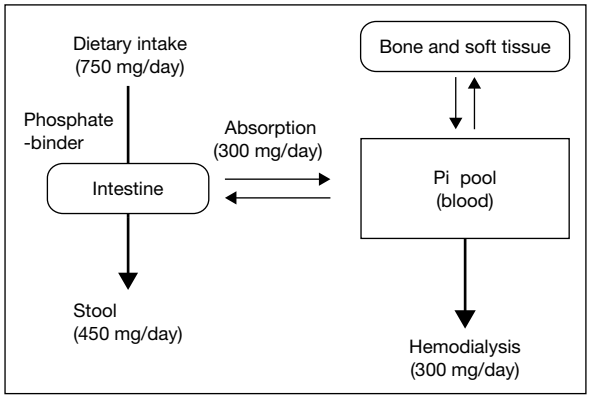

Fig. 2. Phosphate balance in hemodialysis patients.

Table 1. Menu for dialysis and predialysis patients

Person for	Menu	Energy (kcal)	Protein (g)	Phosphorus (mg)
Normal	Boiled rice (160 g)	269	4.0	54
	Ginger pork sauté	258	18.0	177
	Vegetable salad	80	1.0	27
	Fruit yogurt	90	3.0	84
	Total	698	25.9	342
Dialysis	Boiled rice (160 g)	269	4.0	54
	Shabu–shabu (boiled pork)	149	9.2	97
	Potato salad	158	1.8	38
	Baked apple	125	0.2	8
	Total	701	15.2	197
Predialysis	Boiled rice (140 g)	235	3.5	48
Level 1	Deep-fryed meatball with vegetable sauce	175	8.0	83
	Vinegared salad of bean thread noodles	122	0.2	17
	Simmered apple and sweet potato	166	0.4	16
	Total	699	12.1	163
Predialysis	Boiled low protein rice (180 g)	300	0.5	23
Level 2	Onion and pork sauté	180	4.6	68
	Mayonnaise salad of bean thread noodles	164	1.0	34
	Canned apple	58	0.2	3
	Total	702	6.2	128

Table 2. Formulas for patients with chronic renal failure

Formulas	Company	Calories/ml	Protein (g/l)	Phosphorus (mg/l)
Renalen Pro1.0	Meiji Dairy Co.	1.6	16	320
Renalen Pro3.5	Meiji Dairy Co.	1.6	56	560
Renawel A	Terumo	1.6	6	160
Renawel 3	Terumo	1.6	24	160
NovaSouce Renal	Novartis	2.0	74	650
Magnacal Renal	Novartis	2.0	75	800
Suplena	ROSS	2.0	30	730
Nepro	ROSS	2.0	70	685
Renacal	Nestlé	2.0	34.4	–
NutriRenal	Nestlé	2.0	70	700

of current dialysis strategies, the ongoing use of phosphate-binding medications represents the primary intervention to manage phosphorus retention in patients with end-stage renal disease [41]. Agents that do not contain either calcium or aluminum have the distinct advantage of allowing wide-ranging adjustments in dosage without incurring dose-related side effects.

Sevelamer, or poly-allyl-amine hydrochloride, is an ion exchange resin that effectively binds phosphorus in the lumen of the gastrointestinal tract and prevents its absorption. Recently, 46 patients undergoing maintenance hemodialysis therapy were randomly divided into two groups, and treated with either 3 g sevelamer hydrochloride + 3 g of calcium bicarbonate ($CaCO_3$), or 3 g of $CaCO_3$ alone. Serum FGF23 levels were determined by a sandwich enzyme-linked immunosorbent assay system that detects the intact form of FGF23 molecules. Although the serum inorganic phosphate levels were comparable before treatment, the levels were significantly lower in the patients treated with sevelamer hydrochloride + $CaCO_3$ than those with $CaCO_3$ alone after 4 weeks of treatment [42]. Serum FGF23 levels significantly decreased after 4 weeks of treatment with sevelamer hydrochloride + $CaCO_3$ from the pretreatment levels, while no changes were found in the patients treated with $CaCO_3$, alone. This therapeutic approach may favorably influence the process of vascular calcification in patients with end stage renal disease. Thus, coronary artery calcification scores and the extent of calcification in the thoracic aorta did not change after 12 months of follow-up in hemodialysis patients given sevelamer to control serum phosphorus concentration [43]. For patients with marked hyperphosphatemia in whom modest doses of calcium are inadequate to control serum phosphorus concentrations, aluminum hydroxide can be used for periods limited to a few

