Invited review

Steatotic liver disease, MASLD and risk of chronic kidney disease

Josh Bilson[1,2*], Alessandro Mantovani[3*], Christopher D. Byrne[1,2*], Giovanni Targher,[4,5*]

[1]School of Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK

[2]National Institute for Health and Care Research, Southampton Biomedical Research Centre, University Hospital Southampton and University of Southampton, Southampton, UK

[3]Department of Medicine, Section of Endocrinology, Diabetes, and Metabolism, University of Verona, Verona, Italy

[4]Department of Medicine, University of Verona, Verona, Italy

[5]Metabolic Diseases Research Unit, IRCCS Sacro Cuore – Don Calabria Hospital, Negrar di Valpolicella, Italy

*All authors contributed equally to the manuscript

Conflicts of interest statement: nothing to declare.

Funding information: No funding was received for this study. GT was supported in part by grants from the School of Medicine, University of Verona, Verona, Italy. CDB was supported in part by the Southampton National Institute for Health and Care Research Biomedical Research Centre (NIHR203319), UK.

Word count: 244 abstract; 6801 text (*excluding* title page, references, tables and figure legends. **Table** =1, **Figures** =4

Address for correspondence:
Prof. Giovanni Targher, MD
Metabolic Diseases Research Unit
IRCCS Sacro Cuore – Don Calabria Hospital
37024 Negrar di Valpolicella, Italy
E-mail: giovanni.targher@univr.it

Abstract

With the rising tide of fatty liver disease related to metabolic dysfunction worldwide, the association of this common liver disease with chronic kidney disease (CKD) has become increasingly evident. In 2020, the more inclusive term metabolic dysfunction-associated fatty liver disease (MAFLD) was proposed to replace the old term nonalcoholic fatty liver disease (NAFLD). In 2023, a modified Delphi process was led by three large pan-national liver associations. There was consensus to change the fatty liver disease nomenclature and definition to include the presence of at least one of five common cardiometabolic risk factors as diagnostic criteria. The name chosen to replace NAFLD was metabolic dysfunction-associated steatotic liver disease (MASLD). The change of nomenclature from NAFLD to MAFLD and then MASLD has resulted in a reappraisal of the epidemiological trends and associations with the risk of developing CKD. The observed association between MAFLD/MASLD and CKD and our understanding that CKD can be an epiphenomenon linked to underlying metabolic dysfunction support the notion that individuals with MASLD are at substantially higher risk of incident CKD than those without MASLD. This narrative review provides an overview of the literature on (a) the evolution of criteria for diagnosing this highly prevalent metabolic liver disease, (b) the epidemiological evidence linking MASLD to the risk of CKD, (c) the underlying mechanisms by which MASLD (and factors strongly linked with MASLD) may increase the risk of developing CKD, and (d) the potential drug treatments that may benefit both MASLD and CKD.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) are two global public health problems that affect almost 30% and up to ~10-15%, respectively, of the general adult population in many parts of the world [1-3]. Both chronic conditions are also expected to increase dramatically in the foreseeable future and are closely associated with poor outcomes, premature mortality, decreased quality of life, and high societal costs [1-3].

A rapidly expanding body of clinical evidence supports the assertion that NAFLD can identify a group of individuals who are at increased risk of developing CKD and who need more careful surveillance and treatment to reduce their risk of incident CKD [4]. For example, an updated meta-analysis of 13 observational cohort studies (including more than 1.2 million people) showed that NAFLD was significantly associated with a nearly 1.5-fold increased risk of incident CKD over a median follow-up of ~10 years [5].

As discussed in more detail later, the newly proposed fatty liver disease nomenclature changing from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD) and metabolic dysfunction-associated steatotic liver disease (MASLD) necessitates a reappraisal of the epidemiological associations with the risk of CKD and cardiovascular disease (CVD) (that represents the predominant cause of mortality in people with MAFLD or MASLD) [6-8]. Our recent understanding that CKD can occur as a consequence of metabolic dysfunction strongly suggests that persons with MAFLD or MASLD (who, by definition, have hepatic steatosis and at least one or more metabolic risk factors) are at amplified risk of developing CKD.

In this narrative review, we summarize the recently proposed nomenclature change from NAFLD to MAFLD and MASLD and discuss the clinical associations between this common liver disease and the risk of developing CKD, as well as the underlying mechanisms potentially linking MAFLD/MASLD to the risk of developing CKD. Furthermore, we also discuss the pharmacotherapies that may benefit fatty liver disease and CKD.

2. From NAFLD to MAFLD and MASLD: evolution of terminology and diagnostic criteria for a metabolic liver disease

The initial descriptions in the early 1980s by Dr. Ludwig et al. [9] and by Dr. Schaffner and Thaler [10] first coined the terms nonalcoholic steatohepatitis (NASH) and NAFLD, respectively. These authors described a fatty liver disease in moderately obese individuals, most of whom had type 2 diabetes mellitus (T2DM), arising in the absence of excessive alcohol consumption or other

competing causes for hepatic steatosis. Since then, important conceptual advances have been made in understanding the pathophysiological mechanisms of this highly prevalent liver condition. Over the last two decades, there have been concerns expressed by several experts and scientific societies regarding the inaccuracy and possible “negative” consequences of using the term “NAFLD” to describe a fatty liver disease associated with metabolic dysfunction. In particular, the adjective “non-alcoholic” present in the NAFLD definition overemphasizes the absence of significant alcohol consumption and could be perceived as stigmatizing. It also does not recognize the pathogenic role that overweight/obesity, T2DM, and insulin resistance play in the development of this liver disease and its most relevant adverse extra-hepatic complications (such as CVD, CKD or certain extra-hepatic malignancies) [11-14].

