e-seminars

DIABESITY
Diabetes and obesity Working Group

Non-Alcoholic Fatty Liver Disease and Chronic Kidney Disease – what is the link

Speaker:
Enrique Morales,
Spain

Panellist:
Therese Adrian,
Denmark

Panellist & Moderator:
Esteban Porrini,
Spain

07 JUN

Tuesday June 7, 2022
From 5:00 to 6:00 PM (CEST)

Dr P Ravichandran MD DM
Neph E Club no 2890

This e-seminar is an exclusive benefit for the ERA Members who can earn ECMEC® credits by participating LIVE!

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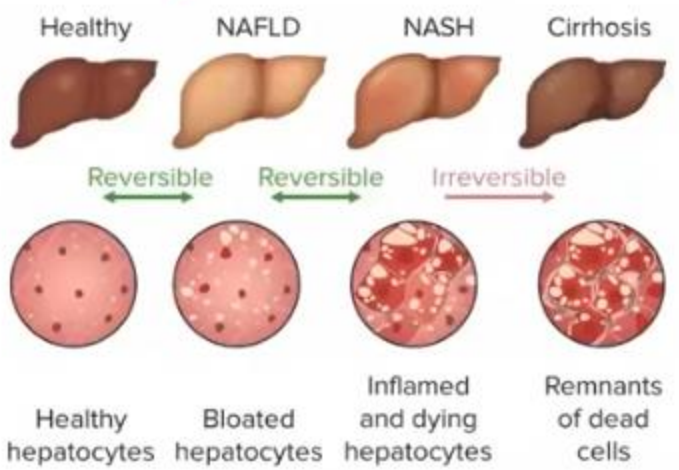
Introduction

- Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, involving approximately **25%** of the general population and increasing in prevalence in patient populations afflicted with metabolic syndrome and type 2 diabetes (T2DM).
- Nonalcoholic fatty liver disease (NAFLD) includes **different types of liver damage**, ranging from simple steatosis and nonalcoholic steatohepatitis (NASH) to liver cirrhosis and even hepatocellular carcinoma.
- NAFLD is diagnosed by the presence of **more than 5%** fat accumulation in liver cells.



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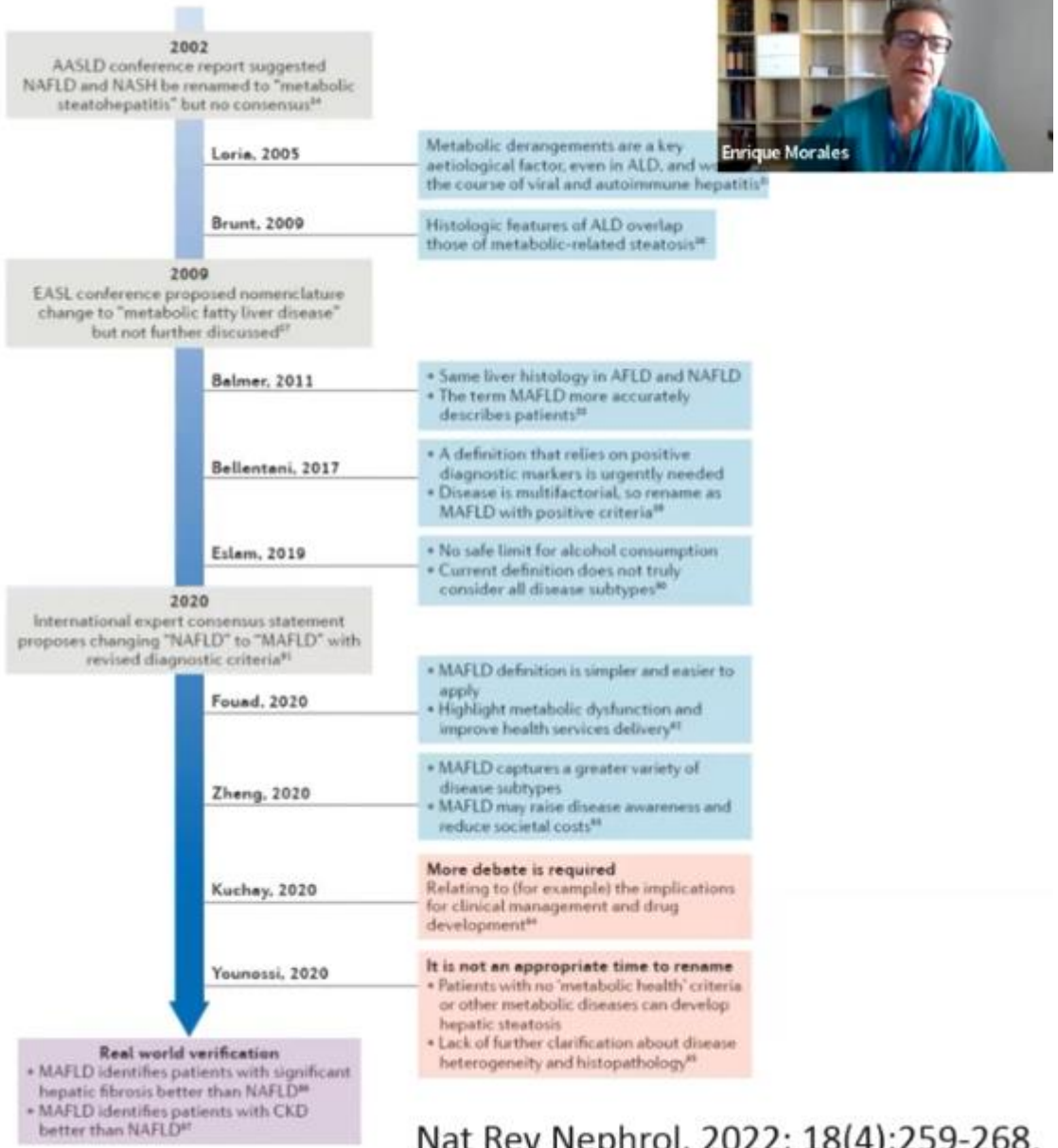
"From NAFLD to MAFLD"

Due to the variety of metabolic comorbidities it accompanies, such as **hypertension, insulin resistance, diabetes mellitus (DM), dyslipidemia, and central obesity**, international experts decided to change its name to **metabolic dysfunction-associated fatty liver disease (MAFLD).**



Nat Rev Nephrol. 2022; 18(4):259-268.

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OVERLAP

Hypertension, dyslipidemia, obesity, insulin resistance

NAFLD 20-30% adult population

CKD >25% adult population >65 y

"Some studies have confirmed that the presence of **NAFLD increases the risk of CKD** and that the degree of liver fibrosis is related to CKD stage, while other studies have found that the incidence of **CKD is not affected by NAFLD"**

Adams LA, *et al*. *Gut* 2017;**66**:1138–1153.

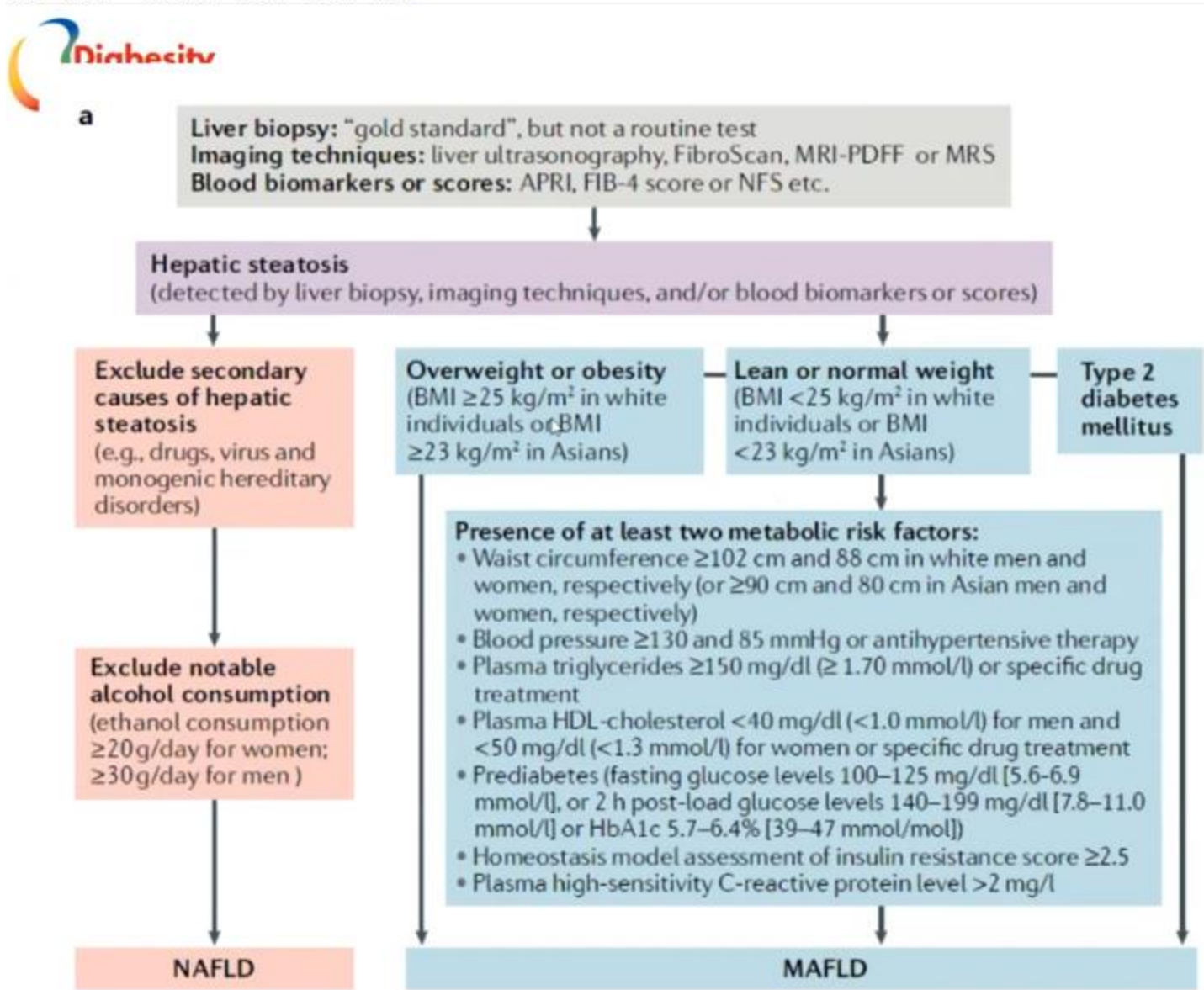
Liver biopsy remains the most definitive approach for identifying NASH and fibrosis

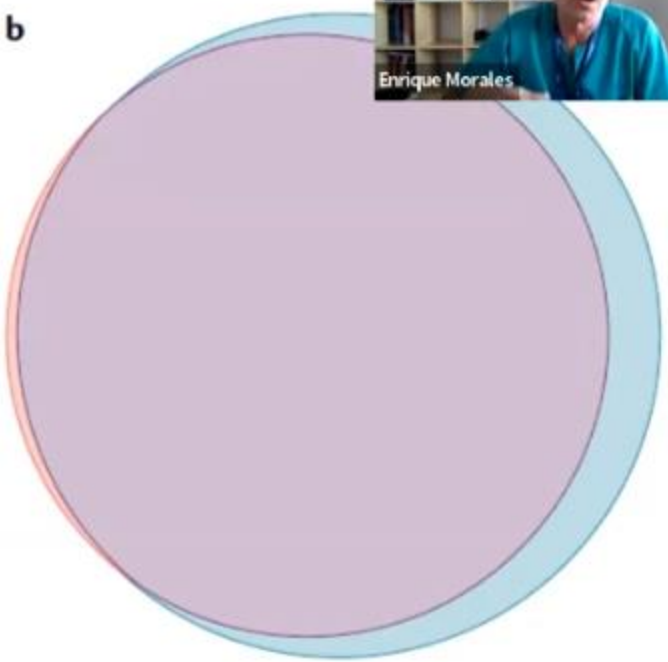
	Parameters and biomarkers	Cutoffs for advanced fi
Non-invasive biomarker detection methods		
NAFLD fibrosis score[50]	Age, BMI, IFG and diabetes, AST-to-ALT ratio, platelets, and albumin	≤−1·455 >0·676
FIB-4 index[51]	Age, AST, ALT, and platelet	<1·3 >2·67
Enhanced liver fibrosis test[54]	Age, hyaluronic acid, aminoterminal propeptide of type III collagen, and tissue inhibitor of matrix metalloproteinase 1	≥9·8
FibroTest (FibroSure)[55]	Total bilirubin, γ-glutamyltransferase, α2-macroglobulin, apolipoprotein A1, and haptoglobin, corrected for age and sex	>0·30 >0·70
Non-invasive imaging		
VCTE[56]	Ultrasound-based measurement of low-frequency (50 Hz) elastic shear-wave velocity	>9·6
MRE[57]	MRI-based imaging of low-frequency mechanical waves	>3·64

*Some indices have two cutoffs (to maximise sensitivity or specificity), which create grey zones of indeterminate values. For example, for the NAFLD fibrosis score, when applying the low cutoff score (−1·455) advanced fibrosis could be excluded with high accuracy (negative predictive value of 93% in the estimation groups, and 88% in the validation groups). By applying the high cutoff score (0·676), the presence of advanced fibrosis could be diagnosed with high accuracy.[50] NAFLD=non-alcoholic fatty liver disease. IFG=impaired fasting glucose. AST=aspartate aminotransferase. ALT=alanine aminotransferase. FIB-4=fibrosis-4. VCTE=vibration-controlled transient elastography. MRE=magnetic resonance elastography.

Table 1: **Non-invasive estimation of fibrosis**

Lancet Diabetes Endocrinol. 2019;7(4):313-324.





Nat Rev Nephrol. 2022; 18(4):259-268.

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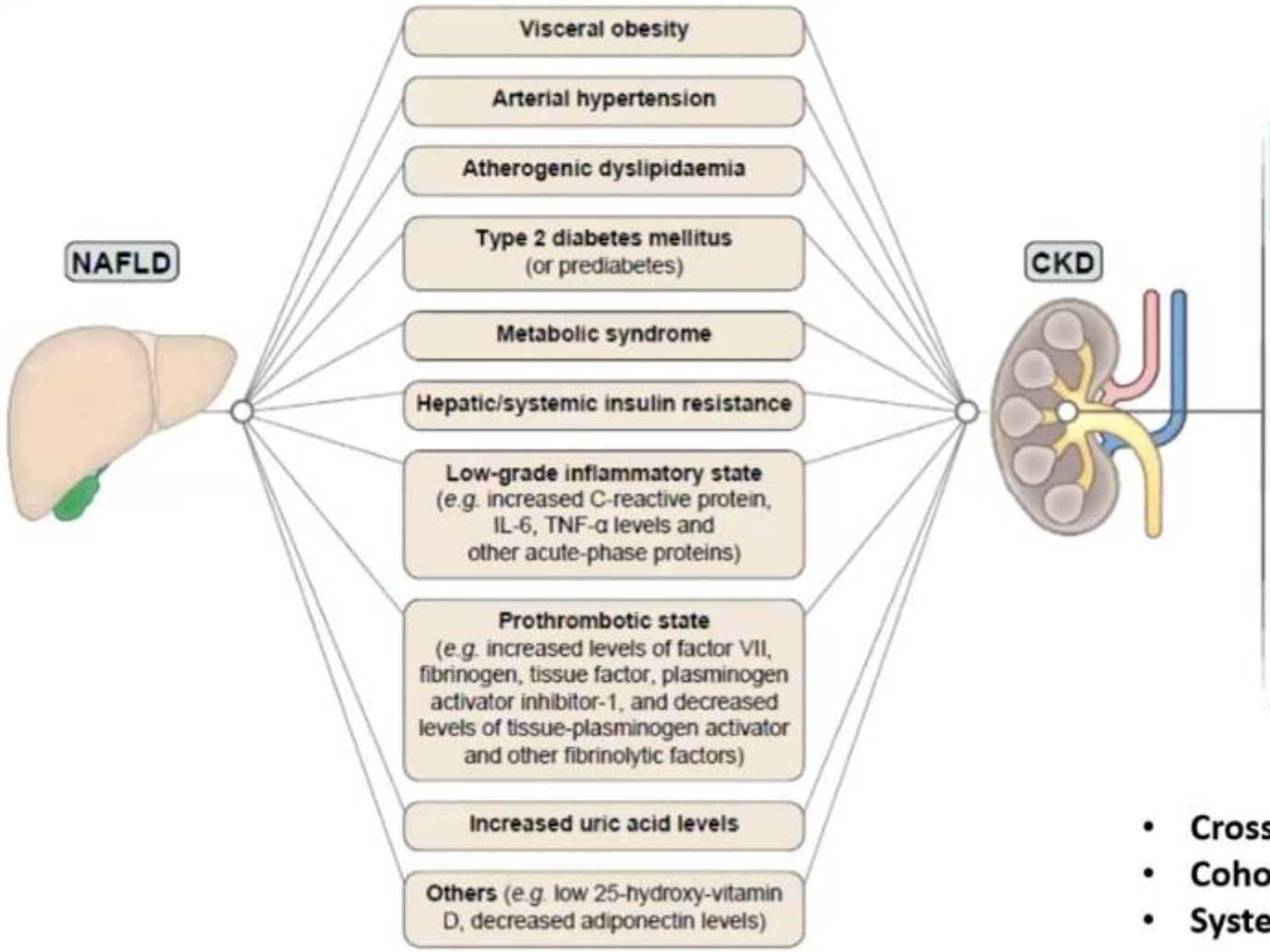
Interconnections between NAFLD and CKD

The key questions regarding the link between these two conditions are:

- (1) whether shared cardiometabolic risk factors are the basis of the association;
- (2) or whether NAFLD itself may, independently of shared cardiometabolic risk factors, contribute to CKD development;
- and (3) or whether the CKD development risk is dependent on the degree of liver disease in patients with NAFLD.