weeks, with little risk of aluminum retention or aluminum toxicity. This approach may be useful, particularly in patients with overt hypercalcemia.

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Eiji Takeda, MD, PhD
Department of Clinical Nutrition, Institute of Health Biosciences
University of Tokushima Graduate School
3-18-15 Kuramoto-cho
Tokushima 770-8503 (Japan)
Tel. +81 88 633 7093, Fax +81 88 633 7094, E-Mail takeda@nutr.med.tokushima-u.ac.jp

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Salt and Excess Food Intake Produced Diabetic Nephropathy in Japan

Hiroshi Takane, Yoshihiko Kanno, Yoichi Ohno, Soichi Sugahara, Hiromichi Suzuki

Department of Nephrology, Saitama Medical University, Saitama, Japan

Abstract

The purpose of this study is to retrospectively analyze the clinical characteristics of patients with diabetes mellitus who started dialysis therapy. First, we reviewed 120 cases of end-stage renal failure due to diabetic nephropathy who started dialysis therapy in 1996 and 1997. Presenting features were as follows: men, 62.5%; mean age at starting dialysis, 57 ± 1 year; and mean serum creatinine level, 7.3 ± 0.2 mg/dl. To find any clinical characteristics in the population, we divided patients into three groups according to age, as follows: Young age group (<40 years old: 12 patients), Senior age group (>65 years: 32 patients) and Middle age group: 76 patients (>40 and <65 years). The Young age group, (mean age: 36 ± 1 years) had lower serum creatinine levels (6.1 ± 0.4 mg/dl) ($p < 0.05$) and greater cardio-thoracic ratio (61.1 ± 1.3%) ($p < 0.05$), obtained from the chest X-ray film, than the other two groups. There were no significant differences between the Middle age group (59 ± 1 year) and the Senior age group (72 ± 1 year) in the levels of serum creatinine and cardio-thoracic ratio. To further analyze the clinical characteristics, the other 113 patients in 1998 and 1999 who were matched with the Middle age group in the former study, were retrospectively analyzed. The mean age was 61 ± 2 years, and the proportion of men was 54% (62/113). The percentage of changes in body weights were as follows: 9.5 ± 2.8% ($p < 0.05$) from teens to 20s and 19.2 ± 3.2% ($p < 0.05$) from teens to 30s in men. The percentage of changes in body weight in women were as follows: 9.6 ± 2.1% ($p < 0.05$) from teens to 30s and 18.6 ± 2.4% ($p < 0.05$) from teens to 40s. The age at the start of dialysis therapy was 54 ± 2 years old in men and 59 ± 3 years in women. There was a significant difference ($p < 0.05$) between men and women. In summary, the study suggests that young patients with diabetic nephropathy received dialysis therapy because of hypervolemic symptoms compared to older patients, and that renal deterioration progressed more rapidly in male subjects than in female subjects with diabetic nephropathy. These differences should be borne in mind in clinical practice.

The number of end-stage renal failure (ESRF) patients needing dialysis therapy increases year by year. Since 1998 in Japan, diabetic nephropathy has been the most common cause of ESRF [1]. It is thought that a possible cause is an increase in the number of patients with diabetes mellitus because of changing dietary habits, and an aging population because of better health care. From a medical economic standpoint, an understanding of the disease state of diabetic nephropathy and prevention of progression of diabetic nephropathy is extremely important.