As recently described by Dr. George [15], the year 2020 witnessed a paradigm shift in how we conceptualized and thought about fatty liver disease, which is responsible for most of the cases we routinely observe in our clinical practice. Indeed, in 2020, a large panel of international experts proposed a change of terminology and definition for NAFLD in adult individuals — i.e., metabolic dysfunction-associated fatty liver disease (MAFLD) [16]. This proposal of terminology change from NAFLD to MAFLD has subsequently received widespread acceptance in clinical practice guidelines [17], [18], [19], and many other stakeholders [20].

A direct comparison of the diagnostic criteria used for identifying NAFLD and MAFLD in adult individuals is summarized in **Figure 1**. The criteria for diagnosing MAFLD are based on the identification of hepatic steatosis (detected by liver biopsy, imaging techniques or blood-based biomarkers) in the presence of one of the following three metabolic disorders: overweight/obesity, T2DM, or metabolic dysregulation in individuals who are nonobese or don’t have T2DM [20]. It is important to underline that the new “positive” diagnostic criteria of MAFLD recognize that this metabolic liver disease can coexist with significant alcohol intake or other known causes of hepatic steatosis, but the exclusion of these conditions is not a pre-requisite criterion for diagnosing MAFLD. Persons with MAFLD who have one (or more) of these conditions should be defined as having a dual (or more) etiology of fatty liver disease [20]. Strong evidence suggests that the MAFLD definition identifies better individuals who are at higher risk of liver disease progression and those at increased risk of all-cause mortality, fatal/nonfatal cardiovascular events, or other adverse extra-hepatic outcomes than the old term NAFLD [7, 8, 11, 21-23].

In 2023, three large multinational liver associations, along with various national hepatology societies and patient advocacy organizations, convened a steering committee to evaluate the need for revisiting the NAFLD nomenclature [24]. Using a representative, patient-centric Delphi process, a total of 236 panelists (including many authors from the MAFLD proposal) from 56 countries

systematically addressed all the issues and views over the past 2-3 years and, through consensus arrived at a new nomenclature and definition [24]. As shown in **Figure 1**, the MASLD definition does not appear to be substantially different from that of MAFLD but replacing “fatty” with “steatotic” is a further element in reducing the social stigma associated with the existing terminology. Other key differences are a more pragmatic set of diagnostic criteria and the presence of at least one of five common metabolic risk factors in the setting of hepatic steatosis (without establishing any priority of overweight/obesity or T2DM as the strongest metabolic risk factors for adverse liver-related outcomes). Furthermore, HOMA-IR score and plasma hs-CRP concentrations proposed amongst the MAFLD diagnostic criteria are not included. The MASLD definition also retains existing levels of weekly alcohol consumption (as established with NAFLD). That said, a new category outside “pure” MASLD has been created, termed “MetALD” (i.e., metabolic liver disease associated with alcohol intake) that identifies individuals with MASLD who drink greater amounts of alcohol per week (i.e., 140-350 g/week for women and 210-420 g/week for men, respectively) [24]. The panelists of this Delphi process have recognized that the newly proposed nomenclature has limitations regarding the subclassification of NAFLD resulting from data gaps. Nevertheless, this new fatty liver disease nomenclature can provide a foundational structure/matrix for which definitions and subclasses may be adjusted as new epidemiological data emerges about the underlying pathophysiology and related risk factors [24]. Emerging evidence from population-based cohort studies from the USA, Brazil and China indicates that the newly proposed change in diagnostic criteria for MASLD does not significantly impact disease prevalence, or associated mortality outcomes compared to MAFLD [25-28].

Collectively, therefore, although the recently proposed change in nomenclature from NAFLD to MAFLD and MASLD is still under debate, it should be noted that this new fatty liver disease nomenclature is not a simple semantic revision. Rather, it better reflects the pathophysiology and cardiometabolic implications of this common and burdensome liver disease. This new nomenclature change represents the first step toward better identifying this metabolic liver disease for improved health promotion, case identification, patient awareness, ongoing clinical trials, and health services delivery [14].

3. Epidemiological evidence linking MASLD to the risk of chronic kidney disease

In 2008, two pioneering prospective studies reported that NAFLD (assessed by ultrasonography) was associated with an increased risk of incident CKD in both patients with [29] and without T2DM [30], independently of common renal risk factors. After these pioneering studies, other longitudinal studies confirmed a close association between NAFLD and the risk of incident CKD. In 2022, a

comprehensive meta-analysis of 13 longitudinal studies (published until August 2020), including a total of about 1,2 million middle-aged individuals (28.1% of whom had NAFLD), showed that NAFLD was associated with a moderately increased risk of incident CKD stage ≥3 (defined as the occurrence of estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2, with or without accompanying proteinuria) over a median follow-up period of 9.7 years (random-effect hazard ratio [HR] 1.43, 95% confidence intervals [CI] 1.33-1.54) [5]. This risk was independent of age, sex, obesity, hypertension, T2DM and other traditional renal risk factors. Interestingly, this meta-analysis also showed that CKD risk was further increased with more advanced liver disease, especially with the severity of hepatic fibrosis [5]. This finding has also been further corroborated by some cohort studies of patients with biopsy-proven NASH and liver fibrosis [31].