EVIDENCE OF AN ASSOCIATION BETWEEN NAFLD AND CKD



Stages of CKD	Qualitative description	GFR (ml/min/1.73 m²)
1	Kidney damage with normal or elevated eGFR	≥90
2	Kidney damage with mild eGFR decrease	60-89
3A	Mild to moderate eGFR decrease	45-59
3B	Moderate to severe eGFR decrease	30-44
4	Severe eGFR decrease	15-29
5	Kidney failure	<15 or chronic dialysis

- **Cross-sectional studies**
- **Cohort studies**
- **Systematic reviews and meta-analyses**

Cross-sectional studies

The prevalence of CKD ranged from approximately 20% to 55% among patients with NAFLD compared to 5% to 30% among their counterparts without NAFLD.

Non-Alcoholic Fatty Liver Disease Is a Risk Factor for the Development of Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus

N=

PLoS ONE 10(11): e0142808.

Hepatic steatosis and non-alcoholic fatty liver disease are not associated with decline in renal function in people with Type 2 diabetes

N=993 **NO**

Diabet. Med. 31, 1039–1046 (2014)

Non-alcoholic fatty liver disease is associated with low-grade albuminuria in men without diabetes mellitus

N=3867 **YES**

Int. J. Med. Sci. 2019, Vol. 16

Nonalcoholic fatty liver disease associated with impairment of kidney function in nondiabetes population

N=1412 **NO**

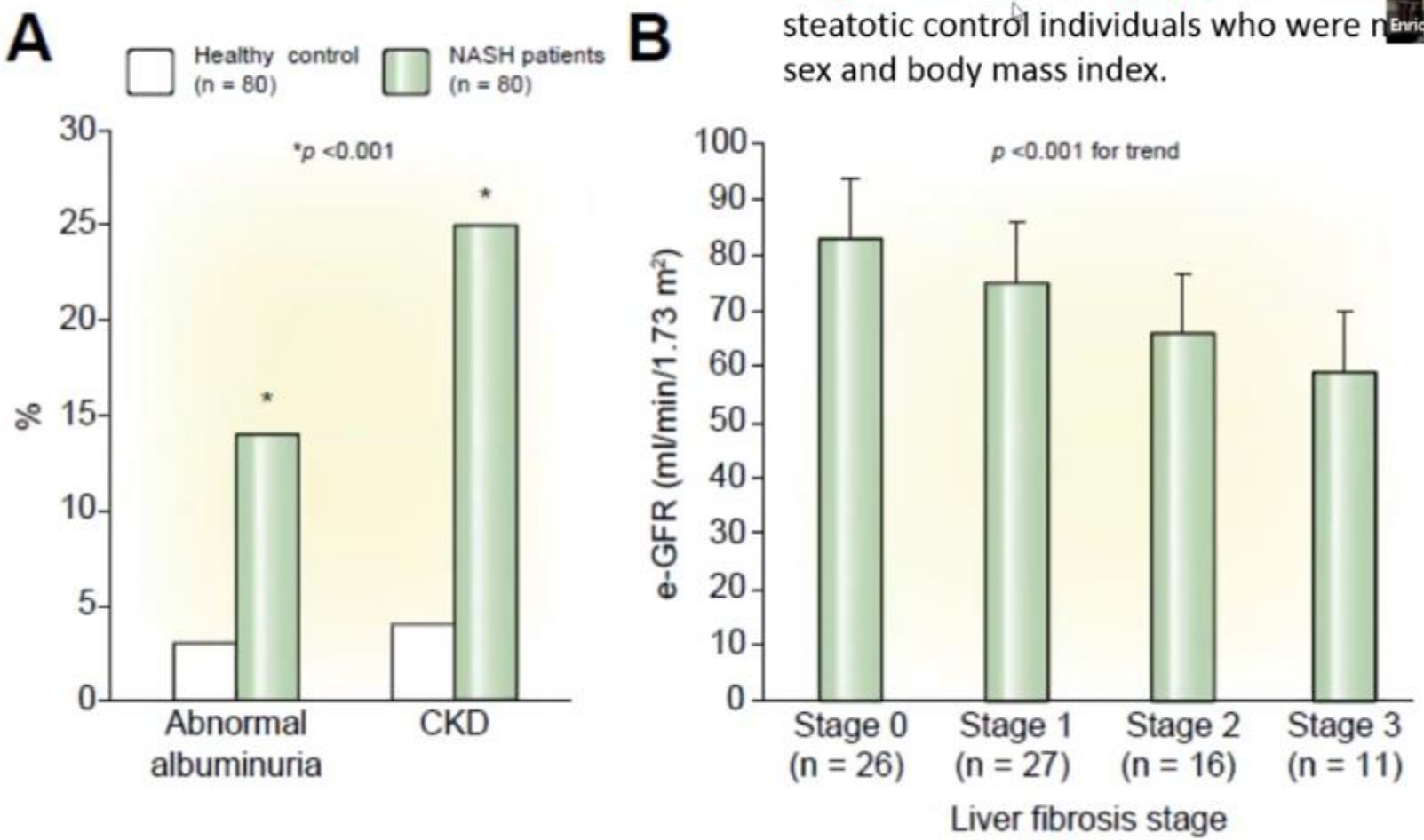
Biochemia Medica 2012;22(1):92–9

Diabesity

80 patients with biopsy proven NAS

steatotic control individuals who were n

sex and body mass index.



Non-alcoholic fatty liver disease and clinical outcomes in chronic kidney disease

Ultrasound imaging

The prevalence of **NAFLD was 17.9% in our secondary care CKD cohort.**
Prevalence was much **higher (30.7%) in diabetics.**

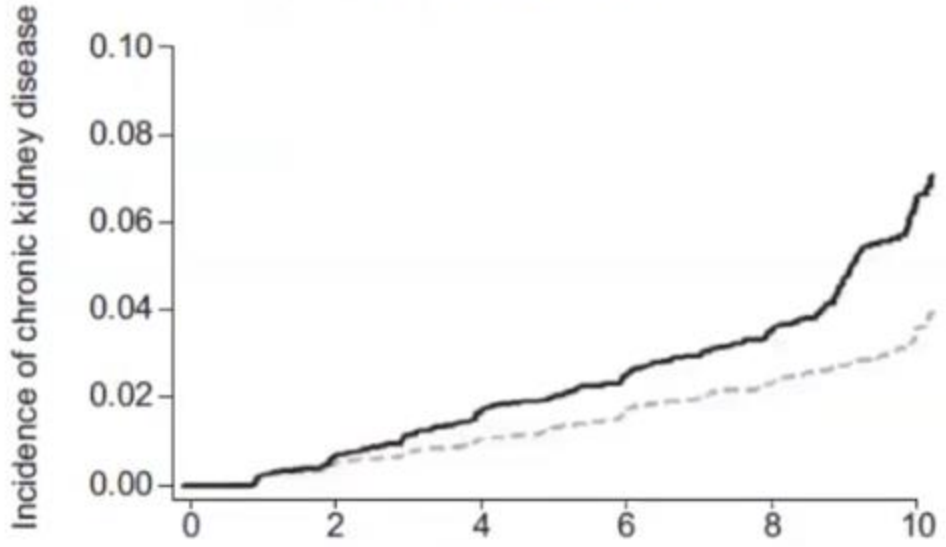
Table 3. Comparison of outcomes between NAFLD and normal patients in both total and matched samples

Events	Total sample				Matched sample			
	Total 852	NAFLD $n=183$	Normal $n=669$	P-value (NAFLD versus normal)	Total 276	NAFLD $n=138$	Normal $n=138$	P-value (NAFLD versus normal)
NFCVE, *n* (%)	128 (15.1)	46 (25.1)	82 (12.25)	<0.001	60 (21.73)	40 (28.9)	20 (14.5)	0.04
Cardiac event, *n* (%)	52 (6.1)	18 (9.84)	34 (5.08)	0.02	21 (7.6)	14 (10.14)	7 (5.07)	0.11
Cerebrovascular event, *n* (%)	34 (4)	12 (6.55)	22 (3.28)	0.04	19 (6.88)	12 (8.8)	7 (5.1)	0.24
CCF, *n* (%)	28 (3.3)	12 (6.55)	16 (2.39)	0.005	16 (5.79)	11 (7.97)	5 (3.67)	0.12
PVD, *n* (%)	14 (1.6)	4 (2.18)	10 (1.49)	0.52	4 (1.4)	3 (2.2)	1 (0.73)	0.31
ESRD, *n* (%)	160 (18.7)	26 (14.2)	134 (19.1)	0.07	31 (11.15)	15 (11.02)	16 (11.76)	0.85
All-cause mortality, *n* (%)	271 (31.8)	50 (27.32)	221 (33.03)	0.14	85 (30.8)	38 (27.5)	47 (34.05)	0.24
Deaths due to cardiovascular causes[a], *n* (%)	77 (38.5)	10 of 32 (31.25)	67 of 168 (40.5)	0.36	19 (30.1)	7 of 23 (30.4)	12 of 40 (30)	0.97
Age at death (years)	73 (67–79)	73 (66–77)	73 (68–80)	0.51	78.2 (72.1–83.8)	77.2 (71.8–82.9)	79.7 (72.4–84.4)	0.31
Follow-up (months)	65 (38–99)	74.7 (48–107)	63 (36–93.9)	0.09	78.2 (48.45–114.2)	77 (48.7–108.2)	79.5 (47.9–116.3)	0.55

Development of chronic kidney disease in patient with non-alcoholic fatty liver disease: A cohort stu

41,430 adults

The presence of non-alcoholic fatty liver disease was associated with the future decline of renal function.



Number at risk						
No NAFLD	27,207	22,012	14,593	9,126	5,491	1,446
NAFLD	14,223	11,317	7,417	4,886	3,176	946

Journal of Hepatology **2017** vol. 67 | 1274–1280

Metabolic associated fatty liver disease is factor for chronic kidney disease

Cross-sectional study of 27,371 participants

Groups: non-FLD without MD, non-FLD with MD, FLD without MD, and MAFLD groups

Table 5 | Hazard ratio for incident chronic kidney disease according to the presence of fatty liver disease and/or metabolic dysfunction among the participants whose estimated glomerular filtration rate ≥75 mL/min/1.73 m^2

	Unadjusted model	*P* value	Adjusted model	*P* value
Non-fatty liver disease without metabolic dysfunction	1 (Reference)	–	1 (Reference)	–
Non-fatty liver disease with metabolic dysfunction	1.57 (1.26–1.94)	<0.001	1.34 (1.07–1.67)	0.012
Fatty liver disease without metabolic dysfunction	0.81 (0.35–1.59)	0.560	0.73 (0.31–1.44)	0.387
Metabolic dysfunction-associated fatty liver disease	1.73 (1.36–2.17)	<0.001	1.57 (1.22–2.02)	<0.001
Creatinine (μmol/L)			1.05 (1.03-1.08)	<0.001
Men	–	–	0.31 (0.19–0.50)	<0.001
Age (per 1 year)	–	–	1.06 (1.05–1.07)	<0.001
Habit of exercise	–	–	1.09 (0.85–1.39)	0.487
Ex-smoker	–	–	1.02 (0.77–1.35)	0.917
Current smoker	–	–	1.10 (0.85–1.42)	0.461
Logarithm (alcohol consumption + 1) (Δ1 incremental)	–	–	1.01 (0.96–1.06)	0.656

Conclusions: MAFLD was associated with a risk of CKD, whereas FLD without MD was not a risk for CKD.

J Diabetes Investig 2022; 13: 308–316

Cohort Studies

Although the current evidence, from cross-sectional studies, for the existence of an association between NAFLD and increased prevalence of CKD is robust and consistent across different ethnicities and patient populations, whether NAFLD is also a **"driving force"** for the development and progression of CKD remains uncertain.

Non-alcoholic fatty liver disease is associated with increased risk of chronic kidney disease

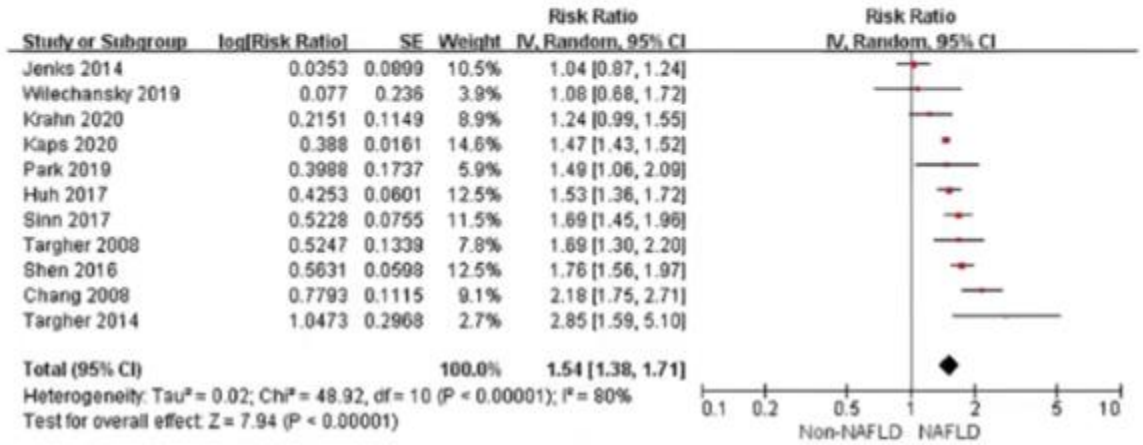
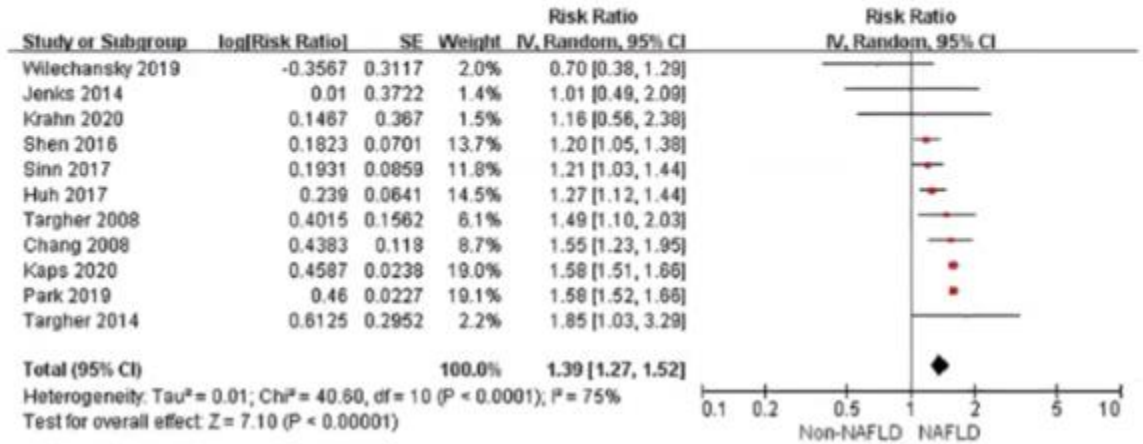


Figure 2. Forest plot of unadjusted risk of CKD associated with NAFLD.
CI, confidence interval; CKD, chronic kidney disease; df, degrees of freedom; NAFLD, non-alcoholic fatty liver disease; SE, standard error.