It has been assumed that control of blood glucose and blood pressure is important in preventing progression of diabetic nephropathy [2]. In particular, salutary effects of angiotensin-converting enzyme inhibitors have been reported in various non-clinical [3] and clinical studies [4–6]. Angiotensin receptor blockers developed in recent years are expected to be more effective in counteracting the renin– angiotensin system than angiotensin-converting enzyme inhibitors [7].

However, in spite of progress with these therapies, the consequences of diabetic nephropathy are extremely deleterious, and it has a shorter course from onset to dialysis compared with other renal diseases. Furthermore, prognosis after initiation of dialysis is extremely poor in comparison with other disorders. For these reasons, it is important that we investigate the pathophysiology of diabetic nephropathy [8].

As for diabetic nephropathy, the speed of its progression and clinical presentation are not uniform [9], and it has been suggested that diabetic nephropathy can be divided into a number of clinical subgroups [10]. However, a trial to define the clinical categories has not been performed. To understand the pathophysiology of the progression of diabetic nephropathy, we selected outpatients who started dialysis therapy, and retrospectively analyzed all subgroups by age and by gender, and reviewed the clinical characteristics.

Patients and Methods

Retrospective Study of Clinical Characteristics at Initiation of Dialysis

We reviewed the clinical characteristics of about 120 cases of ESRF due to diabetic nephropathy, except those positive for hepatitis C virus antibody, who started hemodialysis therapy in our hospital from January 1, 1996 to December 31, 1997.

Demographics were as follows: men, 62.5% (75 males and 45 females); mean age at start of therapy, 57 ± 1 years. To find any clinical characteristics in the population, we divided the patients into three subgroups according to the age at start of dialysis; Young age group (<40 years old; 12 patients), Senior age group (>65 years old; 32 patients), and Middle age group (>40 but <65 years old; 76 patients).

We analyzed the following clinical parameters: age at start of hemodialysis, duration of diabetes, fasting serum glucose, blood urea nitrogen, HbA1c, serum creatinine concentration, cardio-thoracic ratio, degree of visual handicap due to retinopathy, and blood pressure control.

Retrospective Study of Clinical Characteristics Before Initiation of Dialysis

We reviewed the clinical characteristics of the Middle aged group, (age >40 but <65 years old) of patients with ESRF because of diabetic nephropathy, except those positive for hepatitis C virus antibody, that were started on hemodialysis therapy at our hospital from January 1, 1998 to December 31, 1999. Medical records were analyzed for the following: (1) changes in body weight according to age group, (2) the age of maximum body weight, diabetes mellitus diagnosis, diabetic nephropathy diagnosis, and initiation of dialysis, (3) glycemic control and diabetes mellitus treatment history, (4) blood pressure control and antihypertensive agent history. The diagnosis of diabetes mellitus was determined as the point in time when diabetes mellitus was diagnosed by a qualified physician. The age of nephropathy diagnosis was taken as the point in time when it was noted that 'renal function decreased'.

Statistics

All values are expressed as mean with standard error (SE). We used analysis of variance for the comparison of the three groups using Scheffe's F-test. Kruskal-Wallis test was used to determine the degree of visual disturbance by retinopathy and blood pressure control. Student's unpaired t-test was used for comparison of variables between age groups and changes with time were compared using Student's paired t-test. Statistical significance was set at $p < 0.05$.

Results

Retrospective Study of Clinical Characteristics at Initiation of Dialysis

Clinical data at the start of dialysis therapy are shown in table 1. There was no significant difference among the three groups with respect to fasting blood glucose. In the Young age group, HbA1c tended to be lower than in the other two groups, but the difference between the three groups was not statistically significant. Serum creatinine level was significantly lower in the Young age group than the other two age groups. Therefore, in the Young age group, renal function was better preserved at initiation of dialysis compared with the other two groups. At the same time, the cardio-thoracic ratio of the chest X-ray was

