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REVIEW

Therapeutic implications of shared mechanisms in non-alcoholic fatty liver disease and chronic kidney disease

Mehmet Kanbay[1] · Mustafa C. Bulbul[2] · Sidar Copur[2] · Baris Afsar[3] · Alan A. Sag[4] · Dimitrie Siriopol[5] · Masanari Kuwabara[6] · Silvia Badarau[5] · Adrian Covic[5] · Alberto Ortiz[7]

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Abstract

The most common cause of liver disease worldwide is now non-alcoholic fatty liver disease (NAFLD). NAFLD refers to a spectrum of disease ranging from steatosis to non-alcoholic steatohepatitis, causing cirrhosis, and ultimately hepatocellular carcinoma. However, the impact of NAFLD is not limited to the liver. NAFLD has extra-hepatic consequences, most notably, cardiovascular and renal disease. NAFLD and chronic kidney disease share pathogenic mechanisms including insulin resistance, lipotoxicity, inflammation and oxidative stress. Not surprisingly, there has been a recent surge in efforts to manage NAFLD in an integrated way that not only protects the liver but also delays comorbidities such as chronic kidney disease. This concept of simultaneously addressing the main disease target and comorbidities is key to improve outcomes, as recently demonstrated by clinical trials of SGLT2 inhibitors and GLP1 receptor agonists in diabetes. HIF activators, already marketed in China, also have the potential to protect both liver and kidney, as suggested by preclinical data. This review concisely discusses efforts at identifying common pathogenic pathways between NAFLD and chronic kidney disease with an emphasis on potential paradigm shifts in diagnostic workup and therapeutic management.

Keywords Chronic kidney disease · Hepatosteatosis · Inflammation · Oxidative stress · Uric acid

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease [1]. NAFLD is associated with metabolic syndrome and obesity, and the growing worldwide prevalence of obesity is driving the increased prevalence of NAFLD, currently estimated at 24% [2]. NAFLD is considered a spectrum of liver disease ranging from steatosis (only intrahepatic triglyceride accumulation) to non-alcoholic steatohepatitis (NASH) to fibrosis ultimately leading to cirrhosis [3]. At the current rate of growth in prevalence, NAFLD will likely outpace hepatitis C as the leading indication for liver transplantation [1]. Importantly, NAFLD is linked to other metabolically-related disorders, such as cardiovascular diseases (CVD), diabetes mellitus (DM), and chronic kidney disease (CKD) [2].

The pathogenic mechanisms underlying NAFLD development include increased free fatty acids accumulation, inflammatory cytokines and insulin resistance [1–3]. In addition, higher serum fetuin A levels and decreased serum adiponectin levels are associated with NAFLD [4]. Hepatic oxidative stress, lipotoxicity leading to cell death, mitochondrial

✉ Mehmet Kanbay
drkanbay@yahoo.com; mkanbay@ku.edu.tr

1 Division of Nephrology, Department of Medicine, Koc University School of Medicine, 34010 Istanbul, Turkey

2 Department of Medicine, Koc University School of Medicine, Istanbul, Turkey

3 Department of Internal Medicine, Division of Nephrology, Suleyman Demirel University School of Medicine, Isparta, Turkey

4 Division of Vascular and Interventional Radiology, Department of Radiology, Duke University Medical Center, Durham, USA

5 Nephrology Clinic, Dialysis and Renal Transplant Center, 'C.I. PARHON' University Hospital, and 'Grigore T. Popa' University of Medicine, Iasi, Romania

6 Department of Cardiology, Toranomon Hospital, Tokyo, Japan

7 Dialysis Unit, School of Medicine, IIS-Fundacion Jimenez Diaz, Universidad Autónoma de Madrid, Avd. Reyes Católicos 2, 28040 Madrid, Spain

injury, endoplasmic reticulum (ER) stress, iron overload (not in all patients), chronic immune system activation, distorted gut microbiome (increased Proteobacteria and Bacteriodetes along with a decrease in Firmicutes) are all implicated in the development of NAFLD (Fig. 1) [5].

These pathogenic mechanisms may also play a role in other systemic diseases, therefore numerous recent studies evaluated the association between NAFLD and other systemic diseases. CKD prevalence is approximately 13% worldwide [1], whereas CKD prevalence in patients with NAFLD has been estimated at approximately 20–25% two-fold higher than inpatients without NAFLD [6].