As summarized in **Table 1** [31-40], after the publication of the meta-analysis mentioned above [5] and following the proposal to change the nomenclature from NAFLD to MAFLD in 2020 [16], several longitudinal studies have examined the prognostic impact of MAFLD on the risk of developing CKD. Other studies have also compared the effects of NAFLD and MAFLD definitions on the risk of developing CKD. Currently, there are no studies examining the impact of MASLD on the long-term risk of developing CKD. In a longitudinal study of 3,627 Chinese individuals with T2DM, Wei et al. reported that MAFLD on ultrasonography was associated with an increased risk of incident CKD during a 10-year follow-up, even after adjusting for age, sex, obesity, hypertension, dyslipidemia, serum liver enzymes and baseline eGFR (adjusted-HR 1.28, 95% CI 1.09-1.50) [37]. In another longitudinal study enrolling 6,873 Chinese individuals, Liang et al. reported that ultrasound-detected MAFLD was independently associated with a higher risk of incident CKD over a median of 4.6 years (adjusted-HR 1.64; 95% CI 1.39-1.94) and that a comparable association was also observed for NAFLD (adjusted-HR 1.70; 95% CI 1.43-2.01) [34]. Similar findings were reported by Jung et al. [36]. Conversely, in a longitudinal study of 13,159 Japanese adult individuals, Tanaka et al. showed that ultrasound-detected MAFLD (adjusted-HR 1.12; 95% CI 1.02–1.26), but not NAFLD, was significantly associated with an increased risk of incident CKD over a mean of 6.3 years, even after adjusting for conventional cardio-renal risk factors [40]. Interestingly, in that study, adding MAFLD to the conventional risk factors for CKD significantly improved the discriminatory capacity of identifying patients at higher risk of developing CKD [40]. Similarly, in a longitudinal study of 21,713 South Korean adults undergoing at least two serial health examinations, Kwon et al. reported that patients with ultrasound-detected MAFLD (adjusted-HR 1.97, 95% CI 1.49-2.60), but not those with NAFLD, had a higher risk of developing CKD during a median of 5.3 years, even after adjustment for common cardio-renal risk factors, baseline eGFR, NAFLD fibrosis score or pre-existing CVD [38]. An association between MAFLD and the risk of end-stage renal disease (ESRD) was also recently observed. In a longitudinal study involving 337,783 participants from the UK Biobank, Chen et al.

found that patients with MAFLD had a ~2-fold increased risk of developing ESRD than those without MAFLD over a median follow-up of 12.8 years [39].

The coexistence of MAFLD and CKD may also predict the risk of ischemic heart disease (that is the leading cause of mortality in patients with MAFLD as reported in [41]) more accurately than MAFLD or CKD alone. It is also important to recognize that ischemic heart disease may reflect the presence of macroscopic renal vascular disease that will further increase the risk of CKD. As regards this, in a cohort study of 14,141 Japanese adults, Miyamori et al. [42] found that the coexistence of MAFLD and CKD, but not MAFLD or CKD alone, was a significant risk factor for ischemic heart disease during a mean follow-up of 6.9 years. These results remained significant after adjustment for age, sex, smoking, family history of ischemic heart disease, and presence of obesity, diabetes, hypertension, or dyslipidemia (adjusted-HR 1.51, 95% CI 1.02-2.22). Other prospective studies also showed that NAFLD was significantly associated with higher risks of adverse clinical outcomes and all-cause mortality in patients with CKD [43].

Little is currently known regarding the association between temporal changes in fatty liver (NAFLD) status and the risk of incident CKD. In a community-based cohort study of 4,042 Chinese adults free of CKD at baseline, Zuo et al. reported that developing incident NAFLD on ultrasonography was independently associated with an increased risk of developing CKD during a mean follow-up of 4.4 years [32]. The authors also found that the risk of incident CKD was not significantly different between subjects with either resolution NAFLD or persistent NAFLD at follow-up [32]. In addition, liver fibrosis progression (non-invasively assessed by NAFLD fibrosis score) was associated with a significantly higher risk of incident CKD [32]. Similarly, Terasaka et al. showed that patients with a worsening FIB-4 index category from baseline to 5 years had a higher risk of developing CKD than those with an improved FIB-4 index category [44].

Therefore, many epidemiological studies indicate that the NAFLD and MAFLD definitions can effectively identify a subgroup of patients at higher risk of developing CKD stage $\geqslant$3 over time. Additionally, it seems that advanced hepatic fibrosis is associated with the highest CKD risk. However, given the observational design of the published studies, a causal relationship between NAFLD or MAFLD (or MASLD) and increased incidence CKD cannot be firmly established. Hence, future prospective cohort studies, including Mendelian randomization ones, are timely needed.

4. Putative mechanisms linking MASLD to kidney disease

As discussed earlier, a growing body of evidence indicates a clear epidemiological association between the presence of NAFLD/MASLD and an increased risk of CKD. However, it is essential to highlight that the precise pathophysiological mechanisms linking these diseases are not fully understood and likely involve the liver and many extra-hepatic organs. Indeed, CKD is a multisystem disease that shares a plethora of cardiometabolic risk factors with NAFLD/MASLD, making it challenging to dissect causative relationships between the two conditions. As discussed below, a complex combination of metabolic and hemodynamic changes, lipid nephrotoxicity, and genetic predisposition is likely to drive the development of CKD in individuals with NAFLD/MASLD. In this section, we consider both hepatic and non-renal tissue dysfunction in developing macro- and micro-vascular renal complications driving kidney dysfunction and CKD.

Metabolic syndrome and liver-mediated mechanisms

Many of the cardiometabolic features of MASLD are shared risk factors with both CVD and CKD and can contribute to the progression of both liver disease and CKD by creating a systemic environment of metabolic and vascular dysfunction and low-grade inflammation. The pro-atherogenic dyslipidemia often observed in individuals with obesity and/or metabolic syndrome also contributes to renal vascular disease and a reduction in eGFR, potentially increasing the risk of CKD [45]. In addition to changes in plasma lipoprotein concentrations in MASLD and CKD, changes in the composition of small molecules, proteins and fatty acids in lipoproteins have been suggested to further contribute to renal damage, inflammation, and fibrosis [45]. Other systemic factors in MASLD, including hypertension and chronic hyperglycemia (as occurs with poorly controlled T2DM), typically form a cluster of metabolic risk factors which, along with abdominal obesity, are known to increase the risk of CKD and contribute directly to the development of macro- and micro-vascular renal complications [4]. Such systemic metabolic risk factors can promote renal oxidative stress and the infiltration and activation of pro-inflammatory immune cells, which modulate the renal microenvironment, potentially resulting in albuminuria and a reduction in eGFR [46].