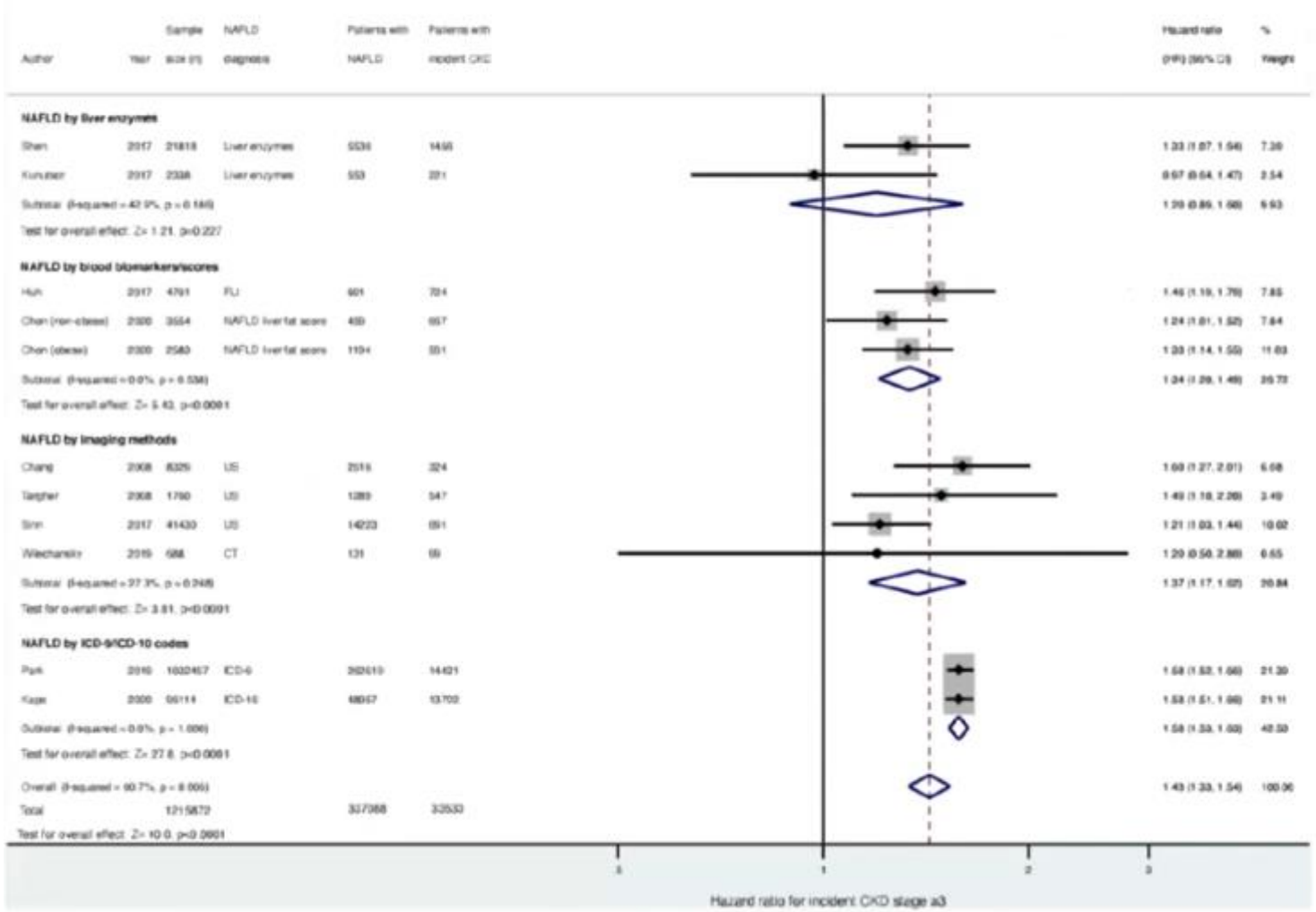


11 cohort studies were included comprising 1,198,242 participants

Conclusion: NAFLD is associated with an increased risk of incident CKD independent of established cardio-renal risk factors.

Ther Adv Chronic Dis
2021, Vol. 12: 1–11

Non-alcoholic fatty liver disease and risk of incident chronic kidney disease: an updated meta-analysis



What are the new findings?

- This meta-analysis of 13 observational longitudinal studies involving nearly 1 200 000 middle-aged individuals (28.1% with NAFLD; n=343 248) from different countries indicates that the long-term risk of developing CKD stage ≥3 is increased ~1.45-fold in individuals with NAFLD. This risk seems to parallel the severity of NAFLD, especially the severity of liver fibrosis. However, more studies are required to further support this finding.

Mantovani A, *et al*. *Gut* 2022;**71**:156–162.

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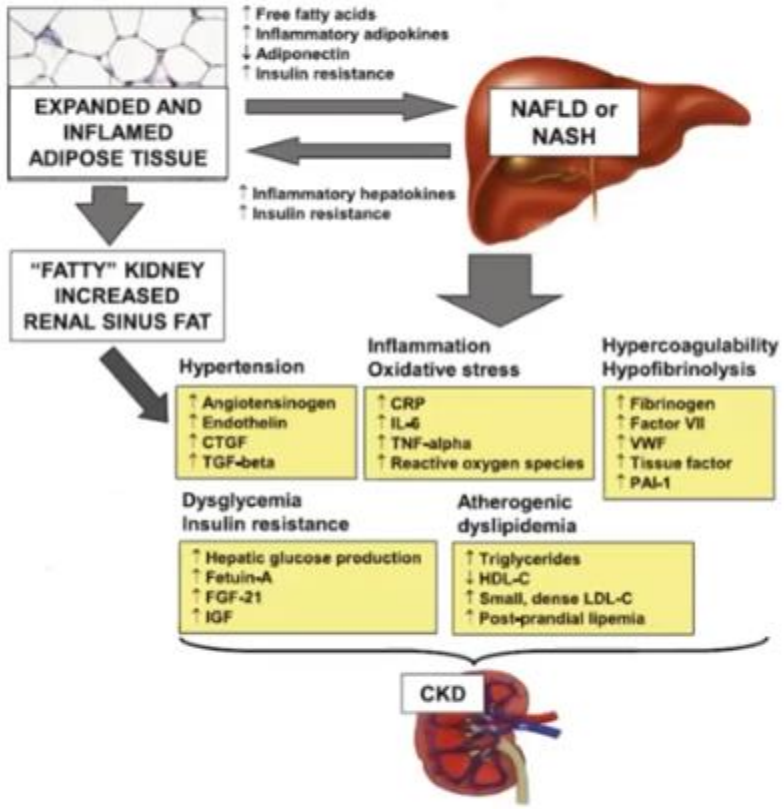
Systematic reviews and meta-analyses

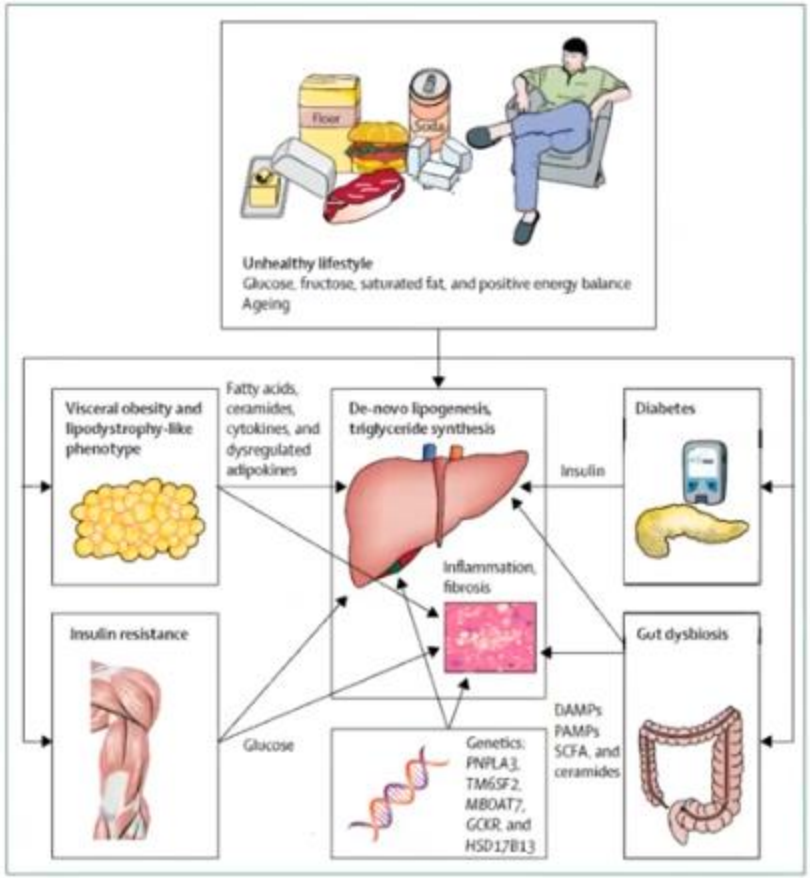
- These updated metaanalysis confirmed that NAFLD (detected by serum liver enzymes, fatty liver index or ultrasonography) was **associated with a nearly 40% increase** in the long-term risk of incident CKD.

Study limitations



- It should be noted that the observational design of the available studies does **not allow us to establish a causal association** between NAFLD and risk of CKD stage ≥3, and that it is currently uncertain whether NASH or NAFLD with advanced **fibrosis** carry a higher risk of incident CKD than simple steatosis.
- **No studies used liver biopsy**, which is considered the 'gold standard' for diagnosing and staging NAFLD.
- Almost all studies adjusted their results for BMI, but only a few of these studies additionally adjusted their results **for body fat distribution.**
- The use of the **MDRD or the CKD-EPI equations** to calculate eGFR, neither of which are reliable in the presence of severe obesity or cirrhosis.
- Most of the available cohort studies have been conducted in **Asian countries.**
- **No large prospective studies** are available that have examined the rates of CKD progression to kidney failure (stage 5 CKD) in cohorts of patients with NAFLD, nor in cohorts of patients with advanced CKD.

T2DM and metabolic syndrom



- In **centrally obese individuals** with T2DM, **insulin resistance** frequently occurs along side other cardiometabolic risk factors that increase the risk of both NAFLD and CKD.
- **NAFLD as a metabolic liver disease (MAFLD)** with cardiovascular and metabolic risk factors; many of which have the potential to cause kidney dysfunction.
- Activation of hepatic macrophages and hepatic inflammation is associated with an increase in **proinflammatory cytokines** and hepatic/systemic insulin resistance, **increased activity of the renin-angiotensin-aldosterone system and oxidative stress** mediated by proinflammatory and profibrotic mediators.

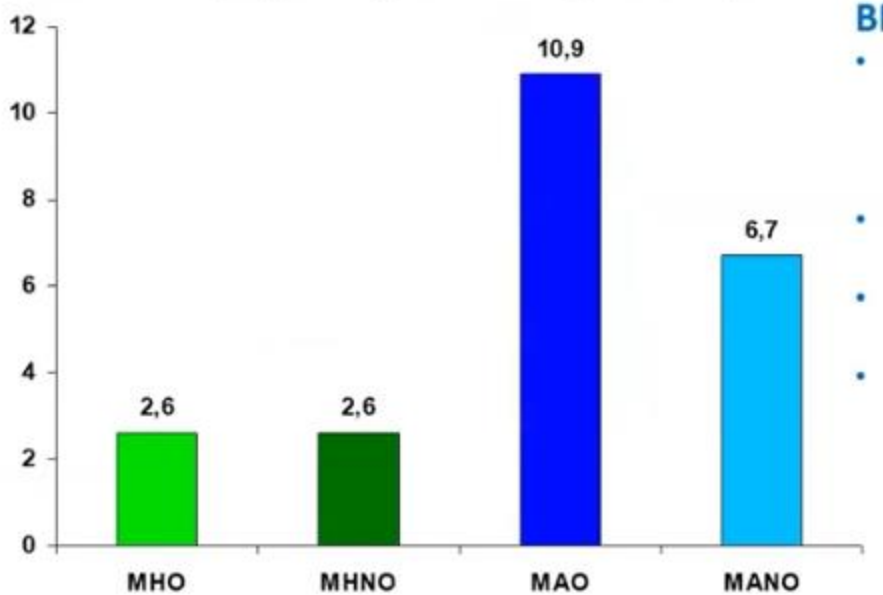
Metabolically Healthy Obesity and Risk of Incident CKD

Yoshitaka Hashimoto, Muhei Tanaka,* Hiroshi Okada,† Takafumi Senmaru,* Masahide Hamaguchi,* Mai Asano,* Masahiro Yamazaki,* Yohei Oda,* Goji Hasegawa,† Hitoshi Toda,‡ Naoto Nakamura,* and Michiaki Fukui**

Abstract

Background and objectives Metabolically healthy obesity (MHO) is a unique obesity phenotype that apparently protects people from the metabolic complications of obesity. The association between MHO phenotype and incident CKD is unclear. Thus, this study investigated the association between MHO phenotype and incident CKD.

Design, setting, participants, & measurements A total of 3136 Japanese participants were enrolled in an 8-year follow-up cohort study in 2001. Metabolically healthy status was assessed by common clinical markers: BP, triglycerides, HDL cholesterol, and fasting plasma glucose concentrations. Body mass index ≥25.0 kg/m² was defined as obesity. CKD was defined by proteinuria or eGFR of <60 ml/min per 1.73 m². To calculate the odds ratio for incident CKD, logistic regression analyses were performed.



BMI>25.0 kg/m2

- **Systolic BP>130 mmHg and/or a diastolic BP>85 mmHg** or who were under medical treatment were considered to have hypertension.
- **Triglyceride level >150 mg/dl** or treatment of hyperlipidemia.
- **HDL cholesterol level <40 mg/dl** in men and <50 mg/dl in women.
- **Fasting plasma glucose >100 mg/dl** or who were under medical treatment were considered to have impaired fasting glucose or diabetes.

Clin J Am Soc Nephrol 10: 578–583, 2015.