Due to the high morbidity and mortality of CKD [1, 7], early detection and treatment are key to prevent premature death. The association between NAFLD and CKD in diverse epidemiological studies (Table 1) that are associated with the prevalence and severity of CKD [8] suggests that NAFLD patients should be considered at high risk of CKD and screened for CKD by assessing eGFR and albuminuria (Table 2). Thus, histologically proven cirrhosis correlated with increased risk of CKD. In addition, NAFLD was associated with proteinuria [8]. In 1525 CKD patients followed for 10 years, NAFLD was independently associated with a larger decline in estimated glomerular filtration rate (eGFR) and with CKD progression [7]. In addition, NAFLD was associated with a higher incidence of CKD in 1760 patients with type 2 DM followed for 6.5 years and this was independent of other confounding factors such as age, gender and hypertension [9]. The prevalence of nephrolithiasis was also higher in patients with NAFLD referred to computed tomography (CT) due to clinically suspected renal colic [10].

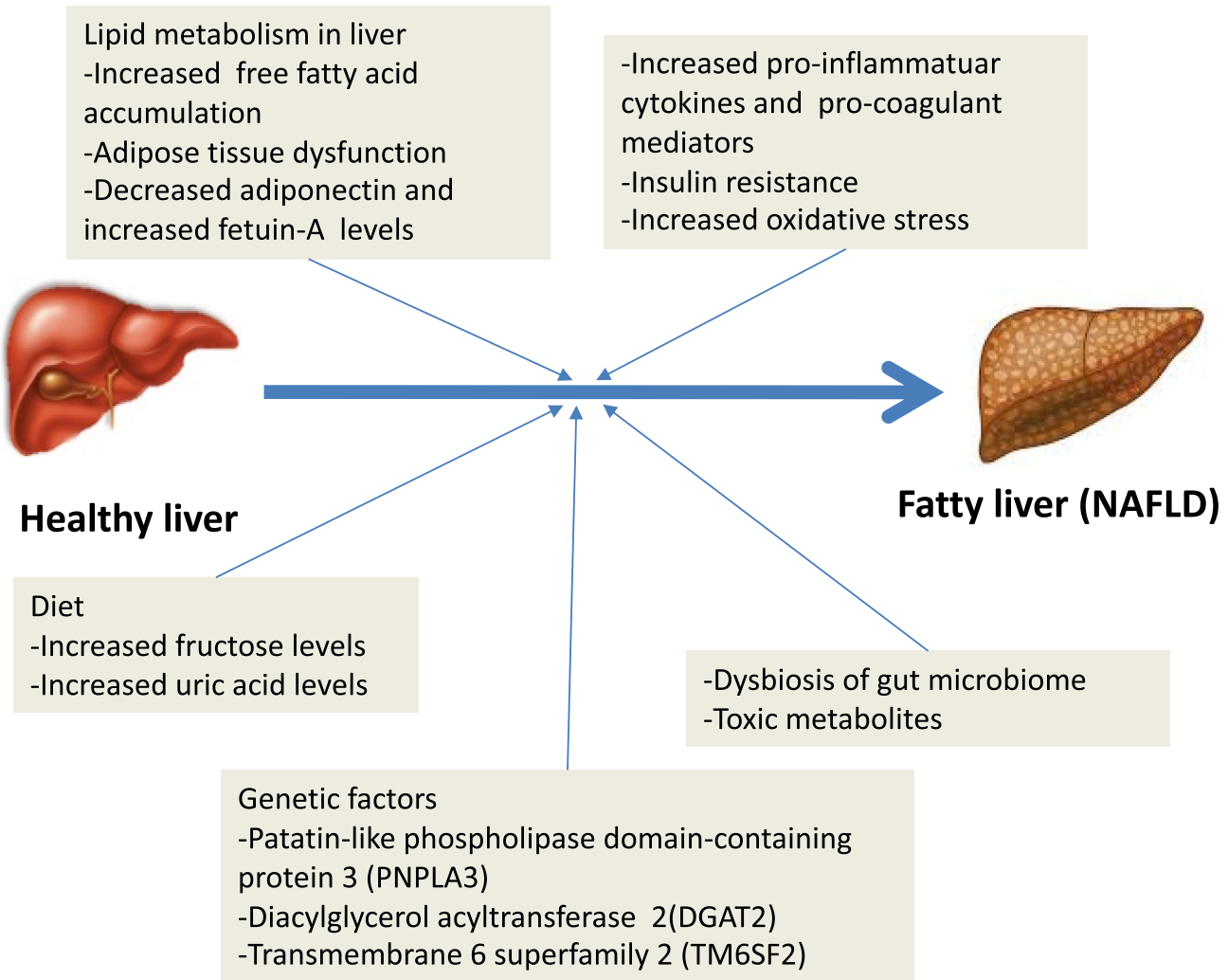

Fig. 1 Multi-hit model for development of non-alcoholic fatty liver disease (NAFLD). NAFLD formation has a complex pathophysiology and many components such as impaired lipid metabolism, insulin resistance, inflammatory cytokines, oxidative stress, increased fructose and uric acid levels, dysbiosis of microbiome and genetic factors may play a role on NAFLD pathophysiology