Table 1. Clinical data at the start of dialysis therapy

	Younger	Middle	Senior
Number	12	76	32
Age	36 ± 1**	54 ± 1**##	72 ± 1##
Fasting serum glucose (mg/dl)	136 ± 9	128 ± 3	128 ± 4
HbA1c (%)	6.5 ± 0.4	7.1 ± 0.2	7.0 ± 0.2
Hemoglobin (g/dl)	9.3 ± 0.3	9.0 ± 0.1	8.8 ± 0.2
BUN (mg/dl)	70.3 ± 5.6	76.5 ± 2.7	82.6 ± 4.0
Serum creatinine (mg/dl)	6.1 ± 0.4*	7.4 ± 0.2	7.6 ± 0.4
CTR (%)	61.1 ± 1.3	57.1 ± 0.7#	56.9 ± 1.1#
Duration of diabetes	12.6 ± 0.8*	16.0 ± 0.7	18.7 ± 1.4

BUN: Blood urea nitrogen; CTR: Cardio-thoracic rate.
**, * means $p < 0.001$ and $p < 0.05$ vs. senior group, respectively.
##, # means $p < 0.001$ and $p < 0.05$ vs. young group, respectively.

significantly greater in the Young age group compared with the other two groups. In addition, the duration of diabetes was significantly shorter in the Young age group compared with the other two groups. Four patients (33.3%) in the Young age group, 15 patients (19.7%) in Middle age group, and 5 patients (15.6%) in the Senior age group had visual impairment. The Young age group tended to have a higher ratio, but the difference was not statistically significantly different. As for the use of the frequency of antihypertensive agents, a large difference was not observed between the three groups (fig. 1).

Retrospective Study of Clinical Characteristics Before Initiation of Dialysis

Of 148 patients with type 2 diabetes mellitus, 113 had all evaluations performed. Patients were <65 years old and <40 years old when they started dialysis. Mean age was 56 ± 2 years old, 62 patients were male (54 ± 2 years old) and 51 patients were female (59 ± 3 years old). The female menopause age was 44 ± 3 years old.

Changes in Body Weight According to Age

Changes in body weight according to age of dialysis patients with diabetic nephropathy are shown in figure 2. In men, body weight increased significantly

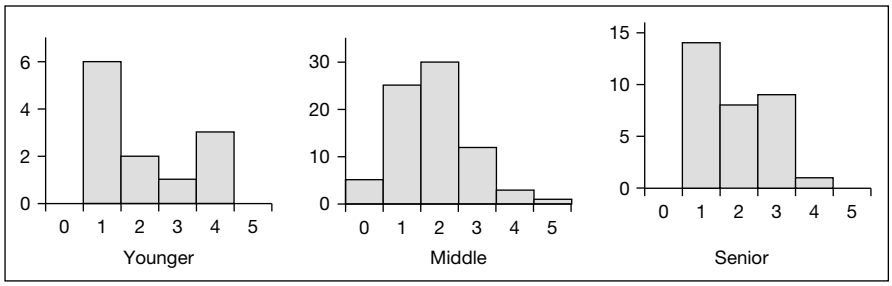

Fig. 1. Histogram of the numbers of antihypertensive agents used at the start of receiving dialysis therapy. No significant difference was observed in the distribution.

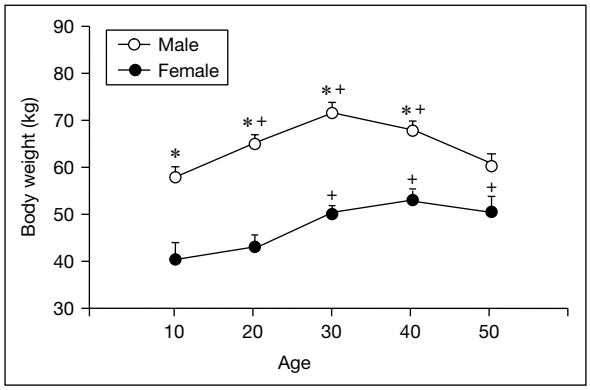

Fig. 2. Changes in body weight of dialysis patients with diabetic nephropathy. The peak of body weight was in the 30s in males, and in the 40s in females (* and + express $p < 0.05$ vs. female, and vs. body weight in teens, respectively).