Role of non-alcoholic fatty liver disease in the evolution of renal function in patients with diabetes mellitus

Lucía Aubert[1], Justo Sandino[1], Elena Gutiérrez-Solís[1], Flo
Julián Segura[1,3], Esteban Porrini[4] and Enrique Morales

Nephrol Dial Transplant (2022) 37: 1125–1131

Ultrasonography and NAFLD score

Table 1. Basal characteristics of the cohort ($n = 102$)

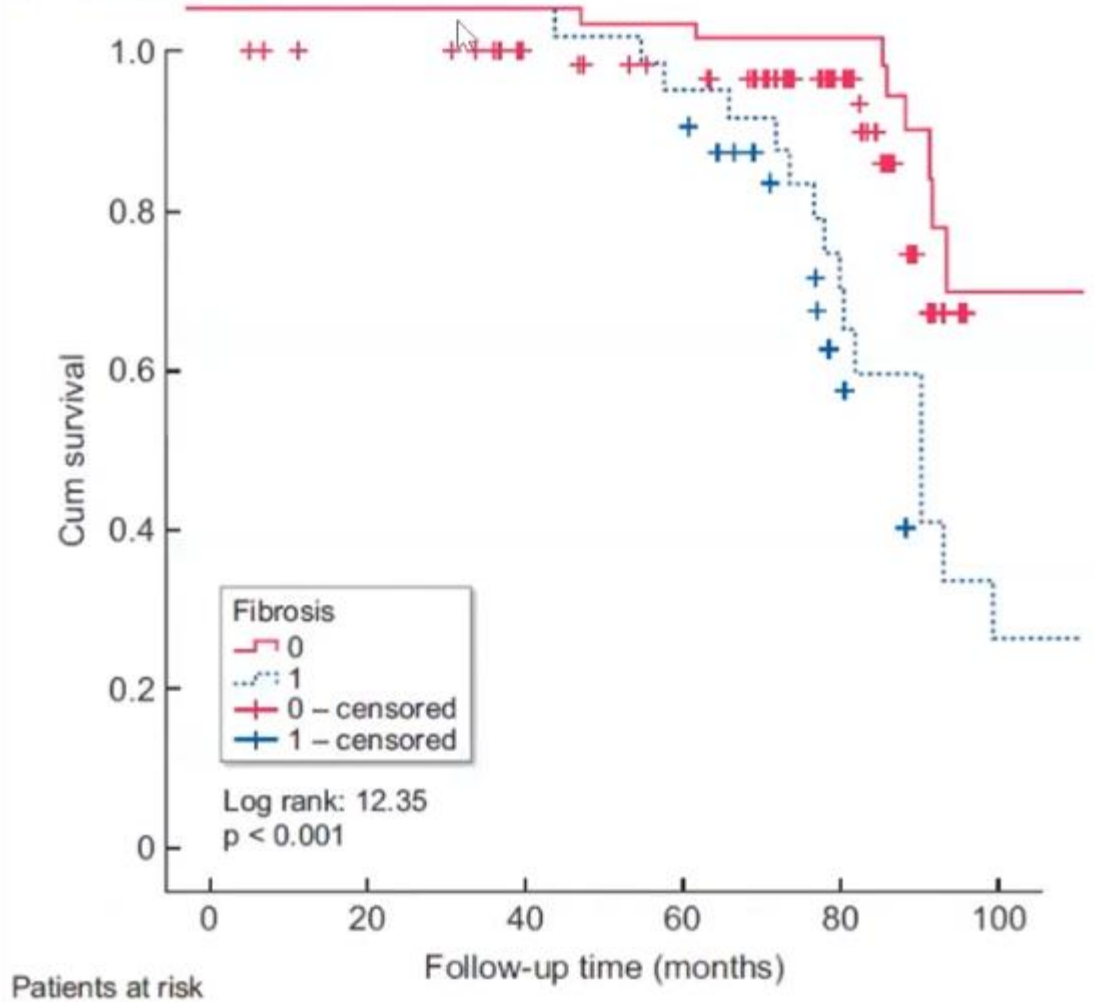
Gender (male), %	67.6
Age (years), mean	58 ± 7
Race, %	
Caucasian	93.1
Hispanic	4.9
Others	2.0
HTN, %	96.1
DL, %	78.4
Smoking habit, %	
Active smoker	24.5
Former smoker	33.3
Non-smoker	42.2
Family history of DM, % ($n = 63$)	49.2
Diabetic retinopathy, % ($n = 74$)	39.2
Antidiabetic treatment, %	
Diet	1.0
Insulin	25.5
Oral antidiabetic	59.8
Both	13.7
BMI (kg/m^2), mean ± SD	31.1 ± 5.9
Obesity, %	50
Initial SCr (mg/dL), mean ± SD	1.18 ± 0.45
eGFR (mL/min/1.73 m^2), mean ± SD	73.7 ± 32.9
Proteinuria (g/24 h), mean ± SD	1.0 ± 1.8
HbA1c (%), mean ± SD	7.1 ± 1.6
Cholesterol (mg/dL), mean ± SD	173.5 ± 43.2
Triglycerides (mg/dL), mean ± SD	168.7 ± 112.3
AST (mg/dL), mean ± SD	22.7 ± 11.4
ALT (mg/dL), mean ± SD	25.9 ± 17.7
Platelets (×10^9/L), mean ± SD	227.9 ± 71.6
Serum albumin (g/dL), mean ± SD	4.3 ± 0.6

Variable	NAFLD score <-1,85 Group 1 ($n = 34$)	NAFLD score -1,85-0,18 Group 2 ($n = 34$)	NAFLD >0,18 Group 3 ($n = 34$)	P-value
Gender (male), %	33	31.9	34.8	0.87
Age (years), mean ± SD	55.5 ± 7.8	59.1 ± 7.5	60.7 ± 6.1	0.01*
Family history T2DM, %	22.6	45.2	32.3	0.82
HTN, %	32.7	34.7	32.7	0.33
Systolic blood pressure (mmHg), mean ± SD	133 ± 18	133 ± 18	145 ± 22	0.03**
DL, %	30	38.8	31.3	0.08
Diabetic retinopathy, %	27.6	31	41.4	0.87
Evolution of T2DM (months), mean ± SD	84.7 ± 78.9	90.1 ± 64.9	102.2 ± 85.2	0.46
RAASi, %	33.7	33.7	32.6	0.85
Antidiabetic, %				0.73
Insulin	30.8	34.6	34.6	
Oral antidiabetics	37.7	31.1	31.1	
Both	21.4	42.9	35.7	
BMI (kg/m^2), mean ± SD	28.8 ± 4.9	30.1 ± 4.9	34.5 ± 6.4	0.01*
Metabolic syndrome, %	28.9	28.9	42.1	0.35
Triglycerides (mg/dL), mean ± SD	132 ± 52	191 ± 128	182 ± 131	0.06
Cholesterol (mg/dL), mean ± SD	164 ± 31	179 ± 53	176 ± 43	0.28
AST (mg/dL), mean ± SD	21.8 ± 10.9	22.6 ± 10.4	23.6 ± 12.9	0.80
ALT (mg/dL), mean ± SD	28.5 ± 20.7	26.7 ± 15.9	22.2 ± 15.7	0.33
Platelets (×10^9/L), mean ± SD	282.7 ± 80.1	220.0 ± 43.9	180.9 ± 43.7	0.02**
Serum albumin (g/dL), mean ± SD	4.4 ± 0.5	4.5 ± 0.5	4.0 ± 0.7	<0.001*
Initial HbA1c (%), mean ± SD	7.2 ± 1.5	7.2 ± 1.5	6.9 ± 1.8	0.83
Initial SCr (mg/dL), mean ± SD	1.07 ± 0.43	1.26 ± 0.47	1.19 ± 0.45	0.25
eGFR (mL/min/1.73 m^2), mean ± SD	84.8 ± 40.4	64.9 ± 23	71.4 ± 30.6	0.03***
Proteinuria (g/24 h), mean ± SD	0.56 ± 0.77	0.82 ± 1.08	1.59 ± 2.70	0.05*

Table 3. Evolution of HbA1c, proteinuria and eGFR by groups

Variable	Group 1 ($n=34$)	Group 2 ($n=34$)	Group 3 ($n=34$)	P-value
Follow-up time(months), mean ± SD	71.4 ± 26.2	78.0 ± 18.1	78.0 ± 26.5	0.86
Initial HbA1c (%), mean ± SD	7.1 ± 1.5	7.2 ± 1.5	6.9 ± 1.8	0.83
Final HbA1c (%), mean ± SD	6.7 ± 0.9	6.9 ± 1.1	6.5 ± 1.2	0.32
Initial proteinuria (g/24 h), mean ± SD	0.56 ± 0.77	0.82 ± 1.09	1.59 ± 2.70	0.05*
Final proteinuria (g/24 h), mean ± SD	1.03 ± 3.01	1.14 ± 1.51	1.27 ± 1.47	0.91
Initial eGFR (mL/min/1.73 m^2), mean ± SD	84.8 ± 40.4	64.9 ± 23.0	71.4 ± 30.6	0.03**
Final eGFR (mL/min/1.73 m^2), mean ± SD	66.6 ± 33.3	50.6 ± 26.9	36.8 ± 23.1	<0.01*
Loss of eGFR, %	20.1	23.2	47.0	<0.01*
eGFR loss per year (mL/min/1.73 m^2), mean ± SD	−2.53 (−4.83 to −0.92)	−1.47 (−2.81 to −0.71)	−4.18 (−6.86 to −2.29)	0.36
Initiation of RRT, *n* (%)	4 (21.1)	8 (42.1)	7 (36.8)	0.43
Deceased, *n* (%)	1 (14.3)	2 (28.6)	4 (57.1)	0.50

*Statistical significance between Groups 1 and 3.
**Statistical significance between Groups 1 and 2.



What this study adds?

- The results of this study illustrate the impact of the presence of NAFLD, especially when associated with a higher **degree of hepatic fibrosis, in the progression of CKD** independent of other risk factors.
- Therefore the presence of NAFLD and the degree of hepatic fibrosis **should be included in the global evaluation** of cardiovascular risk factors in patients with CKD, especially in obese and diabetes mellitus patients.

What impact this may have on practice or policy?

- The **presence of NAFLD in diabetic patients is an additional risk factor for renal progression** independent of other risk factors. Hence evaluation and treatment should be mandatory to prevent the progression of CKD.

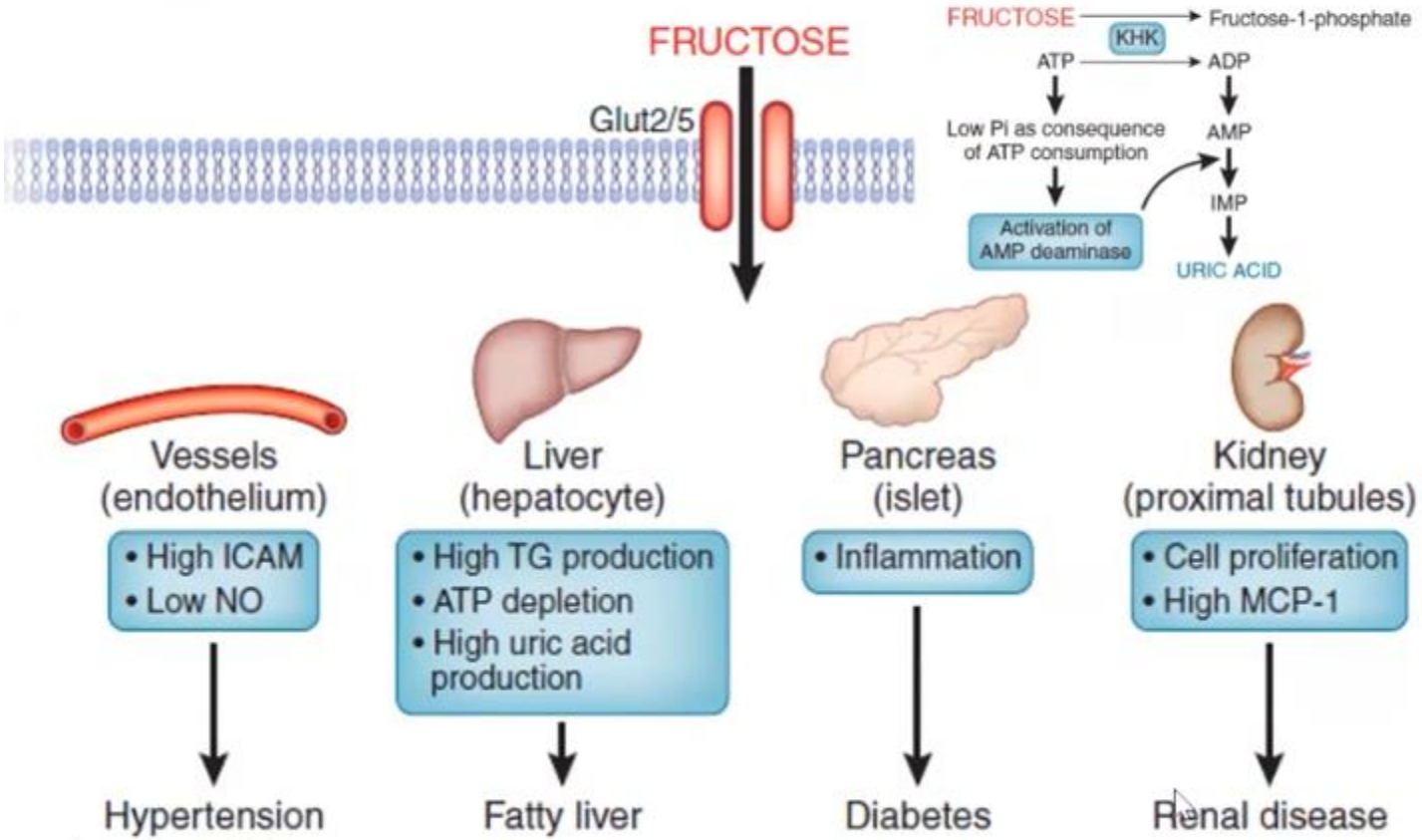
Nephrol Dial Transplant (2022) 37: 1125–1131

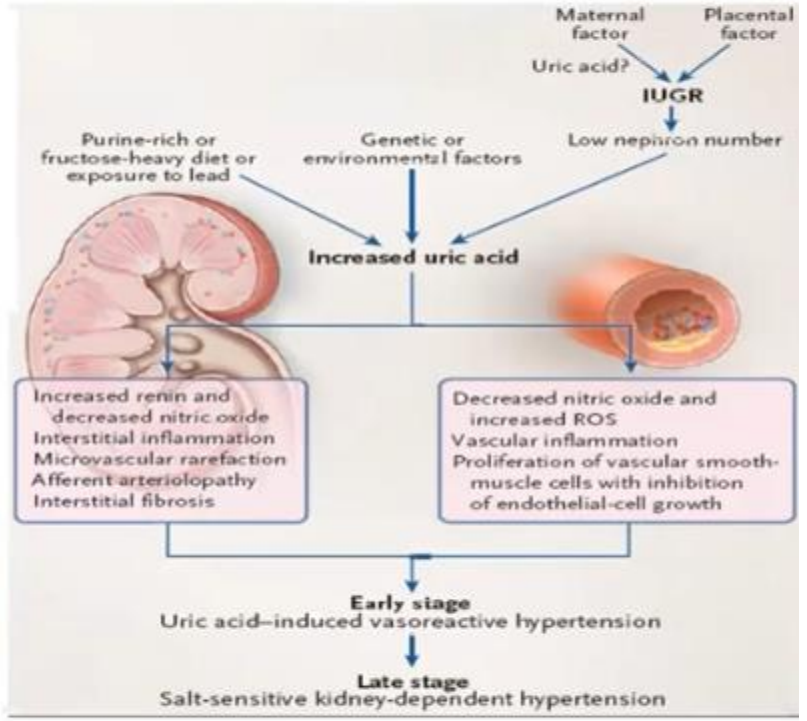
Diabesity

Dietary choices: Fructose and Uric Acid accumulation

The Effect of Fructose on Renal Biology and Disease

Richard J. Johnson,* L. Gabriela Sanchez-Lozada,† and Takahiko Nakagawa*





Feig DI, et al. N Engl J Med 2008;359:1811-21.