Table 1 Studies linking non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD)

Author (Ref)	Study properties	NAFLD diagnosis	CKD diagnosis	Adjustments	Findings
Jang et al. [7]	Retrospective cohort, 1525 CKD patients average follow-up 6.5 years	Ultrasound	eGFR < 60 ml/min/1.73m^2	Age and sex	Faster decline in eGFR in NAFLD (–0.79% per year, 95% confidence interval(CI) − 1.31%,− 0.27%) than in non-NAFLD (0.30%, 95%CI − 0.14%, 0.76%)
Targher et al. [9]	Prospective cohort, 1760 outpatients with type 2 diabetes mean follow up 6.5 years	Ultrasound	Overt proteinuria or eGFR < 60 ml/min/1.73m^2	Gender, age, BMI, BP, diabetes duration, smoking, HbA_{1c}, lipids, anti-hypertensive, lipid lowering and hypoglycemic drug use	NAFLD associated with increased risk for CKD in type 2 diabetes (hazard ratio(HR) 1.49; 95% CI 1.1–2.2)
Ahn et al. [11]	Cross-sectional, 1706 Koreans olderthan 50 years	Ultrasound	Overt proteinuria or eGFR < 60 ml/min/1.73m^2	Age, gender, smoking, obesity, hypertension, diabetes mellitus, hypertriglyceridemia, liver enzymes, low HDL	NAFLD associated with CKD (odds ratio 1.68, 95%CI, 1.27–2.24)
Sinn et al. [59]	Retrospective cohort, 41,430 outpatients Median follow-up 4.15 years	Ultrasound	eGFR < 60 ml/min/1.73m^2	Age, gender, smoking, BMI, BP, alcohol consumption, HbA_{1c}, hypertension, LDL cholesterol, use of lipid lowering, anti-hypertensive and diabetes drugs	Higherrisk of CKD in NAFLD than in non-NAFLD (HR1.22, 95%CI, 1.04–1.43)
Yeung et al. [60]	Cross-sectional cohort, 1763 Chinese type 2 diabetes patients	Elastography	UrinaryACR > 3.5 mg/mmol (women), > 2.5 mg/mmol (men)	HbA_{1c}, hypertension, BMI, advanced fibrosis	Diabetics with steatosis or advanced fibrosis atincreased risk for albuminuria (no NAFLD vs steatosis vs advanced fibrosis: 41.4% vs 46.2% vs 64.2%)
Yasui et al. [61]	Cross-sectional, 174 Japanese patients (92 NASH/82 non-NASH)	Biopsy	Overt proteinuria or eGFR < 60 ml/min/1.73m^2	Age, gender, hypertension, BMI	CKD prevalence significantly higher in NAFLDthan in non-NAFLD (19/92; 21% vs 5/82; 6%)
Targher et al. [62]	Cross-sectional, 343 patients with type 1 diabetes	Ultrasound	eGFR < 60 ml/min/1.73m^2 or albuminuria (ACR > 30 mg/g)	Age, gender, BMI, HbA_{1c}, diabetes duration, smoking, systolic BP, triglycerides, HDL, physical activity, use of anti-hypertensive and lipid lowering drugs	NAFLD lower eGFR (83 ± 27 vs 93.3 ± 29 ml/min/1.73m^2) and higher prevalence of albuminuria (50% vs 20.5%)
El Azeem et al. [12]	Prospective, 747 patients Mean follow-up 3 years	Ultrasound	Overt proteinuria or eGFR < 60 ml/min/1.73m^2	Age, BMI, hypertension, smoking, metabolic syndrome, dyslipidemia	NAFLD associated with higher prevalence of A2 (32.8% vs 18.4%) and A3 albuminuria (8.9% vs 2.9%) than non-NAFLD
Arase et al. [63]	Retrospective cohort, 5561 patients with NAFLD Mean follow-up 5.5 years	Ultrasound	Overt proteinuria or eGFR < 60 ml/min/1.73m^2	Age, gender, BMI, hypertension, type 2 diabetes, smoking, triglycerides, HDL, liver enzymes	In NAFLD, cumulative incidence of CKD 3.1% at year 5 and 12.2% at year 10