Additionally, early changes in the portal and splanchnic vasoregulation commonly seen in patients with NAFLD are thought to potentially initiate a pathological “hepatorenal reflex”, which likely precedes the development of cirrhosis and the so-called hepatorenal syndrome. Whilst the mechanisms involved in developing hepatorenal reflex are likely complex [47], increased intrahepatic vascular resistance and the impairment of sinusoidal blood flow are core features. In a recent expert opinion, Drs. Baffy and Bosch highlighted the potential importance of subclinical portal hypertension as a potential driver of hepatic dysfunction, inflammation, and fibrosis [48]. We hypothesize that this subclinical portal hypertension may also trigger a subclinical hepatorenal reflex, which, over a prolonged period, could contribute to the development and progression of renal dysfunction and

CKD [47]. That said, such a fascinating hypothesis requires further appropriate exploration and testing.

Alterations in the release of hepatokines in MASLD may also contribute to the development of CKD via close liver-kidney crosstalk. Indeed, various hepatokines have been implicated in CKD pathogenesis and have been the focus of other recent reviews [49, 50]. Fibroblast growth factor-21 (FGF-21) is a hepatokine that has been the subject of considerable interest in recent years, not least because the FGF-21 receptor agonist efruxifermin has shown promise in phase 2 randomized trials and is currently being tested in phase 3 clinical trials for the treatment of NAFLD. Circulating concentrations of FGF-21 are thought to be increased in individuals with metabolic diseases, including T2DM [51], CKD [52] and NAFLD/MASLD [53]. Increased plasma FGF-21 concentrations in the presence of metabolic complications are likely to be an adaptive response that aims to alleviate metabolic dysfunction (i.e., hyperglycemia and insulin resistance)[54]. However, in chronic metabolic diseases such as CKD and MASLD, a state of FGF-21 resistance may suppress the beneficial effects of this hepatokine [52]. While FGF-21 has been shown to improve systemic markers of T2DM and insulin resistance, its direct effects within the kidneys remain elusive, and further work is required to explore any direct effects of FGF-21 on renal function and whether modulating FGF-21 receptor activity is effective in the resolution of CKD.

Adipose tissue, lipid droplets and PPAR-γ dysfunction connecting MASLD and CKD

Adipose tissue dysfunction, rather than obesity *per se,* likely contributes to the development of CKD in MASLD via both direct and indirect (i.e., via the worsening of cardiometabolic risk factors) mechanisms. The inability of adipose tissue to sufficiently expand and/or suppress lipolysis results in the ectopic deposition of lipids in organs such as the liver and kidneys. Indeed, many studies indicate that renal lipid droplet accumulation is a hallmark characteristic of CKD [55]. In the kidney, lipids typically deposit in the perirenal space, kidney sinus and kidney parenchyma (**Figure 2**). Accumulation of perirenal adipose tissue is strongly associated with CKD and may directly contribute to renal dysfunction, although underlying mechanisms are yet to be fully elucidated [56]. Excess perirenal adipose tissue may directly compress the renal vasculature and parenchyma, increasing renal interstitial hydrostatic pressure and renin release and reducing eGFR [57, 58]. Similarly, increased renal sinus fat (considered to be perivascular adipose tissue) is within proximity to renal blood vessels and can produce a plethora of molecules, including adipokines (i.e., leptin and adiponectin), proinflammatory mediators, nitric oxide and reactive oxygen species [59]. Consequently, renal sinus fat accumulation and dysfunction may contribute to renal inflammation, fibrosis, and hypertension, potentially contributing to CKD progression. Further exacerbating this renal dysfunction, kidney parenchymal fat deposition (i.e., fat deposited in the renal cortex and medulla) has also been associated with kidney cell injury, glomerulosclerosis, interstitial fibrosis and

proteinuria [55]. Emerging evidence also indicates that lipid droplets may act as intracellular mechanical stressors, which, within the renal parenchyma, could contribute to inflammation and fibrosis [60].

While renal lipid deposition may have a role in CKD development, it is also important to acknowledge the role of non-renal adipose tissue dysfunction as a potential mechanism linking MASLD and CKD. As shown in **Figure 2**, in addition to contributing to ectopic lipid deposition, obesity-associated adipose tissue dysfunction may also contribute to the development of systemic low-grade inflammation, strongly associated with CKD and MASLD. As reviewed by others, a shift in the profile of adipokines (e.g., adiponectin and leptin) also likely plays a role in the development of CKD and MASLD [61, 62].

Emerging evidence also indicates the potential role of different mature white adipocyte subpopulations in adipose tissue inflammation and insulin resistance [63-65]. However, the role of these subpopulations in MASLD and/or CKD is unclear [63-65]. Interestingly, the adipose tissue-kidney crosstalk appears to be bidirectional. Indeed, increased systemic uremic toxin concentrations resulting from renal dysfunction promote adipose tissue inflammation and alter adipokine profiles [62]. This vicious cycle between adipose tissue and kidney dysfunction likely contributes to systemic metabolic dysfunction, MASLD and CKD and is also exacerbated by intestinal dysfunction (**Figure 2**).