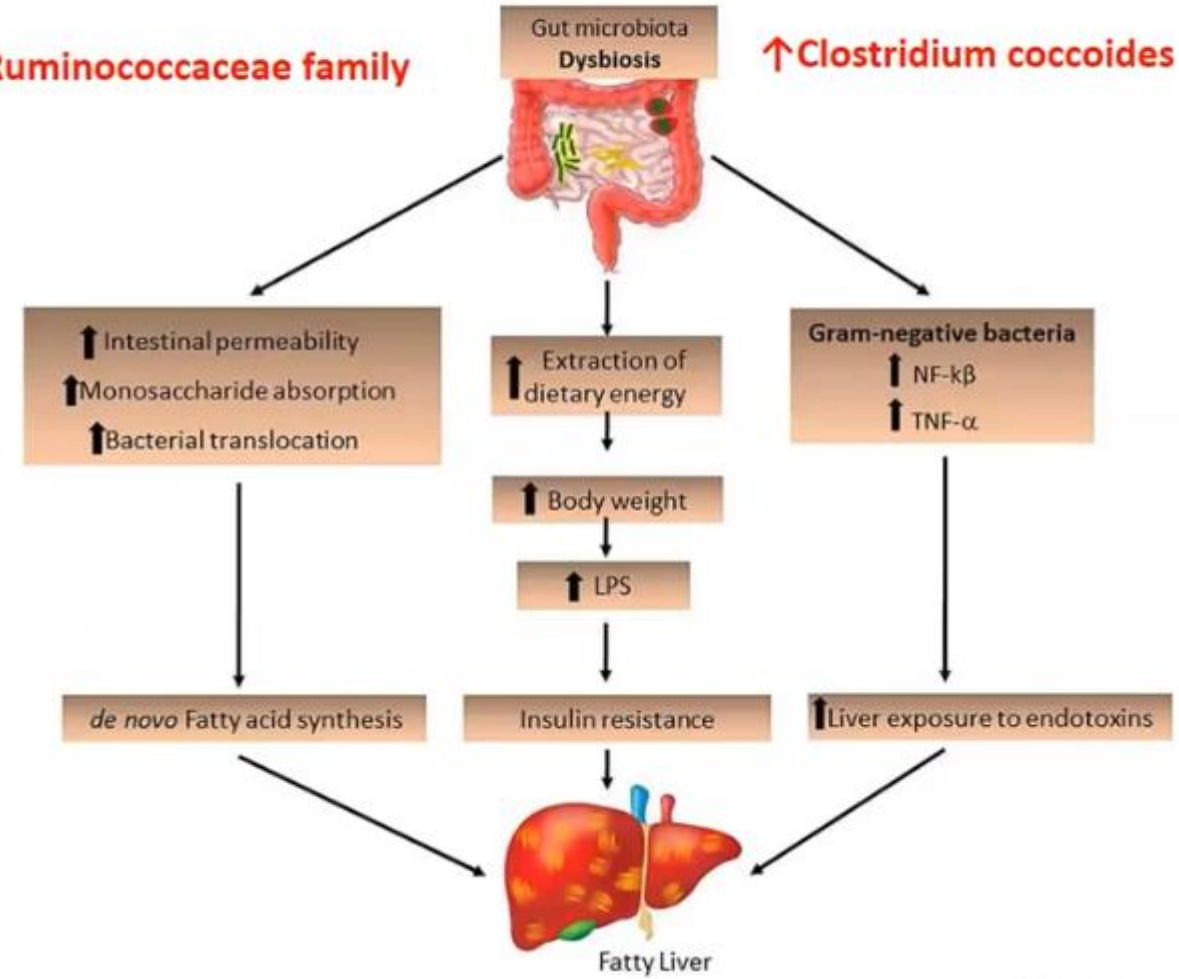
J Am Soc Nephrol 21: 2036–2039, 2010.

e-seminars

Diabesity
Diabetes and Obesity

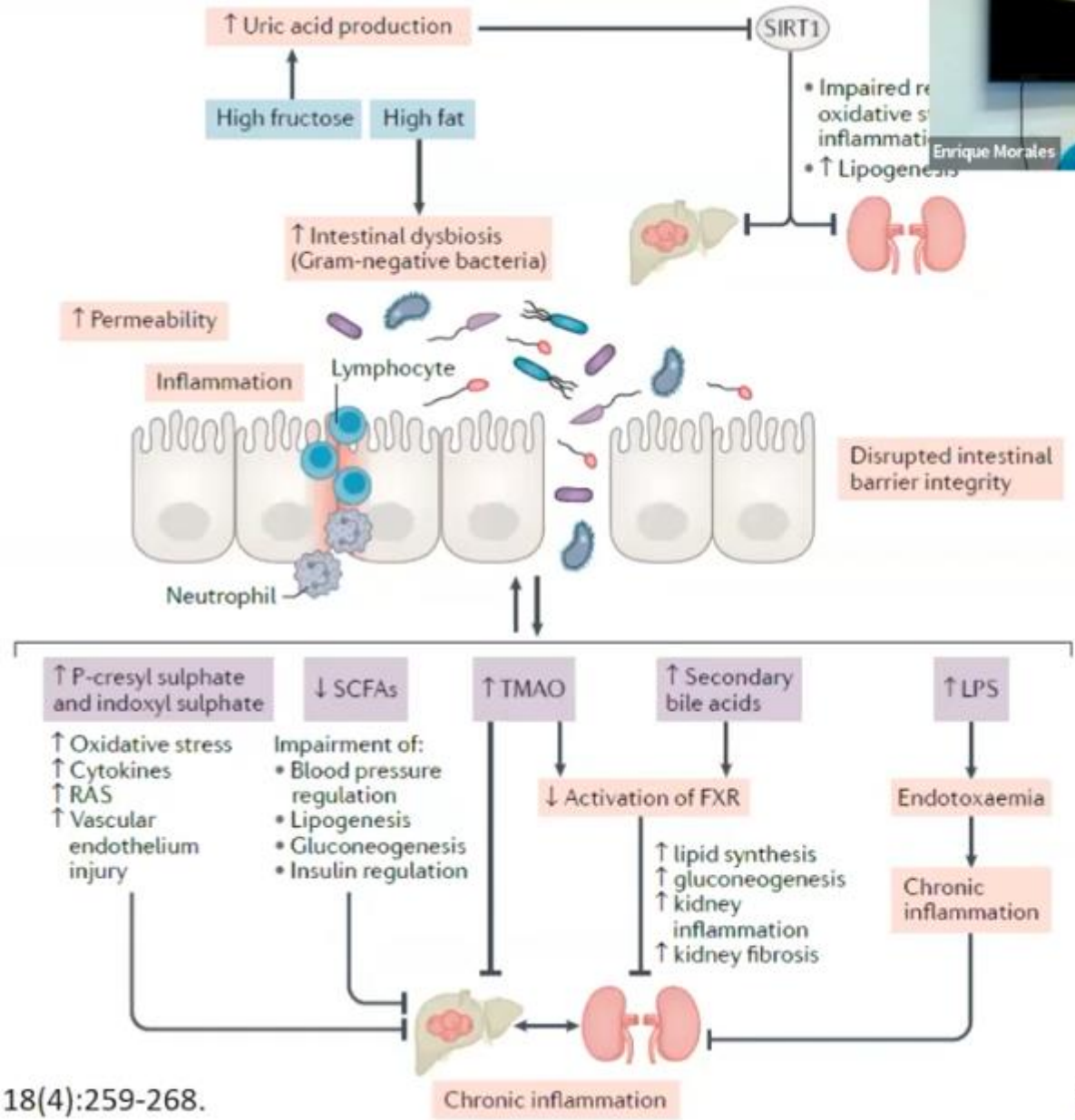
Dysbiosis and perturbed intestinal function affecting NAFLD and CKD

- With perturbation of the gut microbiota (dysbiosis), there is an **increase in gram negative** organisms, lipopolysaccharide, gut permeability, secondary bile acids (BAs) and renal toxins that may increase the risk of development and progression of both NAFLD, and CKD.



Ann Hepatol. 2019;18:416–21

Dysbiosis thus contributes to the development of NAFLD and CKD through changes in intestinal bacterial populations, disruption of the gastrointestinal barrier, and the generation of **proinflammatory toxins, bile acids, lipopolysaccharides, and SCFAs**.



Nat Rev Nephrol. 2022; 18(4):259-268.

Platelet activation as a mediator of the link between NAFLD and CKD

- With oxidative stress and kidney dysfunction, there is a reduction in anti-oxidant protective factors produced by the kidneys, such as the Klotho protein.
- When platelets are activated, **alpha granules and dense granules** are released containing multiple **proinflammatory cytokines, chemokines and growth factors** (EGF, IL-6, PDGF, TGF-beta, HGF, …).

Table 1
Inflammatory peptide and protein mediators released through platelet activation

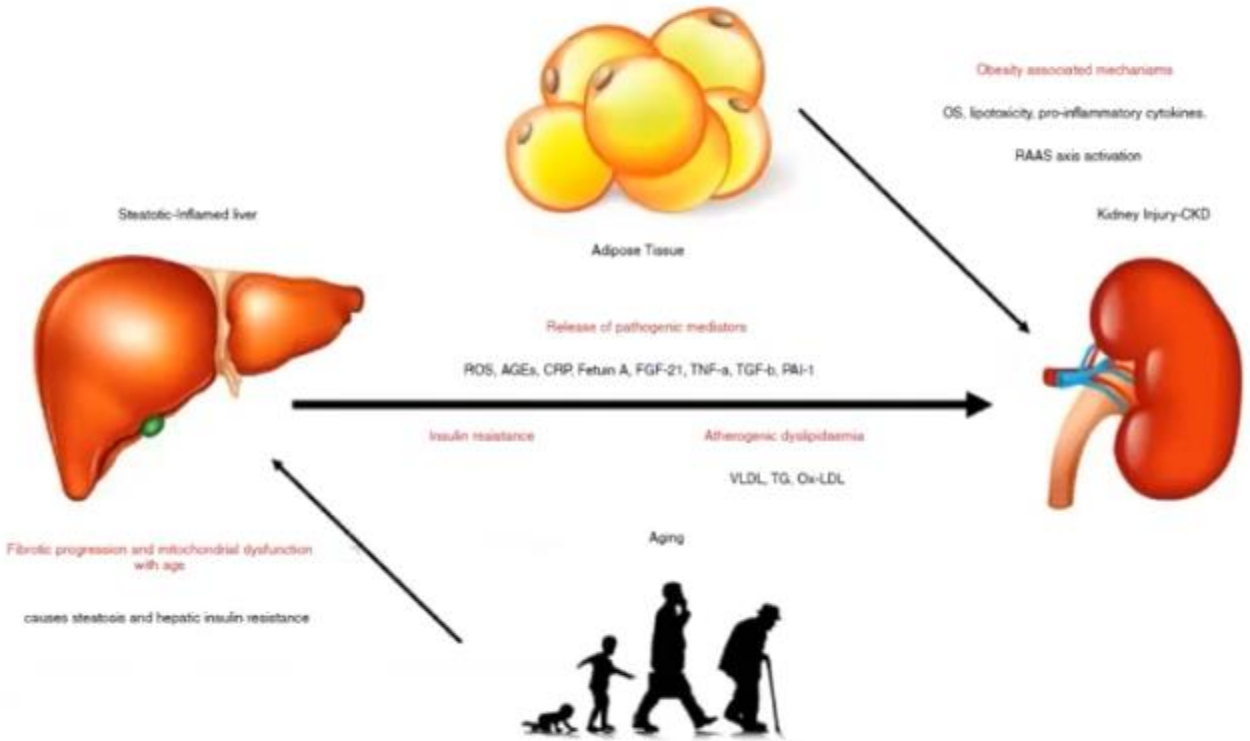
Location	Family	Molecule
Dense granules	Nucleotide	ATP
	Amino acid	Glutamate
	Phosphates	Polyphosphates
	Monoamine	Serotonin
α-Granules	Chemokines	PF4 or CXCL4
		β-Thromboglobulin (CXCL7 or NAP-2)
		RANTES or CCL5
		MIP-1α or CCL3
		MCP-3 or CCL7
		NAP-2 or CXCL7
		TARC or CCL17
		Interleukin-8 (CXCL8)
	Cytokines	CD40 ligand (CD40L)
		TNF-α
		IL-1α
		GRO-α or CXCL1
		ENA-78 or CXCL5
		SDF-1 or CXCL12
	Growth factors	PDGF
		TGF-β
		EGF

Clin Liver Dis 26 (2022) 213–227

Diabesity
Diabetes and Obesity

Premature ageing and age-related changes

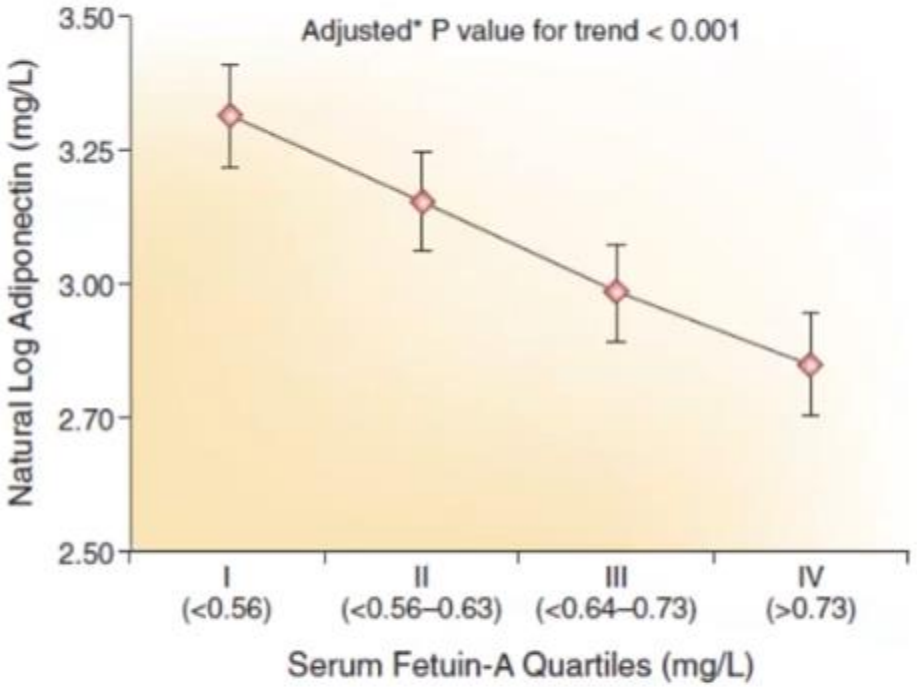
- Old age is a risk factor for NAFLD, CKD and T2DM.
- Decreased urinary Klotho protein occurs with ageing.
- Age-related changes in the liver may also occur with alterations in hepatic sinusoidal endothelial cells, increases in the hepatokine fetuin-A and decreases in adiponectin, potentially linking MetS, NAFLD and CKD.

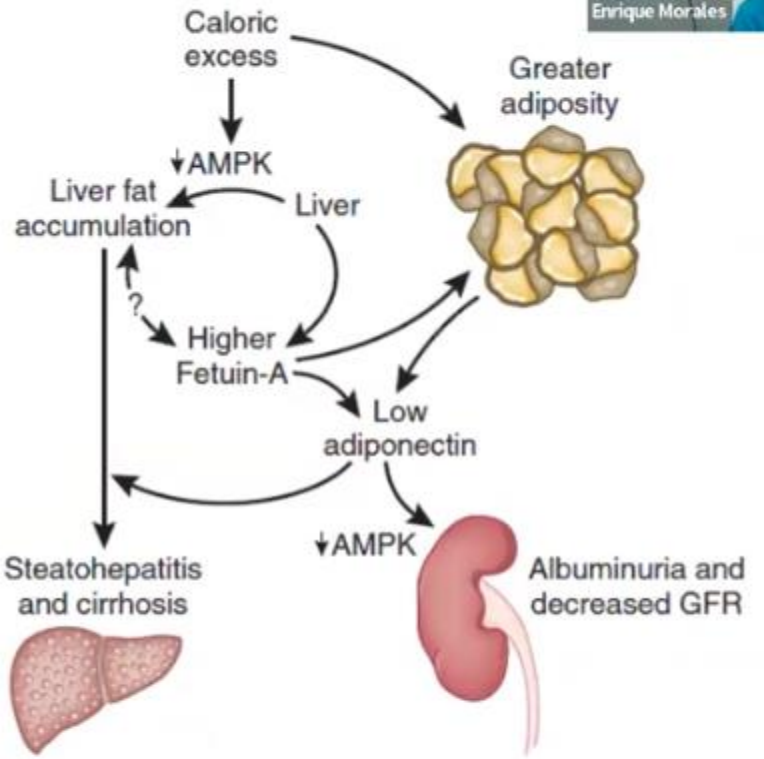


Annals of Hepatology 19 (2020) 134–144

e-seminars

Mechanisms Linking Obesity, Chronic Kidney Disease, and Fatty Liver Disease: The Roles of Fetuin-A, Adiponectin, and AMPK





FETUIN-A INDUCES INSULIN RESISTANCE AND REGULATES ADIPONECTIN

- Fetuin-A is a 64-kDa glycoprotein produced exclusively by the liver and secreted into serum where it is found in relatively high concentrations in humans.
- In humans, higher fetuin-A levels associate with obesity and insulin resistance in the general population and in patients with CKD and ESRD.