Table 1 (continued)

Author (Ref)	Study properties	NAFLD diagnosis	CKD diagnosis	Adjustments	Findings
Hwang et al. [64]	Cross-sectional, 1361 patients with abnormal oral glucose tolerance test (414 type 2 diabetes-947 prediabetes)	Ultrasound	Albuminuria (ACR 30–300 mg/g)	Age, gender, BMI, enzymes, lipid profiles, waist circumference, HbA_{1c}, hypertension, smoking, metabolic syndrome	Higher prevalence of albuminuria (6.3% vs 19% in prediabetes-4.5% vs 32.6% in diabetes) and higher ACR(15 ± 52 mg/g vs 28 ± 64 mg/g in prediabetes-11 ± 21 mg/g vs 45 ± 76 mg/g in diabetes) in NAFLD
Chang et al. [65]	Prospective cohort, 8329 Korean males Mean follow-up 3.21 years	Ultrasound	Overt proteinuria or eGFR < 60 ml/min/1.73m^2	Age, baseline GFR, triglyceride, HDL, LDL, BMI, systolic blood pressure, smoking, alcohol consumption	NAFLD increased risk of incident CKD (crude relative risk 2.18, 95%CI, 1.75–2.71)
Mikolasevic et al. [66]	Cross-sectional, 62 CKD patients	Elastography	eGFR < 60 ml/min/1.73m^2	No adjustment	Steatosis severity negatively correlated with eGFR ($r = -0.413$) andpositively correlated with serum creatinine levels ($r = 0.399$)
Targher et al. [67]	Retrospective cohort of 261 type 1 diabetic adults Mean follow-up period 5.2 years	Ultrasound	eGFR < 60 ml/min/1.73m^2 or macroalbuminuria (ACR > 300 mg/g)	Age, gender, diabetes duration, hypertension, baseline eGFR, HbA_{1c}	NAFLD associated with higher risk of incident CKD (HR 2.85, 95%CI, 1.59–5.10) Did not use the KDIGO definition of CKD (ACR > 30 mg/g)

eGFR estimated glomerular filtration rate, *HbA1c* hemoglobin A1c, *ACR* albumin creatinine ratio, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *BMI* body mass index, *BP* blood pressure, *CI* confidence interval, *KDIGO* kidney disease improving global outcomes

Table 2 Paradigmshifts in the integrated management of non-alcoholic fatty liver disease (NAFLD): focus onchronickidney disease (CKD)

Process	2010	2020
Assessment of NAFLD patients for CKD	No assessment	Yearly eGFR and albuminuria
Referral to Nephrology	No referral	Referral if a) eGFR < 60 ml/min/1.73 m2 or b) urinary albumin:creatinine excretion > 30 mg/g or c) persistent microhematuria or d) eGFR loss faster than 5 ml/min/1.73 m2/year even if a), b) and c) are not met
Assessment of CKD patients for NAFLD	No assessment	Liver sonography and/or elastography at least once
Referral to Hepatology	No referral	Referral to Hepatology if NAFLD present
Therapy for patients with both NAFLD and CKD	No specific indication	Use drugs with the potential to improve both such as telmisartan, GLP1R mimetics and SGLT2 inhibitors

Shared pathogenic mechanisms in NAFLD and CKD

Insulin resistance, atherogenic dyslipidemia, oxidative stress and pro-inflammatory mediators released from liver are considered key contributors in the pathogenesis of CKD [8, 11]. Thus, patients with NAFLD have increased advanced glycated end products, C-reactive protein, tumor necrosis factor-alpha and transforming growth factor-beta levels [9]. Moreover, endothelial dysfunction, decreased adiponectin and increased fetuin-A levels may interact with the renin–angiotensin–aldosterone system (RAAS) and contribute to CKD progression [1]. Gamma glutamyl transaminase (GGT) is specifically increased in NAFLD and is also associated with an increased risk for CKD [12]. Additionally, atherogenic dyslipidemia has also been linked to CKD through actions of oxidized low density lipoproteins (LDLs) on kidney cells, including mesangial cell proliferation and glomerular injury [8]. The shared pathogenic mechanisms in NAFLD and CKD and liver-kidney crosstalk are summarized in Figs. 2 and 3.

Another potential link consists of shared susceptibility gene variants between NAFLD and CKD. One example is *PNPLA3*: gene variants associated with decreased eGFR levels in children with NAFLD [13].