from the teenage years to the 30s (59.3 ± 2.4 kg vs. 70.5 ± 2.3 kg; $p < 0.05$). The maximum body weight was recorded at 38 ± 2 years old, and body weight gradually decreased thereafter. In women, body weight gradually increased from the 20s. The maximum body weight was recorded at 44 ± 3 years old. After the 50s, body weight tended to remain approximately constant. The degree of weight gain was significantly greater from the 20s to the 30s in men compared to women. Body weight increased gradually from the 20s to the 50s in women, and there was little tendency for body weight to change after the 50s (fig. 3).

Mean Age of Each Event in Medical History

Figure 4 shows the mean age at each event; maximum body weight, diabetes mellitus diagnosis, diabetic nephropathy diagnosis, and initiation of dialysis.

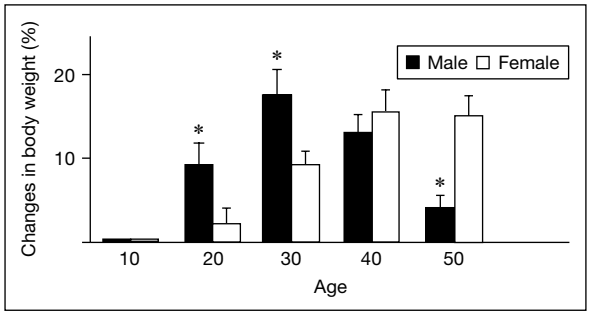

Fig. 3. The gains in body weight from teens. Body weight increased in young age in men, and in older age in women (*$p < 0.05$ vs. female).

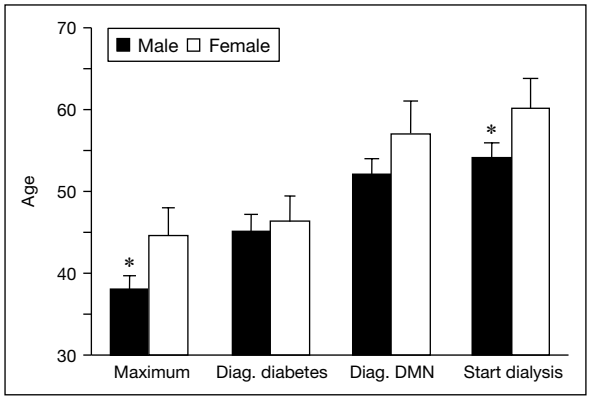

Fig. 4. Ages at the events in clinical course. Maximum: Age at maximum body weight. Diag. diabetes: Age at diagnosis of diabetes mellitus. Diag. DMN: Age at diagnosis of diabetic nephropathy. Start dialysis: Ages at start of dialysis therapy (*$p < 0.05$ vs. female).

The age of maximum body weight was significantly lower in men (38 ± 2 years old) compared to women (43 ± 2 years old). The age of diabetes mellitus diagnosis and diabetic nephropathy diagnosis were also earlier in men compared to women, but the values were not statistically significantly different. The age at start of dialysis therapy was 54 ± 2 years in men and 59 ± 3 years in women, and these were statistically significantly different. The duration from diabetes mellitus diagnosis to the start of hemodialysis calculated from the above data was 12.9 ± 2.0 years in men and 14.0 ± 2.0 years in women. Women had a significantly longer clinical course compared to men.