ADIPONECTIN MEDIATES CROSSTALK BETWEEN ADIPOSE, KIDNEY, AND LIVER

- Adiponectin is a 30-kDa protein secreted from adipose tissue.
- Adiponectin improves insulin sensitivity.
- Individuals with NAFLD have lower serum adiponectin levels than healthy subjects, and among individuals with NAFLD adiponectin levels are inversely correlated with the severity of hepatic fibrosis and inflammation.

J Am Soc Nephrol **21**: 406–412, 2010

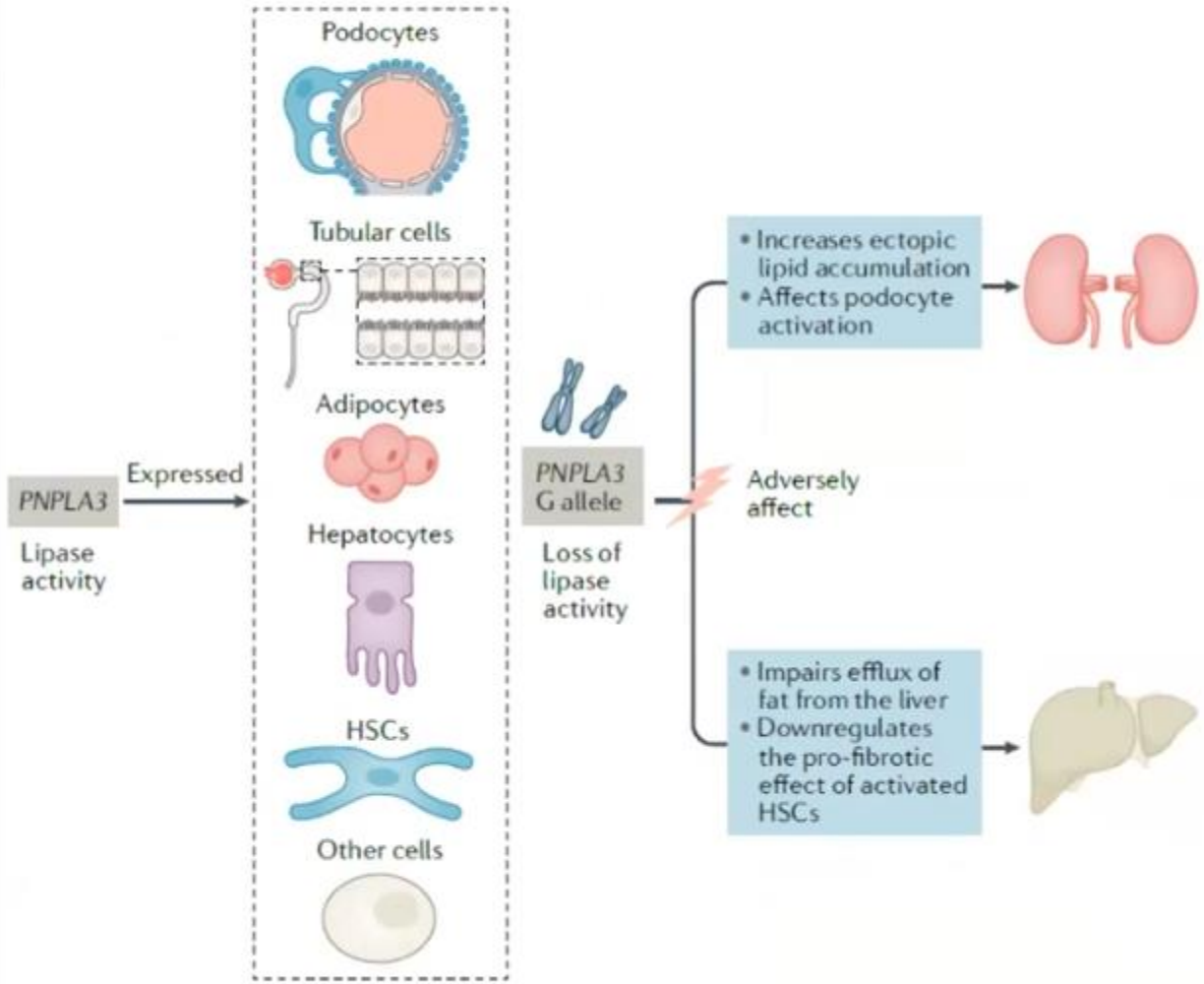
Effect of PNPLA3 polymorphism on renal funct

- Emerging studies suggest that genetic polymorphisms, such as those in **PNPLA3**, HSD17B13, TM6SF2, MBOAT7 and GCKR have an important role in the development and progression of NAFLD.

Table 1 | **Genotypes associated with risk of both NAFLD and CKD**

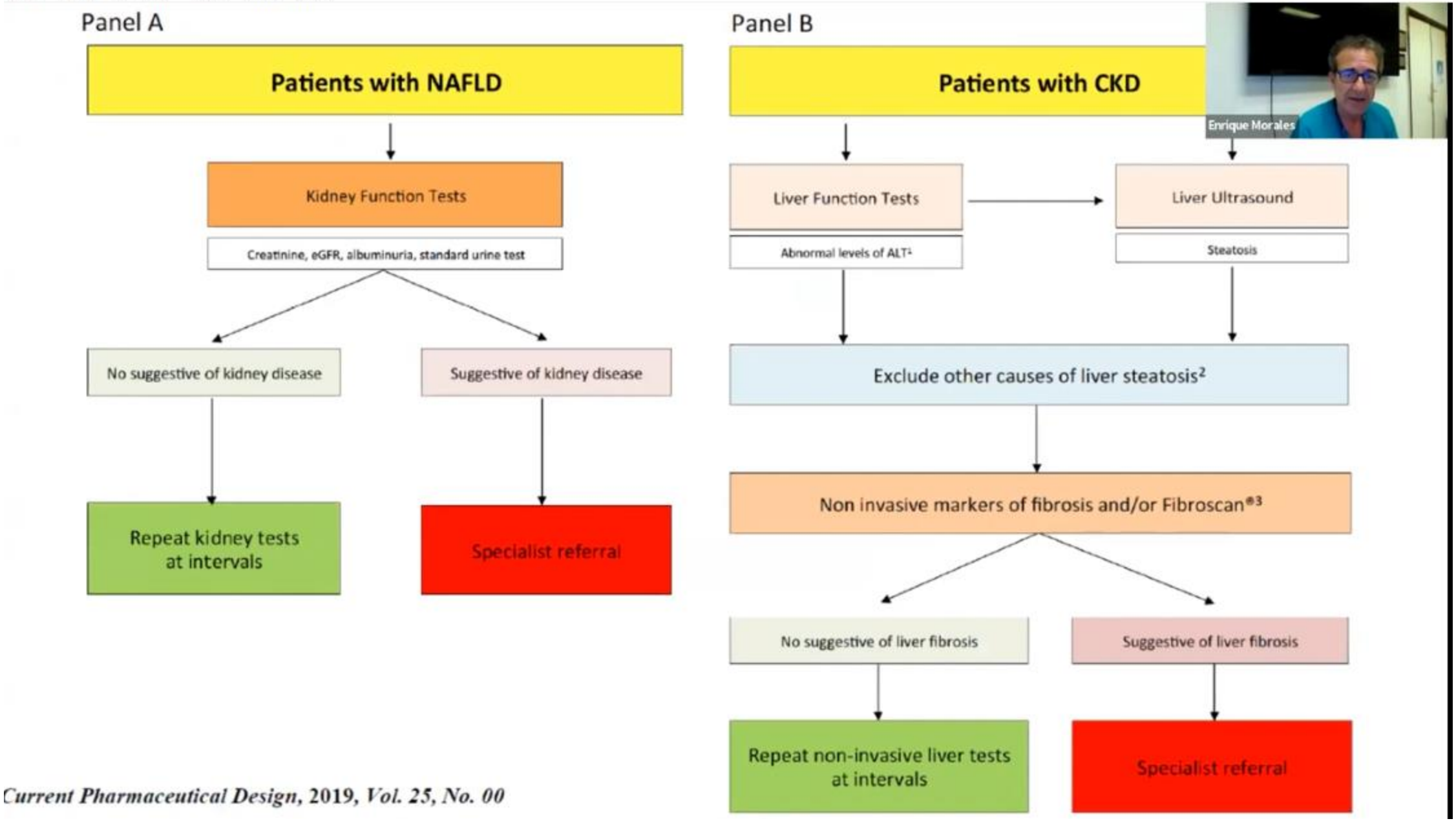
Genotype(s)	Effect on NAFLD	Study population	Kidney findings	
PNPLA3 rs738409 G allele	Risk factor for more severe NAFLD	740 elderly individuals	Associated with lower eGFR in n in overweight individuals	
		202 non-obese, non-diabetic adults	Associated with a higher risk of prevalent CKD, lower eGFR and abnormal albuminuria regardless of NAFLD status	64
		101 post-menopausal women with T2DM	Associated with lower eGFR and a higher risk of prevalent CKD	55
		217 adults with biopsy-proven NAFLD	Associated with a higher risk of prevalent CKD, albuminuria and increased u-NGAL levels	56
		142 children and adolescents with biopsy-proven NAFLD	Associated with lower eGFR and increased 24-h proteinuria	57
		591 obese children	Associated with lower eGFR only in those with NAFLD	54
		230 obese children	Associated with lower eGFR and higher urinary albumin levels only in those with NAFLD	73
		396 adults with biopsy-proven NAFLD	Not associated with eGFR or CKD stages	66
HSD17B13 rs72613567 A allele	Associated with less severe NAFLD	684 obese children	Associated with higher eGFR in obese children with and without NAFLD	60
		215 adults with biopsy-proven NAFLD	Associated with a lower risk of albuminuria, but not with eGFR or u-NGAL levels	61
TM6SF2 rs58542926 T allele	Risk factor for more severe NAFLD	202 non-obese, non-diabetic adults	Associated with higher eGFR, a lower prevalence of albuminuria and CKD	64
		531 obese children	Associated with higher eGFR in obese children with/without NAFLD	65
		396 adults with biopsy-proven NAFLD	Not associated with eGFR or CKD stages	66
		230 obese children	Not associated with eGFR or albuminuria	73
MBOAT7 rs641738 T allele	Risk factor for more severe NAFLD	396 adults with biopsy-proven NAFLD	Associated with increasing CKD stages, but not with eGFR	68
		230 obese children	Not associated with eGFR or albuminuria	73
GCKR rs1260326 T allele	Risk factor for more severe NAFLD	8 prospective studies and 4 case–control studies	Associated with risk of incident CKD or kidney failure	70
		3,314 participants	Associated with higher risk of prevalent CKD	71
		Meta-analysis of 11 studies	Associated with higher eGFR and a trend towards protection from CKD	72
		230 obese children	Not associated with eGFR or albuminuria	73

Nat Rev Nephrol. 2022; 18(4):259-268.

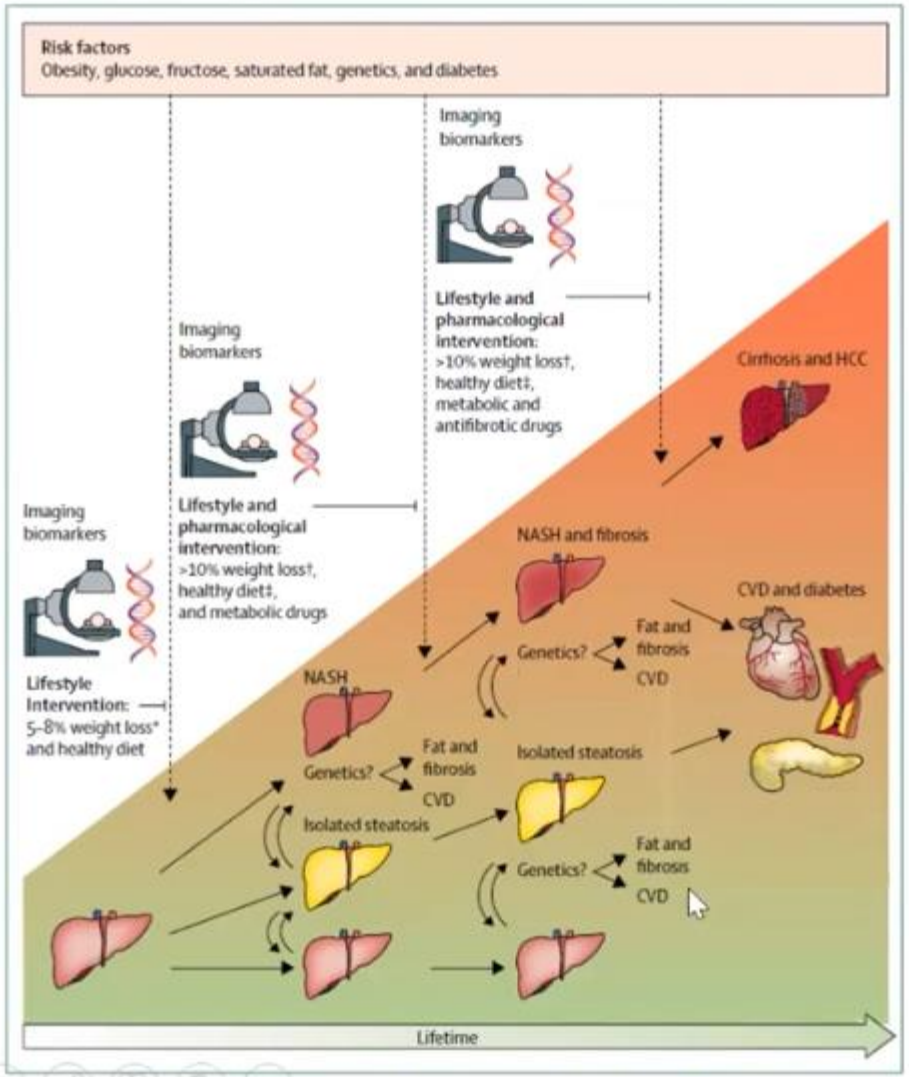


- **PNPLA3 gene** (the mi… rs738409) encoding an Ile148Met change, has been recognized as a major common genetic variant associated with a greater **predisposition to NASH** and progressive liver fibrosis in both paediatric and adult populations.
- PNPLA3 is **highly expressed** in the **liver,** mainly in human hepatic stellate cells (HSCs) and hepatocytes.
- PNPLA3 is also **highly expressed in the kidney** and may lead to lipid accumulation in the kidney.

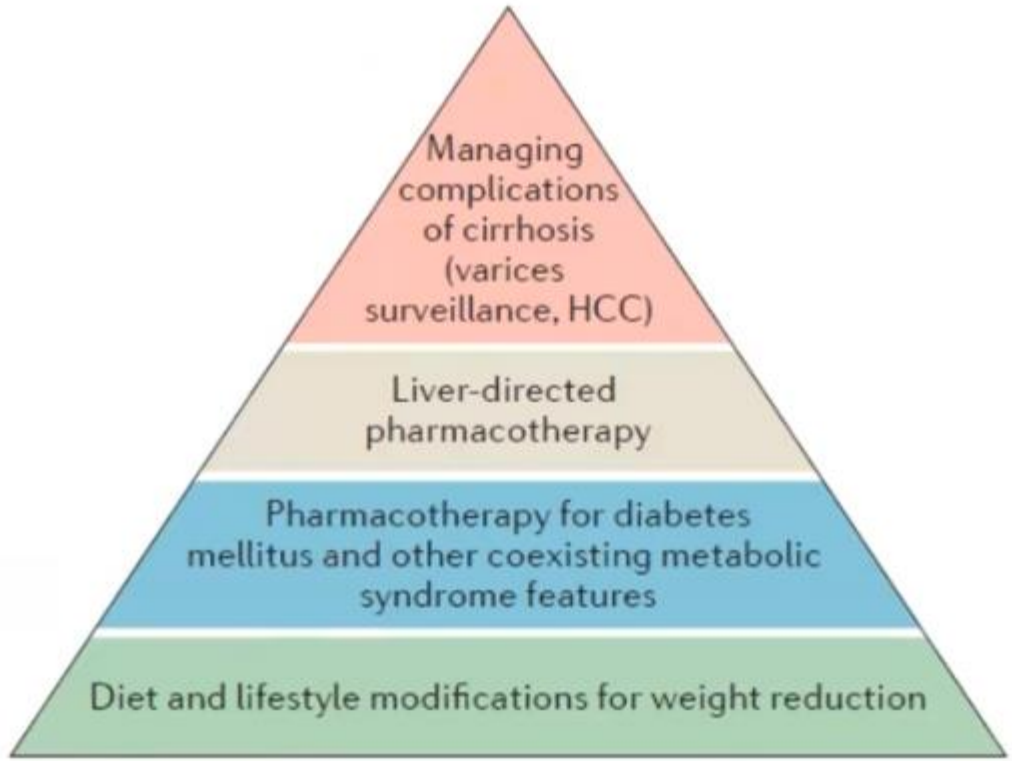
Nat Rev Nephrol. 2022; 18(4):259-268.