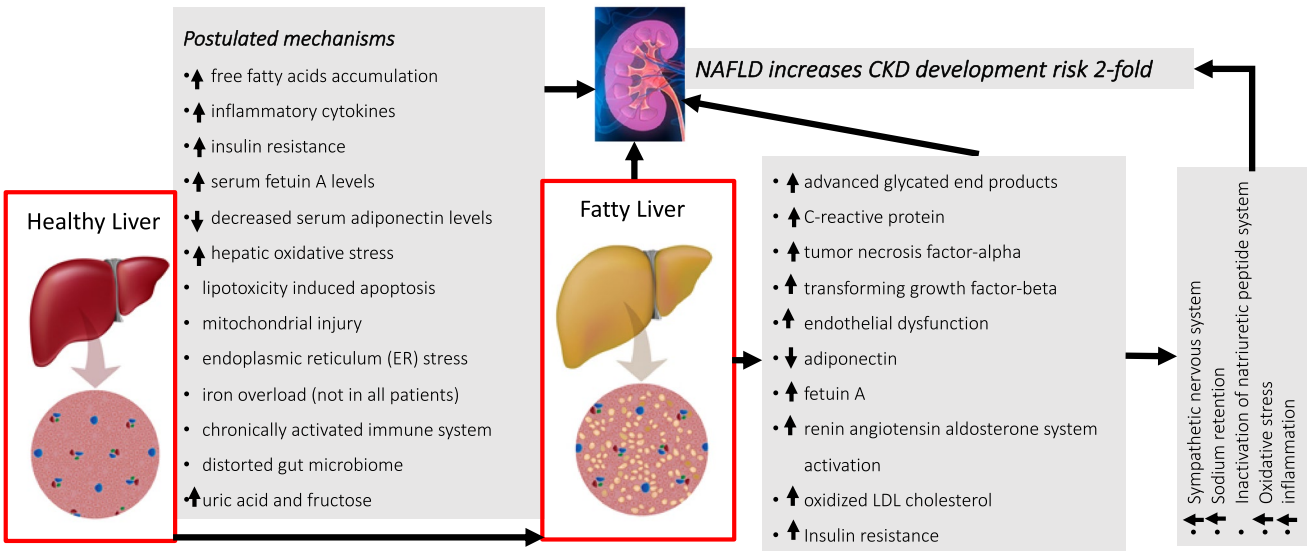

Fig. 2 Pathogenic mechanisms potentially linking non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD). Many mechanisms such as increased free fatty acid accumulation, increased inflammatory cytokines, insulin resistance, decreased hepatic oxidative stress, high uric acid and fructose levels leads to formation of fatty liver. Fatty liver increases the risk of development of CKD with activation of sympathetic nervous system, enhanced sodium retention, oxidative stress and inflammation by causing increased advanced glycated end products, CRP, tumor necrosis factor-alpha, transforming growth factor-beta levels, endothelial dysfunction, increased formation of oxidized LDL cholesterol