Predominantly expressed in the adipose tissue, peroxisome proliferator-activated receptor-gamma (PPAR-γ) is a master regulator of adipocyte biology where it plays crucial roles in facilitating fat storage, metabolic homeostasis and adipogenesis. Disruptions in PPAR-γ signaling compromise adipose tissue function and plasticity, resulting in local and systemic insulin resistance, a central driver for the development of both MASLD and CKD [66, 67]. In the liver, PPARγ has various potentially protective functions, including the improvement in hepatic insulin resistance, inflammation and fibrosis – the latter is thought to be achieved via reversing the activation of hepatic stellate cells [68]. Like adipose tissue and the liver, PPARγ is widely expressed in the kidneys and regulates various metabolic and inflammatory processes. Obesity-associated alterations in PPAR-γ activity may also contribute to renal lipid accumulation, inflammation and fibrosis [67]. Consequently, dysfunction in PPAR-γ signaling with obesity is an important factor contributing to the dysfunction of multiple key tissues, leading to detrimental changes in lipid handling, inflammation and fibrosis that may potentially ‘drive’ the development and progression of both MASLD and CKD.

Intestinal dysfunction and dysbiosis affecting MASLD and CKD

Intestinal dysbiosis is a hallmark characteristic of both NAFLD/MASLD and CKD, and perturbations in intestinal function are likely to contribute to the development of both chronic conditions [69, 70]. Alterations in intestinal bacterial populations in MASLD and CKD typically feature a loss of bacterial richness and diversity and a depletion of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*. Conversely, *Enterobacteria* and *Enterococci* are among the bacterial populations enriched in patients with MASLD and CKD [71]. This dysbiosis is also associated with a loss of intestinal tight-junction cohesion, facilitating lipopolysaccharide (LPS) influx into the systemic circulation. LPS is a potent activator of nuclear factor kappa B (NF-κB), toll-like receptor (TLR)-2 and TLR4-related pathways, and its presence in distal organs, such as the liver and kidneys can exacerbate tissue inflammation and contribute to accelerated renal and hepatic fibrosis [72]. Intestinal dysbiosis is also associated with a shift in the production of a range of gut metabolites proposed to contribute to NAFLD/MASLD and CKD (**Figure 2**).

Increased concentrations of bile acids (particularly secondary bile acids) have been associated with CKD and NAFLD/MASLD [73-75]. Circulating concentrations of deoxycholic acid are elevated in individuals with CKD, and some studies suggest that this secondary bile acid may contribute to vascular calcification mainly via activating transcription factor 4 [76]. Elevated serum urea concentrations secondary to decreased eGFR may subsequently increase gastrointestinal tract urea availability and the formation of microbiota-generated uremic toxins (e.g., trimethylamine, cresol, hippuric acid and indole). Such uremic toxins can exacerbate intestinal permeability and contribute to renal and hepatic dysfunction by activating proinflammatory and profibrogenic pathways [71]. Elevated trimethylamine-N-oxide (TMAO) concentrations may promote the development of hypertension in NAFLD/MASLD and CKD, and TMAO has also been proposed to contribute to renal interstitial fibrosis, eGFR decline and endothelial dysfunction [77, 78]. Similarly, gut dysbiosis-associated reductions in short-chain fatty acid (SCFA) production have been suggested to contribute to CKD and NAFLD/MASLD via various mechanisms, including inflammation and oxidative stress exacerbation [79]. Intestinal dysbiosis may also contribute to the development of hypertension via the gut-brain-kidney axis, which is known to contribute to renal microvasculature damage and CKD [80, 81].

Genetic predisposition to both MASLD and CKD

The role of genetic polymorphisms associated with NAFLD/MASLD as risk factors for renal dysfunction and CKD has been the focus of recent publications [47, 82, 83]. Indeed, while some inconsistency exists between studies, several MASLD-associated polymorphisms, such as those in *PNPLA3, TM6SF2, HSD17B13, MBOAT7* or *GCKR,* have also been shown to increase the risk of incident CKD [82]. The rs738409 C>G single nucleotide polymorphism in the *PNPLA3* gene, encoding for the p.IIe148Met change (I148M), is considered one of the most prevalent and important

NAFLD/MASLD genetic risk factors [84]. Indeed, this common genetic risk variant is known to increase the risk of and contribute to developing hepatic steatosis, inflammation and fibrosis via a range of potential mechanisms [85]. Recent evidence also indicates that the *PNPLA3*-I148M variant in this lipid droplet-associated protein is associated with decreased renal function and an increased risk of kidney dysfunction in adults and children [47, 86-90]. Interestingly, the link between the *PNPLA3*-I148M variant and reduced renal function is independent of other shared metabolic risk factors and hepatic steatosis, inflammation, and fibrosis [86, 90, 91]. Consequently, the direct impact of the *PNPLA3*-I148M variant on renal function has become an area of considerable interest in recent years. Physiologically, PNPLA3 is involved in the hydrolysis of triglycerides (TAGs), with a greater affinity towards monounsaturated and polyunsaturated fatty acids [92].

The *PNPLA3*-I148M variant has been shown to impair the hydrolytic activity of the physiological PNPLA3 protein, resulting in the accumulation of lipid droplets within hepatocytes and adipocytes rich in PUFA-rich TAGs [93]. It is reasonable to hypothesize that the *PNPLA3*-I148M variant may exacerbate the lipid droplet accumulation within renal podocytes by inhibiting PNPLA3's ability to hydrolyze TAG-PUFAs. Such dysmetabolism of lipids and lipid droplet accumulation within renal cells has recently been highlighted as an important causative factor contributing to CKD development [55]. Additionally, the *PNPLA3*-I148M variant has been suggested to impair PNPLA3's physiological retinyl-palmitate lipase activity, resulting in a reduction in the release of retinol from lipid droplets, which, within the kidney, could also contribute to renal dysfunction [83, 94]. We have attempted to summarize the potential underlying mechanisms by which the *PNPLA3*-I148M variant may influence the risk of CKD via alterations in both hepatic and renal functions (**Figure 3**). Further mechanistic studies are required to elucidate better the direct role of the *PNPLA3*-I148M variant on renal function and should focus initially on the influence of this genetic variant on lipid handling within renal podocytes. It is also worth noting that other less frequent genetic polymorphisms have been linked to both liver and kidney disease and have been discussed in-depth by Wang and colleagues [82].