Panel A
Patients with NAFLD
Kidney Function Tests
Creatinine, eGFR, albuminuria, standard urine test
No suggestive of kidney disease
Suggestive of kidney disease
Repeat kidney tests at intervals
Specialist referral
Panel B
Patients with CKD
Liver Function Tests
Abnormal levels of ALT[1]
Liver Ultrasound
Steatosis
Exclude other causes of liver steatosis[2]
Non invasive markers of fibrosis and/or Fibroscan®[3]
No suggestive of liver fibrosis
Suggestive of liver fibrosis
Repeat non-invasive liver tests at intervals
Specialist referral

Common therapeutic options for both NAFLD and



Lancet Diabetes Endocrinol. 2019;7(4):313-324.



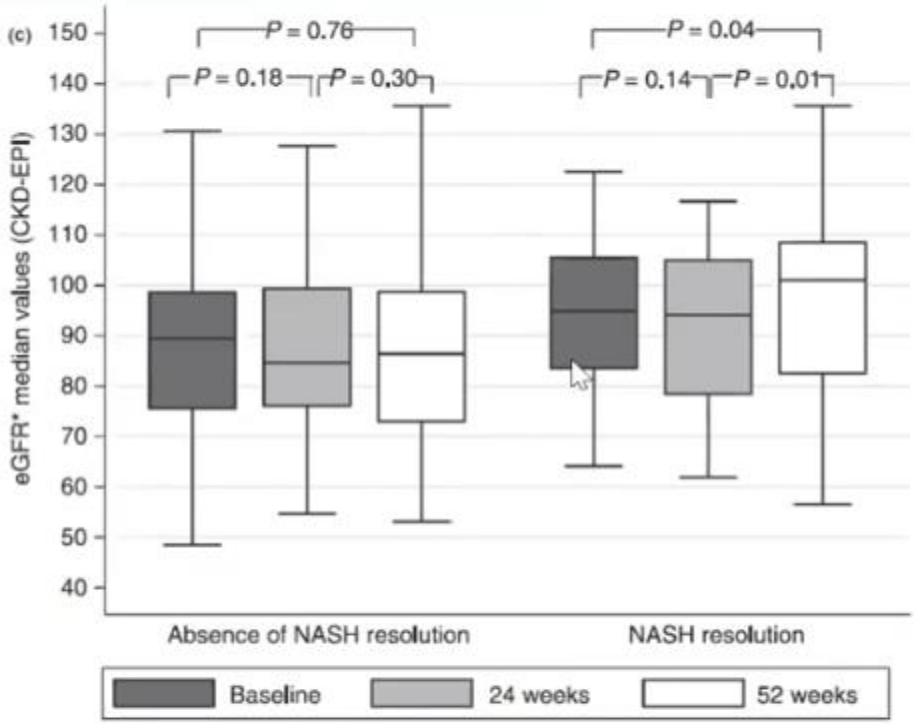
Nat Rev Nephrol. 2017;13(5):297-310

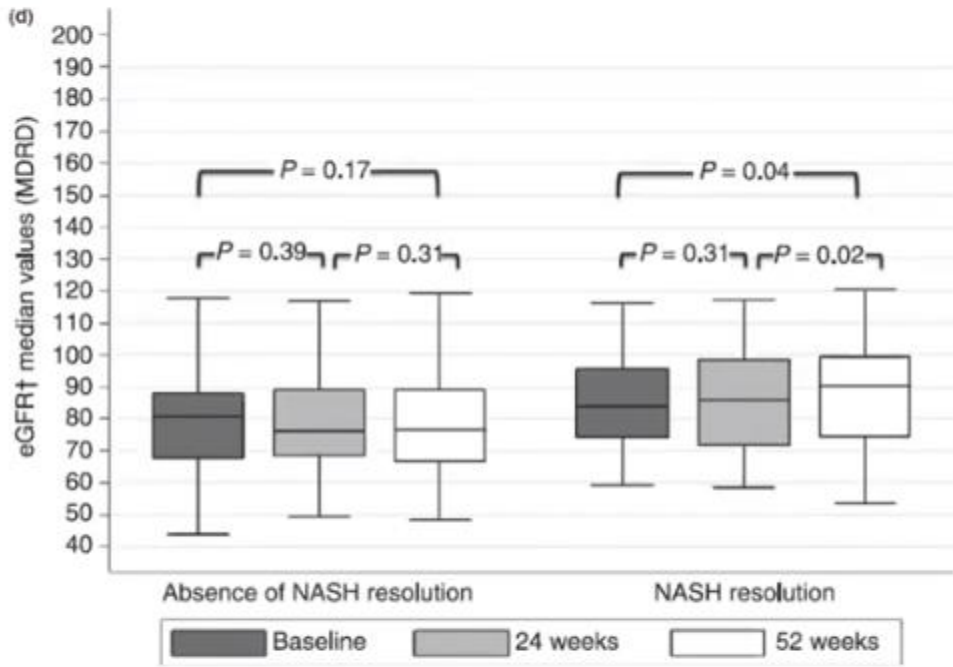
	Cardiometabolic effects			Hepatic effects		
	Insulin resistance	Major cardiometabolic effects	Cardiovascular disease benefit	Steatosis	NAS	
Lifestyle modification	Moderate decrease	Weight loss, and mild decrease in dyslipidaemia and blood pressure	Yes	Moderate decrease	Moderate decrease	
Bariatric surgery	Substantial decrease	Weight loss, and mild decrease in dyslipidaemia and blood pressure	Yes	Substantial decrease	Substantial decrease	Small decrease
Thiazolidinediones						
Pioglitazone	Substantial decrease	Mild decrease in dyslipidaemia and blood pressure	Yes	Substantial decrease	Substantial decrease	Small decrease or no effect
Glucagon-like peptide-1 receptor agonists						
Liraglutide	Small decrease	Weight loss	Yes	Moderate decrease	Moderate decrease	No effect
Exenatide	Small decrease	Weight loss	No	Moderate decrease	NA	NA
Dipeptidyl peptidase-4 inhibitors						
Sitagliptin	No effect	No effect	No	No effect	NA	NA
Vildagliptin	No effect	No effect	No	Small decrease	NA	NA
Sodium-glucose co-transporter-2 inhibitors						
Canagliflozin	Small decrease	Weight loss and small decrease in blood pressure	Yes	Small decrease	NA	NA
Empagliflozin	Small decrease	Weight loss and small decrease in blood pressure	Yes	NA	NA	NA
Dapagliflozin	Small decrease	Weight loss and small decrease in blood pressure	Unknown	No effect	NA	NA
Luseogliflozin*	NA	Weight loss and small decrease in blood pressure	Unknown	Small decrease	NA	NA
Ipragliflozin*	NA	Weight loss and small decrease in blood pressure	Unknown	Small decrease	NA	NA
Antioxidants						
Vitamin E	No effect	Small decrease in oxidative stress and potential small decrease in inflammation	No (potentially harmful)	Moderate decrease	Moderate decrease†	No effect
Phosphodiesterase inhibitors						
Pentoxifylline	No effect	Small decrease in oxidative stress and potential small decrease in inflammation	Unknown	Small decrease	Small decrease	No effect

Data are from randomised controlled trials only. NAS=non-alcoholic steatohepatitis activity score. NA=no data available. *Randomised open-label trials. †No significant effect on NAS in patients with type 2 diabetes.

Table 2: **Lifestyle, weight loss, and pharmacological interventions for the treatment of non-alcoholic fatty liver disease**[89-92,94]

Improvement in liver histology due to lifestyle modification is independently associated with improved kidney function in patients with non-alcoholic steatohepatitis





Conclusions

Improvement in liver histology due to lifestyle modification is independently associated with improved kidney function in NASH. As new drugs for NASH emerge, studies should address whether improvement in histology in response to pharmacotherapies yield the same improvement in kidney function as weight loss.

Aliment Pharmacol Ther 2017; 45: 332–344

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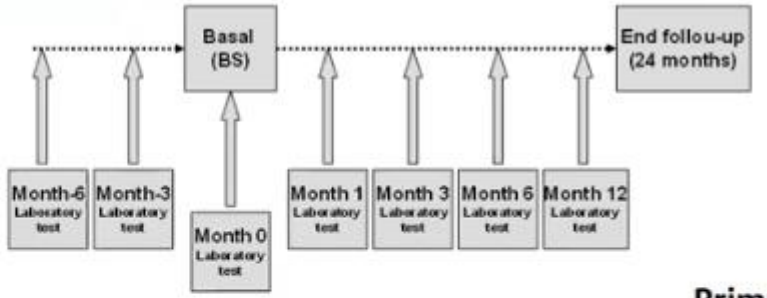


ORIGINAL ARTICLE

Renoprotective role of baria
established chronic kidney

Enrique Morales [1,2], Esteban Porrini
Sergio Luis-Lima[5], Rocío Vila-Bedmar
Pilar Gómez[6], Elías Rodríguez[6], Lucía Torres, Borja Lanzón,
Ana Elena Rodríguez[7], María Maíz[8], Gema Medina-Gómez[4] and
Manuel Praga[1,2]

Obese subjects with chronic kidney disease

Primary Outcome Measures:
Reduction of proteinuria/albuminuria

Study design

Inclusion criteria

- Age 18-70 years (male or female)
- BMI >35 kg/m2
  a) eGFR 30-60 ml/min and proteinuria>1g/24 hours
  b) eGFR> 60 ml/min and proteinuria> 2.5 g/24 hours
- BMI> 40 kg/m2
  eGFR> 30 ml/min and proteinuria> 0.5 g/24 hours

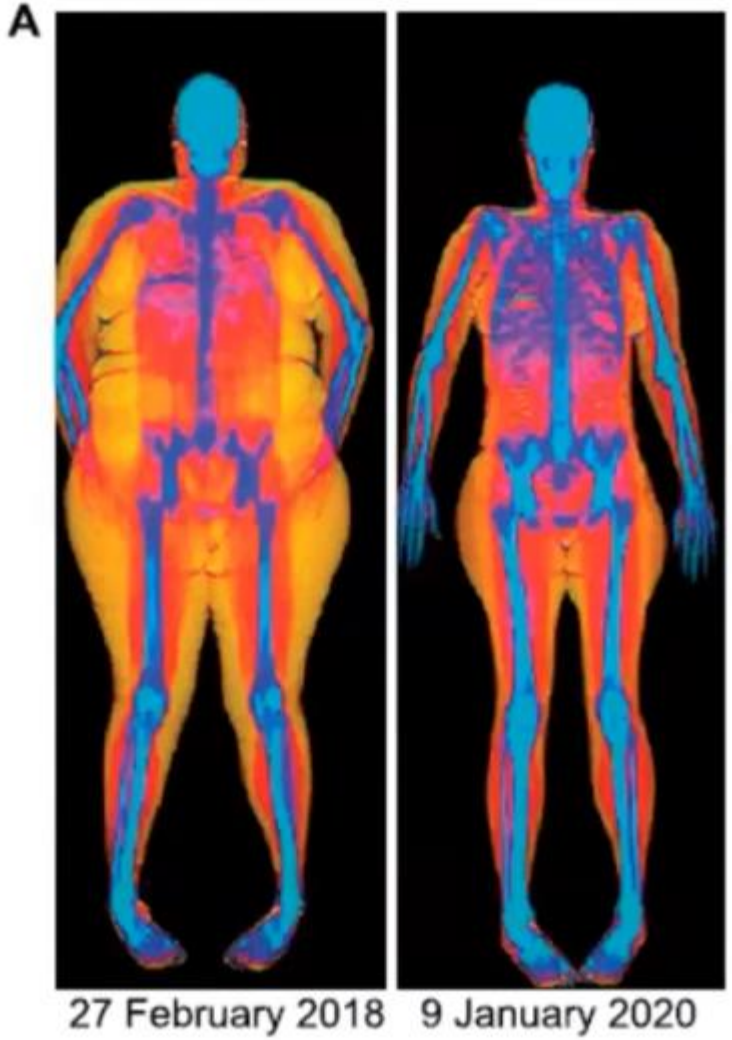
Despite receiving maximally tolerated doses of blocking the renin-angiotensin system.

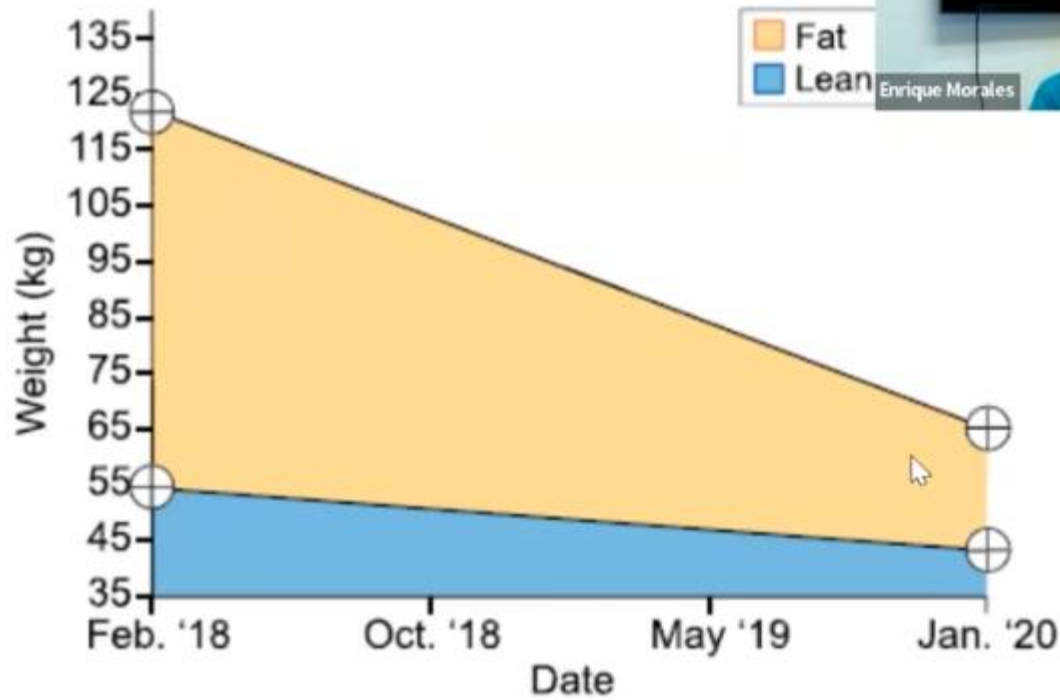
Laboratory for the study of Metabolic Phenotyping (LAFEMEX)
Bioplex technology to measure diabetes & cytokine panels (multiplex immunoassay system)