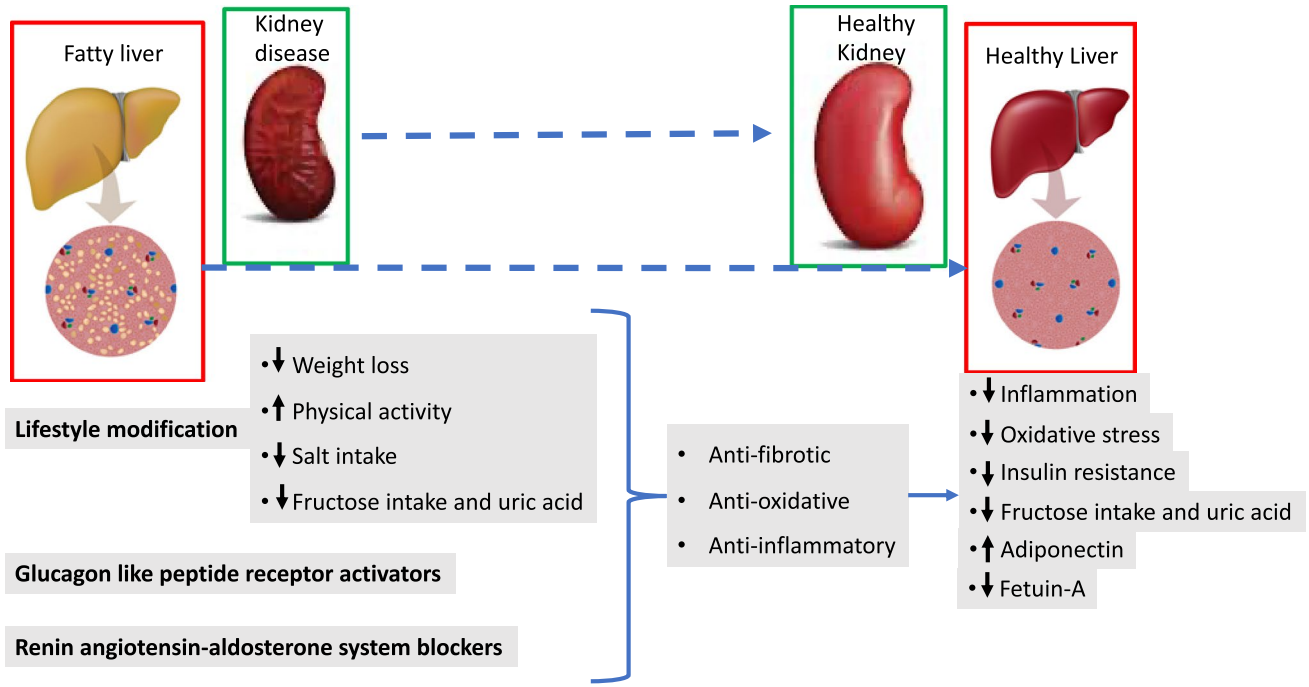

Fig. 3 Potential therapeutic targets in the treatment of non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD). Lifestyle modifications such as weight loss, increased physical activity, decreased salt intake and fructose intake, glucagon like peptide receptor activators and rennin angiotensin-aldosterone system blockers play a potential role for therapeutic intervention of fatty liver by anti-fibrotic, anti-oxidative and anti-inflammatory pathways

NAFLD and CKD with and without obesity

It is well known that obesity is very closely associated with NAFLD [14, 15]. On the other hand, CKD is associated with obesity [16]. In a sample of 2585 adults with a mean follow-up of 18.5 years, body mass index (BMI) was associated with a 23% (odds ratio (OR), 1.23; 95% CI 1.08–1.41) increase in developing kidney disease [17]. Similar findings were observed also in other large studies [18, 19]. Thus, it is possible that, at least in some cases, the problem is between obesity and the kidney rather than a direct link between the liver and the kidney. To say in other words, obesity may both cause NAFLD and CKD and there may not be a direct link between CKD and NAFLD. Thus it is important to underline evidence of kidney involvement in patients with fatty liver without obesity. Unfortunately, there is not satisfactory data in this regard. In one study performed in children partly explained this issue. Pacifido et al. showed that children with NAFLD had lower eGFR and higher albuminuria. More importantly, multivariate logistic regression analysis revealed that NAFLD was associated with decreased eGFR and/or microalbuminuria [OR, 2.54 (95% CI 1.16–5.57); $p < 0.05$] independently of anthropometric variables [20].

Besides, new data showed that there are cases of NAFLD among lean people. Seto et al. suggested that approximately 20% of the Asian population, lean NAFLD is closely linked with insulin resistance, diabetes, and other metabolic complications which are risk factors also for CKD [21]. Thus, we suggest that NAFLD is independently associated with CKD however more studies are needed in this issue.

Insulin resistance

Insulin resistance has been considered as a major pathological factor for development of both NAFLD and CKD, as well as a complication of NAFLD due to elevated liver free fatty acid uptake. Insulin resistance can accelerate CKD progression by modulating renal hemodynamics following the activation of the sympathetic nervous system, sodium retention and inactivation of the natriuretic peptide system [22]. Insulin resistance is also associated with CVD via increased oxidative stress, inflammation and endothelial dysfunction [22].

Fructose metabolism and uric acid

Several recent studies demonstrated that high fructose intake from sweetened beverages is associated with a high risk of NAFLD and progressive CKD [23–26]. Liver fructokinase phosphorylates fructose to fructose-1-phosphate, ultimately resulting in increased accumulation of uric acid. Uric acid may contribute to the development and progression of

NAFLD, CKD and CVD via hepatocyte adenosine triphosphate (ATP) depletion, mitochondrial reactive oxygen species (ROS) generation, enhanced hepatic and renal lipogenesis, reduced nitric oxide (NO) bioavailability, endothelial dysfunction and proinflammatory cytokine secretion [24, 25]. Uric acid also activates aldose reductase and the polyol pathway for endogenous fructose and fat production causing fatty liver [27]. In longitudinal studies, higher uric acid levels were a risk factor for developing insulin resistance [28], dyslipidemia [29] and fatty liver [30, 31]. Hyperuricemia is also a known risk factor for developing CKD [32, 33]. This supports a role for hyperuricemia causes in both CKD and NAFLD.