5. Pharmacotherapies beneficially affecting both MASLD and chronic kidney disease

When considering potential drug treatments that may benefit MASLD and CKD, it is important to consider drug actions that are of benefit, both to ameliorate (or attenuate) fat, inflammation and fibrosis in the liver and factors that have been shown to improve CKD (or risk factors for CKD). Many of the risk factors for CKD are also shared risk factors for CVD, and the development of atherosclerotic vascular disease is a significant risk factor for developing CKD. T2DM increases the risk of both macrovascular disease and microvascular disease. Whereas a decrease in eGFR

defining CKD may be due to macrovascular disease, proteinuria/macroalbuminuria is the hallmark of microvascular disease and, therefore, diabetes can cause both a decrease in eGFR and proteinuria or both macrovascular and microvascular disease within the kidney. Since chronic hyperglycemia occurring in people with diabetes is a significant risk factor for microvascular disease, it is important to treat hyperglycemia with glucose-lowering drugs to attenuate the risk of microvascular disease. Consequently, this section will consider different drug classes with proven beneficial effects not only on fatty liver disease and CKD related to MASLD but also with proven benefits in ameliorating fatty liver disease, cardiovascular risk factors and hyperglycemia. The effects of potential treatments for MASLD with CKD are summarized in **Figure 4**. The figure schematically illustrates the possible direct and indirect actions of drug treatments on processes relevant to liver disease and CKD *per se*, as well as the beneficial effects on CVD risk factors that may, in turn, be relevant to the development and progression of CKD. Management of dyslipidemia in MASLD should include the use of statins as first-line therapy (or other lipid-lowering agents if these drugs are not tolerated) based on plasma lipid levels and atherosclerotic CVD risk scores [95]. Lowering plasma LDL-cholesterol concentration has proven beneficial for patients at high risk of CVD or with established CVD. However, although statin treatment is now known to be safe in people with NAFLD/MASLD, there is currently no convincing evidence that this class of drugs specifically benefits fatty liver disease. Similarly, there is no good evidence that low-dose aspirin or other antiplatelet agents that are commonly used in treating patients with post-myocardial infarction may benefit the liver in NAFLD/MASLD.

As discussed above, CKD is classified according to the level of eGFR and then subclassified according to the level of coexisting abnormal albuminuria or overt proteinuria. When abnormal albuminuria is present, this level of proteinuria is already an indication for specific drug treatments focused on the blockade of the renin-angiotensin system with agents such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers. There is some evidence of potential benefit of the latter on liver fibrosis, and this is considered below. Additionally, treating cardiometabolic risk factors is important and in people with T2DM and CKD, a blood pressure target of <130/80 mmHg is desirable [96].

Sodium-glucose cotransporter-2 inhibitors

In 2021, a meta-analysis of 20 phase 2 RCTs evaluated liver function or structure and compared SGLT2 inhibitors with placebo or other oral glucose-lowering drugs in patients with T2DM. A total of 1,950 type 2 diabetic patients, with or without NAFLD, were treated with SGLT2 inhibitors for at least eight weeks, and 1,900 patients were used as controls [97]. SGLT2 inhibitors significantly improved serum alanine aminotransferase, aspartate aminotransferases and gamma-glutamyl transferase concentrations compared to placebo or other oral glucose-lowering drugs. Random-effect meta-

analysis of the four RCTs evaluating fat liver content measured by magnetic resonance-based techniques showed that SGLT2 inhibitors were associated with a beneficial effect on hepatic steatosis compared to placebo (−3.39% [95% CI −6.01, −0.77%], p<0.01, I^2= 89%) [97]. These results supported the results of another meta-analysis undertaken in 2020 [98]. A recent post-hoc analysis of 2 large double-blind randomized controlled trials (the CANVAS trials) showed that in patients with T2DM, treatment with canagliflozin vs. placebo resulted in significant improvements in some non-invasive fibrosis biomarkers [99]. Besides their possible hepato-protective effects, SGLT2 inhibitors decrease body weight, plasma triglycerides and HOMA-IR score and increase plasma HDL-cholesterol concentrations [100].

Several major randomized controlled cardiovascular and renal outcome trials have been undertaken in people with established T2DM, showing benefits of SGLT2 inhibitors in the kidneys [101-105]. SGLT2 inhibitors decrease afferent arteriolar vasoconstriction and may confer protection in reducing the risk of CKD by benefitting glomerular function via reducing glomerular hyperfiltration [106]. SGLT2 inhibitors may also decrease uric acid-induced renal damage by lowering serum uric acid concentrations [107] and also benefit albuminuria by reducing low-grade inflammation [108], fibrogenic response, apoptosis, and glucose-induced oxidative stress [109]. Thus, in people living with T2DM who have MASLD, there is a strong case for the use of SGLT2 inhibitors for patients with CKD or at high risk of CKD.