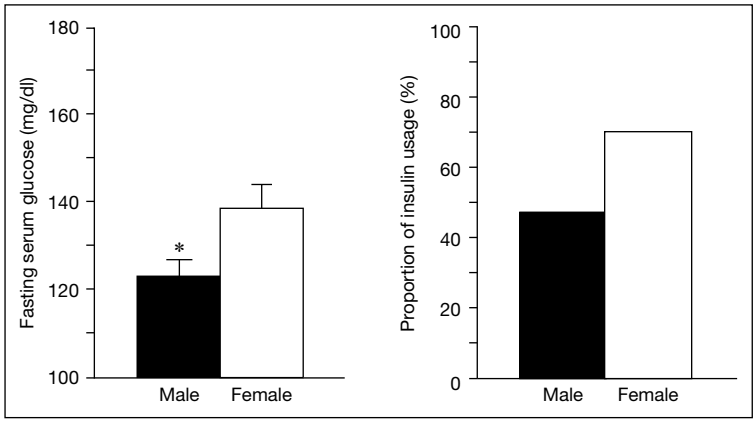

Fig. 5. Glycemic control at the start of receiving dialysis therapy. Fasting serum glucose levels were significantly lower in men at the start of dialysis therapy. Proportion of insulin usage was also lower in men (*$p < 0.05$ vs. female).

Glycemic Control and Treatment of Diabetes Mellitus

Fasting serum glucose level was 123 ± 3 mg/dl in men and 139 ± 5 mg/dl in women, and the proportion of insulin use was 47% in men and 70% in women (fig. 5).

Blood Pressure Control and Use of Antihypertensive Agents

The percentage of men and women who used antihypertensive agents at the start of dialysis therapy was 96.2 and 92.3%, respectively.

Discussion

Diabetes mellitus presents various clinical characteristics, and many classifications have been defined for the understanding of the pathophysiology of this disease up to now. With progress in medical technology, and the increase in knowledge regarding the cause and the origin of diabetes, the WHO and the American Diabetes Association have regularly revised their criteria and classifications [9, 11, 12]. These classifications are mainly dependent on etiology and knowledge of mechanism, and it is not unusual to find patients with different clinical characteristics being classified in the same disease category. Especially, it is very difficult to classify type 2 diabetes mellitus according to the clinical characteristics because of its frequency and complexity. Here, we studied a sub-set of patients, and reviewed the clinical characteristics of patients with diabetic nephropathy who reached ESRF and started dialysis.

When patients were grouped according to age, important differences in clinical characteristics were present at the start of dialysis. In other words, differences in clinical characteristics were present in the Young age group compared with the other two groups. In the Young age group, renal function was relatively well-preserved and a tendency for congestive heart failure was notable at the start of dialysis. This suggested that young patients were started on dialysis because of edema and dyspnea which are symptoms of over-hydration rather than anorexia or vomiting which are symptoms of uremia. In addition, duration of diabetes tended to be comparatively short. By contrast, there was no tendency for congestive heart failure in the Middle age group and the Senior age group. As expected, these patients had most of the clinical features of non-diabetic nephropathy.

In order to define the clinical characteristics, we grouped the patients into three age groups according to the age at which they started dialysis. If we grouped the patients according to the clinical characteristics, it seems that the group with congestive heart failure tended to have a lower mean age. However, it is difficult to group patients objectively according to clinical symptoms. Therefore, we grouped the patients according to age. However, it may be reasonable to expect that we can find the correct clinical characteristics by increasing the number of cases in the future.

If we consider a genetic propensity for developing diabetes, it would make it easier to understand the cause of the disease [13]. Originally, the gene analyses of type 2 diabetes mellitus assumed a multifactorial inheritance. In 1996, Hanis et al. [14] reported non-insulin dependent diabetes mellitus type 2 as one of the candidates for a major susceptibility gene. This is an example of initial success obtained from analysis for late-onset type 2 diabetes mellitus. This evaluation showed the likelihood of the presence of a major susceptibility gene locus. The concept of a 'thrifty genotype' such as insulin receptor, β_3 adrenergic receptor, and PPAR-γ is also important in understanding the etiology of diabetes [15]. However, there are only a few reports of genetic factors associated with nephropathy [16, 17]. In addition, there are many differences in the reports, which are therefore inconclusive [18, 19].