Fetuin-A and adiponectin

Increased fetuin-A levels and decreased adiponectin levels are associated with NAFLD and CKD. Fetuin-A is a 64-kDa liver-secreted serum glycoprotein that promotes insulin resistance by disrupting insulin signaling through 5-AMP activated protein kinase (AMPK) inhibition after binding to insulin receptor tyrosine kinase in hepatocytes and skeletal muscle [34]. Additionally, downregulates adiponectin in adipose tissue through the Wnt-PPAR γ pathway and indeed, Fetuin-A levels are inversely correlated with adiponectin levels [35]. Adipose tissue-secreted Adiponectin improves insulin resistance, thus opposing fetuin-A actions. In this regard, adiponectin levels are inversely correlated with proteinuria [4].

Oxidative Stress

Oxidative stress is another key promoter of NAFLD and CKD. Nuclear erythroid related factor-2 (Nrf2) is a transcription factor that behaves as a master activator of the transcription of many anti-oxidant enzymes and has anti-inflammatory properties [24, 25]. In this regard, the loss of Nrf2 markedly exacerbates nonalcoholic steatohepatitis [36]. By contrast, the Nrf2 activator bardoxolone protected experimental animals from hepatic steatosis and is undergoing clinical trials for CKD, since it increases eGFR [37]. The decrease of both oxidative stress and inflammation may protect from both NAFLD and CKD [25].

The FGF-Klotho axis

α Klotho and β Klotho are essential components of endocrine fibroblast growth factor (FGF) receptor complexes, and are required for binding of FGF23 and FGF19, FGF21, respectively, to their cognate FGF receptors (FGFRs) [38]. The kidney is the key source of αKlotho, a protein with anti-aging properties and kidney injury or systemic inflammation decrease αKlotho [39–41]. While there is little information on α Klotho levels in NAFLD, αklotho reduced liver lipid accumulation in obese mice, suggesting a liver-kidney crosstalk as discussed below [42]. By contrast, FGF19 is a satiety hormone released by the gut upon food ingestion of food that binds the β Klotho-FGFR4 complex in hepatocytes to promote metabolic responses to feeding. By contrast, fasting leads to liver secretion of the starvation hormone FGF21, which induces metabolic responses to fasting and stress responses [38]. FGF19 plays a key role in NAFLD pathogenesis and βKlotho genetic variants have been linked to NAFLD [43].

Liver-kidney crosstalk

Organ cross talk is a newly generated concept to describe and explain signals passing from organ to organ providing interactions between systems. A dysregulated cross-talk results in loss of homeostatic balance, potentially triggering organ damage. The liver and kidney have crosstalk mechanisms that are newly being understood. For example, in hepatorenal syndrome, patients with liver disease develop kidney failure in the absence of any histological abnormality cause [44]. In liver disease, activation of the RAAS and sympathetic nervous systems as compensatory mechanisms against splanchnic vasodilatation may lead to renal vasoconstriction, hypoperfusion and acute kidney injury. Moreover, increased secretion of endogenous vasopressin and the systemic inflammatory response due to translocation of intestinal bacteria are other important mechanisms promoting renal vasoconstriction and decreasing GFR [44].

Conversely, acute kidney injury can contribute to liver injury by promoting systemic inflammation and oxidative stress. Ischemia-induced damage due to decreased blood flow causes increased serum levels of alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), IL-6, IL-10 and TNF-a. Cytokine outflow results in increased vascular permeability causing neutrophil and lymphocyte migration and increased reactive oxygen species [44]. Further elucidation of the homeostatic hepatorenal crosstalk mechanisms is needed so that therapies can be targeted to this cross-talk.

Therapeutic Interventions for NAFLD Complications

Although the link between NAFLD and CKD seems evident from the above discussion, currently, CKD patients are not screened for NAFLD [7] (Table 2). But as discussed above, a diagnosis of co-existing NAFLD may influence CKD treatment and outcomes (Fig. 3).

The obvious first treatment would include lifestyle modification including weight loss, increased physical activity

and smoking cessation [7, 8]. From a pharmacological point of view, some drugs have the potential to improve both NAFLD and CKD and should be first choice therapies for patients with both conditions. Thus, recent studies have tested new therapeutic modalities to delay NAFLD progression. The FANTASY open label study demonstrated that the angiotensin receptor blocker telmisartan, as opposed to losartan, may significantly decrease serum free fatty acids and improve fatty liver although there was no significant decrease in liver enzymes [45].