Peroxisome proliferator-activated receptor-gamma agonists

Evidence shows that pioglitazone treatment has benefits for the cardiovascular system and has been shown to decrease the risk of acute myocardial infarction and ischemic stroke [110]. An elegant review recently reminded us that pioglitazone has become the “forgotten, cost-effective, cardioprotective drug” for T2DM [111]. The European and American guidelines for the treatment of NAFLD recommended the use of the peroxisome proliferator-activated receptor-gamma agonist (PPAR-γ) pioglitazone in adults with biopsy-confirmed NASH, regardless of the presence or absence of T2DM [112, 113]. However, most national Medicines agencies do not approve the pioglitazone use in patients who do not have T2DM. Pioglitazone is a selective agonist regulating the PPAR-γ nuclear receptor activity [114]. A systematic review of randomized clinical trials assessing the efficacy of glucose-lowering agents to specifically treat NAFLD or NASH in adults with or without T2DM showed that treatment with pioglitazone (≥30 mg daily) improved individual histologic scores of NASH and achieved greater resolution of NASH compared to placebo [115]. In patients with prediabetes or T2DM, a phase-2 placebo-controlled RCT showed that pioglitazone treatment (45 mg/day for 72 weeks) was also better than placebo in improving the fibrosis score in patients with NASH (especially in those with T2DM) [116]. This finding was further confirmed by a meta-analysis involving eight RCTs [117]. Safety concerns (moderate weight gain, peripheral edema, and

moderately increased risk of distal bone fractures in postmenopausal women) may limit the long-term use of pioglitazone in clinical practice.

PPAR-γ is abundantly expressed in the kidney in the medullary collecting duct, paraurethral and bladder epithelial cells, as well as podocytes, mesangial cells, and vascular endothelial cells [67]. The PPAR-*γ* function in the kidney ranges from energy metabolism and cell proliferation to inflammatory suppression [67]. Evidence suggests that PPAR-*γ* agonists could also provide protection in a broader spectrum of kidney diseases, such as acute nephrotic syndrome, nondiabetic glomerulosclerosis, and polycystic kidney [118, 119]. However, side effects such as fluid retention occurring via the effects of pioglitazone in the kidneys may result in peripheral edema in ~5-10% of treated patients and this effect, as well as moderate weight gain (~2.5 kg after 72 weeks) largely due to subcutaneous fat accumulation, tends to be worse in patients treated with the highest licensed dose of pioglitazone (45 mg/day) [120]. Fluid retention is potentially important, and therefore pioglitazone is contraindicated in patients at high risk of, or with heart failure. However, as pioglitazone treatment also reduces the risk of acute myocardial infarction and ischemic stroke, in our opinion, pioglitazone should be considered when not contraindicated in patients with MAFLD/MASLD, not least because of benefits in the kidney in patients at risk of CKD.

Lanifibranor is a pan-PPAR agonist that modulates key metabolic, inflammatory, and fibrogenic pathways in the pathogenesis of NASH and a phase 3 RCT is currently underway. A phase 2b placebo-controlled RCT in patients with biopsy-proven NASH treated with different doses of lanifibranor for 24 weeks has been undertaken. These data showed that the percentage of patients with improvement of at least two points in the histologic SAF score (steatosis, activity, and fibrosis) without worsening of fibrosis was significantly greater among those treated with the 1200-mg dose of lanifibranor than with placebo [114]. With the failure of elafibranor (a PPAR alpha and delta agonist) to show benefit in NASH, and bearing in mind the proven benefit of pioglitazone, it seems likely that any benefit conferred by lanifibranor on steatotic liver disease in MASLD will be mediated by its PPAR-γ agonist activity.

Incretin receptor agonists

The two major classes of incretin receptor agonists showing considerable promise in treating the early stages of NAFLD/MASLD are glucagon-like peptide-1 (GLP-1) receptor agonists (especially subcutaneous semaglutide) and dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) agonists (tirzepatide) [121]. These drugs are very effective in facilitating weight loss, and we have recently evaluated their effectiveness in treating NAFLD/NASH [122]. Although there remains uncertainty as to whether there are any benefits on liver fibrosis, these drugs confer indirect benefits on the liver (principally via the benefits of weight loss) to decrease liver

fat and inflammation [122]. Studies investigating the cardiovascular outcomes of GLP-1 receptor agonists have also identified benefits on secondary renal outcomes. For example, the LEADER trial investigated the effects of liraglutide and included 23% of patients with CKD. The results showed an approximately 25% risk reduction of renal failure, doubling of serum creatinine, death due to kidney disease, or macroalbuminuria. Similar effects on macroalbuminuria have been shown with other GLP-1 receptor agonists, such semaglutide (SUSTAIN-6), dulaglutide (REWIND and AWARD-7)), efpeglenatide (AMPLITUDE), lixisenatide (ELIXA) and the dual receptor agonist tirzepatide (SURPASS-4) [123].

GLP-1 receptor agonists are contraindicated in patients with a prior history of medullary thyroid cancer and should be used with caution in those with a history of pancreatitis. These drugs are effective glucose-lowering therapies in patients at high CVD risk [124]. GIP and GLP-1 have anti-inflammatory, anti-reactive oxygen species effects that may benefit the vasculature [123] and by also inhibiting macrophage infiltration and increasing nitric oxide production (GIP) [123], these agonists may confer cardiovascular protection that benefits the kidney in people with MAFLD/MASLD. Patients with MAFLD/MASLD benefit from weight loss not only to benefit liver disease in MAFLD/MASLD but also to treat T2DM. Assuming there is no contradiction to treatment, there is a strong case for prescribing incretin receptor agonist agents as first-line treatments. Although GLP-1 receptor agonist drugs may commonly cause gastrointestinal side effects, they are well tolerated. That said, this class of drugs should be used with caution in people who have had previous pancreatitis or with concomitant use of sulphonylureas or insulin treatment because of the risk of hypoglycemia. More data on tirzepatide, a dual GIP and GLP-1 receptor agonist that predominantly affects GIP rather than GLP-1, will be forthcoming in the foreseeable future. For example, the SURPASS-CVOT (NCT04255433) is a large cardiovascular outcomes trial that compares the cardiovascular safety of tirzepatide against 1.5 mg dulaglutide. This trial will evaluate three major adverse cardiovascular event endpoints (myocardial infarction, stroke, and cardiovascular death), last up to 54 months and is scheduled to end in October 2024 [125]. However, a meta-analysis of data from 4,887 participants treated with tirzepatide versus 2,328 control participants showed a point estimate HR of 0.80 (95% CI 0.57-1.11) for major adverse cardiovascular events, 0.90 (95% CI 0.50, 1.61) for cardiovascular mortality and 0.80 (95% CI 0.51-1.25) for all-cause mortality [126]. Thus, there is a very good case for early treatment of subjects with MASLD who are obese to decrease their risk of developing adverse cardiovascular and renal outcomes.