In younger patients, the duration from diagnosis of diabetes mellitus and nephropathy to the start of dialysis was significantly shorter compared with the other two groups. Many studies have been performed to identify factors that may promote or inhibit progression of nephropathy [20]. Soma et al. noted a high prevalence of hepatitis C virus antibody positivity in patients with diabetic nephropathy, and reported that degree of proteinuria is high and renal survival is poor in the hepatitis C positive patients. Although it is a cause of membranoproliferative nephropathy, hepatitis C virus may aggravate diabetic nephropathy [21]. For these reasons, patients with positive hepatitis C virus antibody were excluded from this study.

The most remarkable difference related to gender was seen in the changes of body weight. In men, body weight increased rapidly from the teenage years to the 40s. Diabetes mellitus was diagnosed when the maximum body weight was recorded at 38 ± 2 years old; thereafter body weight decreased. In women, body weight increased gradually from the 20s to the 50s, and the maximum body weight was recorded at 44 ± 3 years old, at the time of menopause. In women, body weight tended to remain constant after this age. Regarding the changes in body weight, Harris [22] reviewed the maximum body weight, the body weight at the age of 25 years, and at the time of investigation in diabetes mellitus patients with impaired and normal glucose tolerance. The study showed that there were only a few differences in impaired and normal glucose tolerance at the age of 25 years. Body weight difference was the largest between those with normal glucose tolerance. There was no difference in body weight at the time of investigation. In contrast, the glucose tolerance and the correlation with body weight were stronger in women. In addition, the difference in the maximum body weight for a group of diabetes mellitus patients and a group of patients with normal tolerance was maintained at the time of investigation. In this study, body weight decreased after the maximum body weight was recorded in men. Loss of weight was slow and remained approximately constant after the maximum body weight was reached in women. Similar findings were reported in a recent study of rapidly developing obesity in men [23].

In the present study, it was noted that the diagnosis of diabetes mellitus and diabetic nephropathy occurred earlier in men than women. In addition, the age at the start of dialysis was significantly lower in men. Generally, it was reported that men with chronic renal disease showed a more rapid decline in renal function with time than women [24]. In fact, it has been reported that the slower mean GFR decline was, the lower protein diet and blood pressure were [25].

Glycemic control is recognized as a factor in the progression of diabetic nephropathy [26, 27]. Of note, there is also a racial difference [28].

In addition, although glycemic control was rather poor in women, the duration from the diagnosis of diabetes mellitus to the start of hemodialysis was significantly shorter in men compared with women. For these reasons, we hypothesized that gender difference had a bearing on the progression of renal dysfunction in diabetic nephropathy as well as in other diseases. Sex hormone differences have been investigated as a cause of gender difference in the progression of renal disease. Two mechanisms involved are thought to relate to the difference in sex hormone concentration and sensitivity of renal cells [29]. It is thought that hypertension is prevented by inhibition of arterial sclerosis by estrogen as with antioxidant agents [30]. Also, it was reported that sex hormones directly influence mesangial cells [31]. There have been many reports that estradiol may suppress the synthesis of types I and IV collagen, which may have a bearing on the

mechanism of inhibition of progression of renal dysfunction [32]. Likewise, food and protein intake may be greater in men, and serum creatinine concentration may easily attain a high level due to a difference in muscle mass compared to women. The cause of the gender differences found in this study may relate to these reasons.

Conclusion

In conclusion, young patients with diabetic nephropathy received dialysis therapy because of hypervolemic symptoms. Deterioration of renal function was faster in males than in females with diabetic nephropathy as is the case in other renal diseases.

Acknowledgement

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Hiromichi Suzuki
Department of Nephrology, School of Medicine
Faculty of Medicine, Saitama Medical University
38 Morohongo, Moroyama, Iruma
Saitama 350-0495 (Japan)
Tel. +81 49276 1620, Fax +81 49295 7338, E-Mail iromichi@saitama-med.ac.jp

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