Specific therapies tested for NAFLD and CKD are incretin-based therapies such as glucagon like peptide receptor activators (GLP-1-RA) and dipeptidyl peptidase 4 (DPP-4) inhibitors which increase insulin secretion [46]. In a meta-analysis from the Liraglutide Effect and Action in Diabetes (LEAD) program, the GLP-1-RA liraglutide improved hepatic steatosis [47] and liver enzymes in patients with type 2 DM [48]. Besides glycemic control, GLP-1-RA may have a nephroprotective effect by inducing natriuresis with decreased angiotensin II activation and proximal tubular Na–H exchanger 3 inhibition, as shown in clinical trials [46, 49]. In this regard, GLP-1-RA have anti-fibrotic, anti-oxidative and anti-inflammatory actions in the kidneys [46]. By contrast, DPP-4 inhibitors have not provided consistent kidney protection in clinical trials.

Other key drugs are sodium-glucose cotransporter-2 (SGLT2) inhibitors. Together with GLP-1-RA, they are first choice antidiabetic drugs for the CKD patient [49]. In addition to kidney protection in dependently of glycemic control [46], most recently demonstrated in diabetic patients with overt diabetic kidney disease [50], SGLT2 inhibitors may reduce NAFLD progression via their anti-inflammatory, anti-fibrotic and anti-oxidative activities [46]. SGLT2 inhibitors reduce afferent arteriolar vasoconstriction (tubuloglomerular feedback) and may provide nephroprotection by reducing glomerular hyperfiltration, preventing glucose overload-induced oxidative stress and inflammation in proximal tubular cells and other mechanisms [49, 51].

Peroxisome proliferator activated receptor (PPAR) gamma agonists, hypoxia inducible factor (HIF) activation, mTOR complex1 inhibitors and galectin-3 inhibitors are other potential targets in kidney and liver disease [46]. However, the thiazolidinedione PPAR gamma agonists have been withdrawn from many markers due to cardiovascular safety concerns. By contrast, HIF activators are already in the market for uremic anemia in Chine, following phase 3 clinical trials and were recently reported to have a nephroprotective effect in clinical trials [52, 53]. Interestingly, in experimental animals, the HIF activator FG-4497 prevented liver steatosis [47], while JTZ-951 protected from the kidney and liver effects of a high fat diet [54].

Conclusion and future perspective

NAFLD is a major global health problem and its prevalence and impact, like that of CKD, has been growing depending on the increasing prevalence of obesity. NAFLD should be considered a multisystem disease with potential consequences for cardiac and renal health. Thus, NAFLD is associated with increased morbidity from CVD and CKD, and only the detailed characterization of common pathogenic mechanisms will allow the design of drugs that provide a holistic approach to the health problem. Many different pathogenic mechanisms may contribute to CKD progression as a complication of NAFLD. These include, but are not limited to insulin resistance, lipotoxicity, oxidative stress and inflammatory cytokines.

Besides, NAFLD is not homogenous disease and genetic factors especially in some specific patients population such as in hepatitis C patients are important. Hyperhomocysteinemia and the MTHFR C677T polymorphism promote steatosis and fibrosis in chronic hepatitis C patients therefore must be taken into consideration while taking measures regarding lifestyle and pharmacologic interventions [55–57]. We are also aware that above discussed mechanisms both for NAFLD and CKD exists it is not clear directly that if they are co-incidentally present or a real cause and effect relationship exists. Indeed, observational design of most studies do not enable us to establish a cause and effect relationship and it is currently not exactly known whether NAFLD carry a higher risk of incident CKD. There is also another concern that most of the studies used ultrasonography to detect NAFLD, which is the recommended first-line imaging. However liver biopsy is the gold standard method for diagnosing NAFLD as well [58]. The things become even more complicated given the fact that not all patients with NAFLD suffer from kidney damage. Thus genetic, environmental and other unknown factors probably might play a role for the development of CKD in NAFLD which further studies will show.

Future studies should address the relative contribution of these pathogenic mechanisms and the optimal, integrated way to tackle them. Lifestyle interventions such as weight loss and smoking cessation may be beneficial. From a pharmacological point of view, GLP-1-RA and SGLT2 inhibitors reduce the progression of both NAFLD and CKD and HIF activators will become available in the near future. However, only randomized clinical trials will identify the most effective and safe treatment modality. Additionally, an adequate diagnostic work-up, as suggested in Table 2, is required to identify the patients that may benefit from these novel integrated therapeutic approaches.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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