Clinical Kidney Journal, 2021, vol. 14, no. 9, 2037–2046

41:45

e-seminars





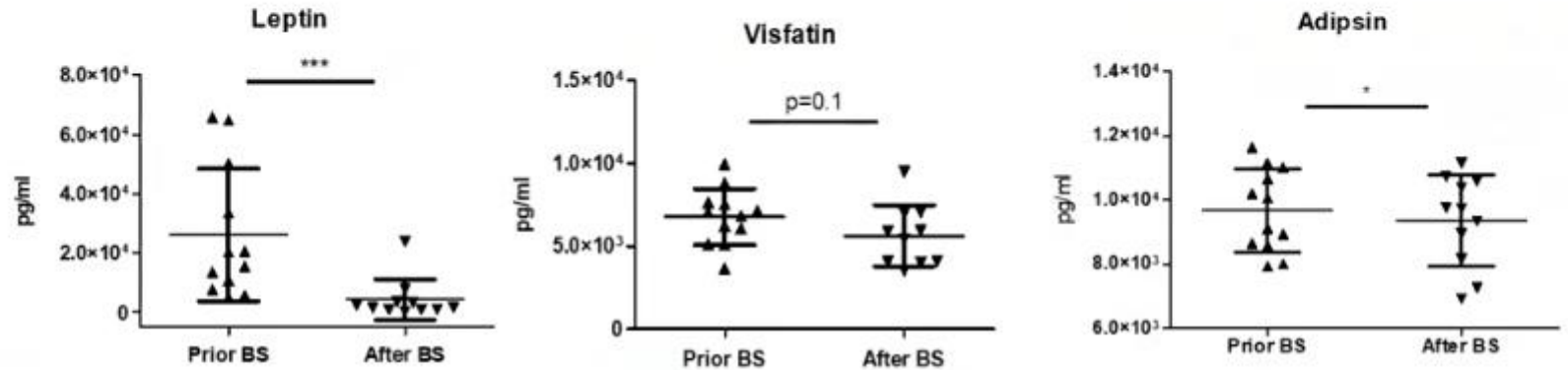
	Baseline	End of study
Body fat (%)	42.5	29.7*
Total fat (g)	44.700	19.778*

Clinical Kidney Journal, 2021, vol. 14, no. 9, 2037–2046

Table 3. Effects of BS on renal function and proteinuria

Variables	6 months pre-BS	3 months pre-BS	Baseline	Month 3	Month 6	Month 12	Month 24
Serum creatinine (mg/dL)	1 ± 0.4	1.1 ± 0.5	1.1 ± 0.4	1 ± 0.4	1 ± 0.4*	1 ± 0.4	1 ± 0.4
eGFR (MDRD, mL/min)	104.8 ± 49.6	89.9 ± 39.5	96.8 ± 49.8	93 ± 42.5	92.9 ± 40.8	84.9 ± 44.5	81.2 ± 44.7
eGFR (CKD-EPI, mL/min)	108.9 ± 48.5	95.2 ± 41.5	97.3 ± 47.8	96.4 ± 43.2	95.9 ± 37.9	86.6 ± 40.2	80.5 ± 40.1
mGFR (iohexol, mL/min)	102.23 ± 44.2	90.9 ± 35.8	94 ± 43.7	67.5 ± 32.9*	72.7 ± 36.6*	65.6 ± 35.5*	79.6 ± 44.5*
Proteinuria (g/24 h)	2.1 ± 1.51	2.3 ± 1.6	2.6 ± 2.9	1.1 ± 0.9*	0.9 ± 0.6*	0.9 ± 0.9*	0.6 ± 0.4*
Median (IQR)	1.6 (0.9–3.7)	1.7 (1–3.6)	1.6 (1–2.7)	0.9 (0.3–1.8)	0.7 (0.4–1.2)	0.6 (0.3–0.9)	0.5 (0.3–0.9)
Proteinuria reduction (%)	–	–	–	49.3 ± 27.2	54.9 ± 26.4	60.7 ± 16.8	63.7 ± 28.2
UACR (mg/g)	1140 ± 1096	1095 ± 859	1912 ± 2233	650.3 ± 871*	478.8 ± 623*	582.4 ± 884*	479.7 ± 540*
Median (IQR)	601 (411–1863)	790 (317–1882)	1004 (554–2078)	296 (139–599)	266 (97–636)	194 (81–671)	220 (87–860)
UACR reduction (%)	–	–	–	61.7 ± 25.5	69.3 ± 23.2	70.6 ± 23.8	mean ± SD

BS-induced weight loss modulates adipose tissue secretion pattern



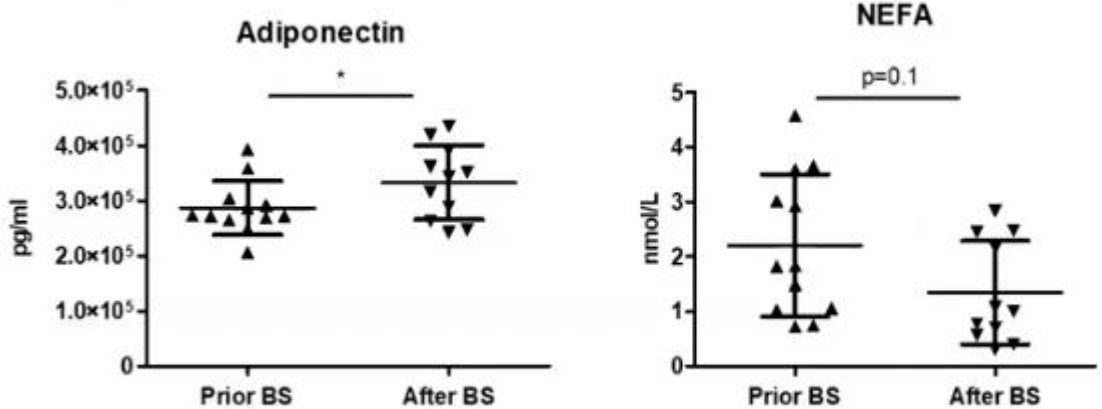
Clinical Kidney Journal, 2021, vol. 14, no. 9, 2037–2046

Evolution of NAFLD's score

At baseline, the composition of the different stages of liver fibrosis was:

- F3–F4 fibrosis (>0.675), four patients; indeterminate score (<1.455–<0.675), five patients; and F0–F2 (<1.455), three patients.
- At the end of the study the change in the score was F3–F4, one patient; indeterminate score, four patients; and F0–F2, seven patients.

There was a reduction in fibrosis values from 0.3 to 1.4 (P<0.001).



* p<0,05; *** p<0,005

Clinical Kidney Journal, 2021, vol. 14, no. 9, 2037–2046

SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA

Pantelis Sarafidis[1], Charles J. Ferro[2], Enrique Morales[3], Alberto Ortiz[4], Jolanta Malyszko[5], Radovan Hojs[6], Khaled Khazim[7], Robert Ekart[6], Jose Valdivielso[8], Denis Fouque[9], Gérard M. London[10], Ziad Massy[11], Petro Ruggenenti[12], Esteban Porrini[13], Andrzej Wiecek[14], Carmine Zoccali[15], Francesca Mallamaci[15] and Mads Hornum[16]

Nephrol Dial Transplant (2019) 34: 208–230

Could dapagliflozin improve kidney and cardiovascular outcomes in patients with CKD?

Randomized
Double-blind
Placebo-controlled
Multicenter

386 sites in 21 countries

N= 4304

GFR 25-75 ml/min

67.5% diabetes type 2

ACR 200-5000mg/g

Outcomes

Kidney
- Decline in GFR at least 50%
- ESKD
- Death from renal causes

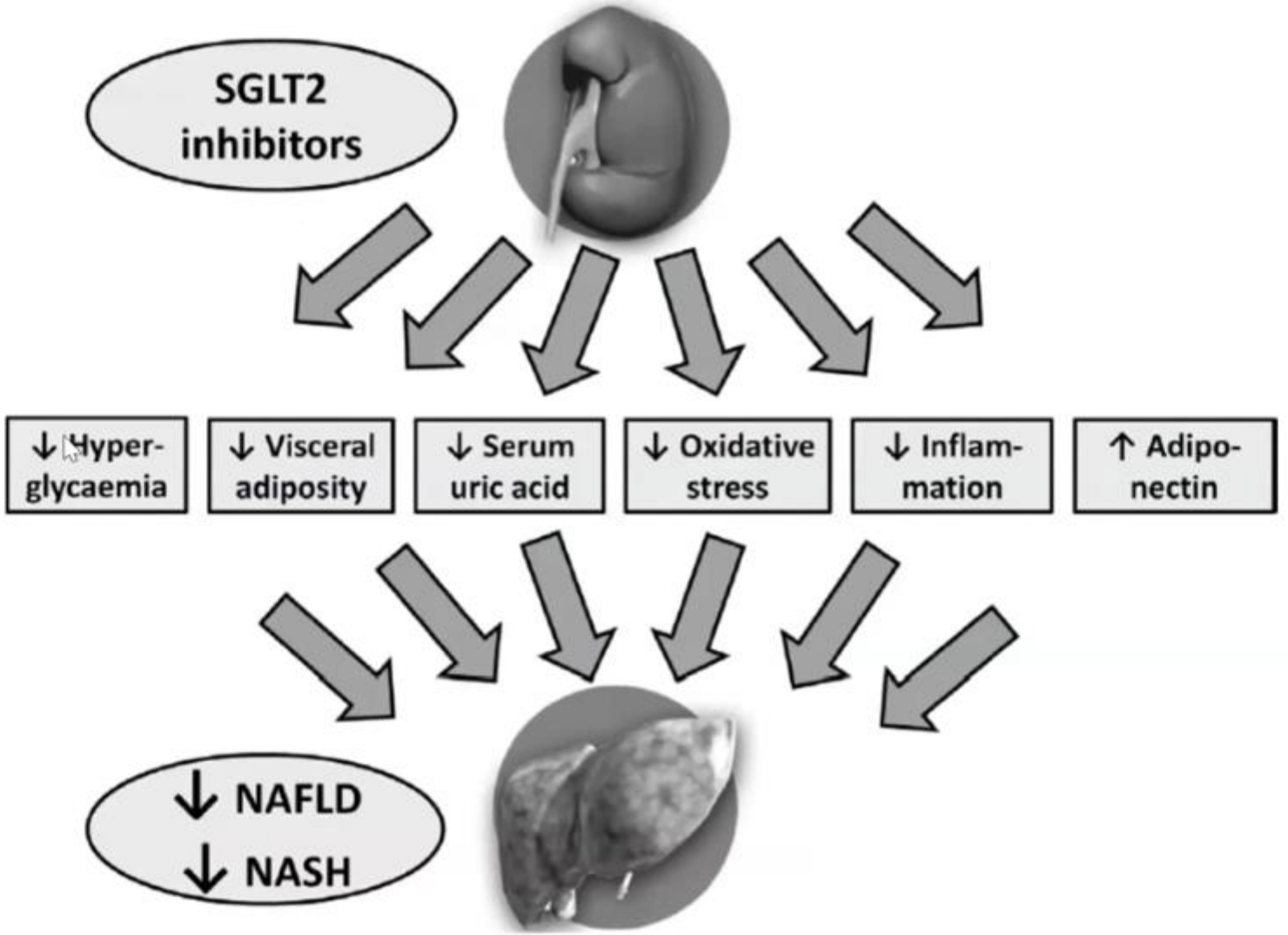
Cardiovascular
- Hospitalization for heart failure
- Death from cardiovascular causes

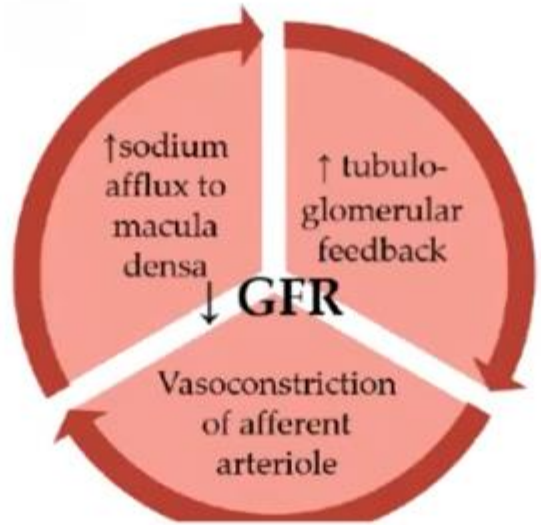
	Primary composite outcome	Composite kidney outcome	Composite cardio-vascular outcome	Death from any cause
Placebo N= 2152	14.5%	11.3%	6.4%	6.8%
Dapagliflozin 10mg/d N= 2152	9.2%	6.6%	4.6%	4.7%
	P<0.001	P<0.001	P=0.009	P=0.004

Conclusion: Among patients with chronic kidney disease, the risk of any composite kidney or cardiovascular outcomes or death was significantly lower with dapagliflozin than with placebo.

Reference: Heerspink HJL *et al.* Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020 Sep 24. DOI: 10.1056/NEJMoa2024816.

Visual abstract: Denisse Arellano, MD @deniise_am


SGLT2 inhibitors
↓ Hyper-glycaemia
↓ Visceral adiposity
↓ Serum uric acid
↓ Oxidative stress
↓ Inflam-mation
↑ Adipo-nectin
↓ NAFLD
↓ NASH



Review

GLP-1 Receptor Agonists and Kidney Protection

(b)

Medicina **2019**, *55*, 233;

Potential cardio-nephroprotective mechanisms of GLP1-RA

Indirect effects

- Improved glycemic control
- Increased insulin sensitivity and decreased plasma insulin levels
- Weight loss
- Improved blood pressure control (1-2 mmHg)
- Reduced neointimal formation
- Improved left ventricular wall motion
- Coronary flow improvement
- Decreased intestinal lipid uptake
- Improved microbioma?

Direct effects

- Modulation of sodium and water homeostasis through NHE3: increased natriuresis and reduced hyperfiltration
- Improved tubulo-glomerular feedback
- Reduced renal and systemic inflammation (reduced plasma levels of α TNF, , MCP1, MR – pro ADM...)
- Reduction in angiotensin II and renin concentrations
- Decreased oxidative stress
- Reduced renal hypoxia and glomerular atherosclerosis
- Renal endothelial dependent vasodilation

Beneficial effects on cardiorenal disease

J Clin Med. 2020 Mar 30;9(4):947.

Diabesity
Diabetes and Obesity

Target	CKD	NAFLD/NASH
Targeting inflammation		
NLRP3 inflammasome inhibitors	**Canakinumab** (IL-1β inhibition): CANTOS trial (NCT01327846): safe, reduced CVD event rates in moderate CKD[65]	**Diacerein**: Phase-3-trial (NCT02242149): reduced liver stiffness in NAFLD with T2DM after two-year treatment[66]
NF-κB inhibitors	**Bindarit**: Phase-2-trial (NCT01109212): Aims to investigate its effects in DKD, but no results yet	Preclinical studies.
Targeting extracellular mediators of inflammation		
Chemokine antagonists	**PF-04634817**: Phase-2-trial (NCT01712061): discontinued clinical development[67]. **BMS-813160**:Phase-2a-trial (NCT01752985): terminated and undisclosed	**Cenicriviroc**: Phase-2b-CENTAUR (NCT02217475): well tolerated, improved fibrosis[68] Phase-3-AURORA (NCT03028740): terminated and undisclosed
Targeting a liver-derived amine oxidase		
VAP-1 inhibitors	**ASP8232**: Phase-2-ALBUM (NCT02358096): safe, reduced albuminuria in DN[69]	Preclinical studies
Targeting common fibrogenic pathways		
Galectin-3 antagonists	**GCS-100**: Phase-2b-trial (NCT02312050): completed but no result	**Belapectin** (GR-MD-02): Phase-2b-NASH-CX (NCT02462967): reduced HVPG and development of varices in patients with NASH and cirrhosis without esophageal varices[70] Phase-2-NASH-FX (NCT02421094): no improvement in non-invasive biomarkers of liver inflammation or fibrosis[71] Phase-2/3-NAVIGATE (NCT04365868): ongoing
ROCK inhibitors	**SAR407899:** Phase-1-trial (NCT01485900):no result	Preclinical studies
EGF inhibitors	Preclinical studies	**Erlotinib**: Phase-1/2-trial (NCT02273362): not recruiting

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Take home messages

- Recent studies have suggested that **NAFLD** is associated with an **increased risk of CKD**, but more proof is needed for confirmation.
- An increasing body of evidence suggests that the newly proposed definition of **MAFLD** may be closely aligned with the underlying pathophysiological mechanisms of CKD than that of NAFLD.
- Inflammatory cytokines, oxidative stress, activation of RAAS, insulin resistance, atherogenic dyslipidemia, and intestinal microbiota dysbiosis were reported as potential **pathogenesis.**
- The patients with **NAFLD should be screened for CKD**, and the clinicians should consider whether patients with **CKD might also have NAFLD**.
- **Weight loss, GLP1RAs and SGLT-2 inhibitors** may benefit both liver and the kidney in individuals with MAFLD and CKD (multidisciplinary team).