Renin-angiotensin-system inhibitors

It is now widely acknowledged that ACE inhibitors and angiotensin II receptor blockers are clinically effective and benefit a range of adverse cardiovascular, renal and diabetes-related outcomes.

However, it has proved very difficult to test the proposed antifibrotic effects of angiotensin II receptor blockers on liver fibrosis [127] in adult patients with NAFLD/MAFLD because co-existing cardio-metabolic diseases necessitate treatment of affected patients with these drugs. Either angiotensin II receptor blockers or ACE inhibitors are frequently used for their proven benefits in patients with T2DM, CVD, or CKD, and most patients with these conditions will most likely be treated with one of these classes of drugs. However, the NASH-Clinical Research Network recently undertook a multicentre, double-masked, placebo-controlled, randomized clinical trial in children (age 8-17 years) with histologically confirmed NAFLD. Children received 100 mg of losartan or placebo orally once daily for 24 weeks. The primary outcome was a change in serum ALT levels from baseline to 24 weeks, and the sample size was n=110. Eighty-three participants were randomized to losartan or placebo, and in an unplanned interim analysis due to the COVID-19 pandemic, there was a low probability of a significant group difference. The Data and Safety Monitoring Board recommended early study termination. Compliance with pill counts and numbers and types of adverse events did not differ by groups, suggesting a null effect of losartan on the liver compared to placebo [128]. Finerenone is a new nonsteroidal, selective mineralocorticoid receptor antagonist, and although its effect on liver disease in MASLD is uncertain [129], treatment with finerenone has been shown to result in lower risks of CKD progression and adverse cardiovascular outcomes in people with T2DM with CKD [130]. Thus, similar to the use of angiotensin II receptor blockers and ACE inhibitors (and also SGLT2 inhibitors), regardless of whether there is any benefit on the liver, these classes of drugs can have a place in the treatment of MASLD, where there is evidence of CKD or where patients are considered to be at high risk of CKD.

6. Conclusions and future directions

The change of terminology and diagnostic criteria of NAFLD has been the subject of ongoing intense debate in the medical community. The rationale of the recent proposal to change from NAFLD to MAFLD and MASLD is intended to address the inherent limitations associated with the term NAFLD and to highlight the key insights into the metabolic pathological mechanisms leading to the development and progression of this common liver disease. The mechanistic links connecting MASLD and CKD are complex and multifactorial and involve various tissues contributing to renal and hepatic dysfunction via direct and indirect mechanisms likely exacerbated by a range of genetic risk factors. Although further evidence is needed in each of the subgroups of MASLD, which have different types of metabolic dysfunction, several different classes of drugs are now known to be of proven benefit in people with, or without, T2DM who are at high risk of CVD and CKD. These drugs should, therefore, be considered for people with MASLD, particularly where subjects have CVD or CKD or are at high risk of these adverse outcomes. These drugs include angiotensin II receptor

blockers or renin-angiotensin-system inhibitors, SGLT2 inhibitors, PPAR-γ agonists such as pioglitazone, and incretin receptor agonists. Regardless of whether there is a benefit on fatty liver disease, these classes of drugs have a place in the treatment of MASLD, specifically where there is evidence of CKD or where patients are considered at high risk of CKD. Since many people living with MASLD are also at high CVD risk (or may have established CVD), healthcare professionals should assess the global cardiovascular risk and advise treatment with a statin where appropriate.

Search strategy and selection criteria

References for this clinical narrative review were identified by the authors through searches of PubMed with the search terms “NAFLD” OR “non-alcoholic fatty liver disease” OR “non-alcoholic steatohepatitis” OR “NASH” OR “metabolic dysfunction-associated fatty liver disease” OR “MAFLD” OR “metabolic dysfunction-associated steatotic liver disease” OR “MASLD” AND “chronic kidney disease” OR “CKD” OR “kidney dysfunction” OR “drug treatment” OR “pharmacotherapy” OR “clinical trials”. We have searched up to October 31, 2023. We have considered the relevant literature cited in these papers. Only articles published in English were considered. The final reference list was generated based on originality and relevance to the broad scope of this review.

Figure legends

Figure 1 – Comparison between diagnostic criteria proposed for identifying nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD) and metabolic dysfunction-associated steatotic liver disease (MASLD). The figure shows the evolution of terminology and diagnostic criteria of the change from NAFLD to MAFLD and MASLD. The principal limitations of the term NAFLD are the reliance on exclusionary confounder terms and the use of potentially stigmatizing language. In the last 2-3 years, two new nomenclatures and a set of “positive” diagnostic criteria have been proposed for identifying steatotic liver disease that better reflects the pathophysiological link between metabolic dysfunction and this highly prevalent liver disease.

Figure 2 – Adipose tissue, gut dysfunction and renal lipid accumulation can contribute to CKD development and progression and form a cycle of worsening disease severity. Non-renal obesity-associated adipose tissue and intestinal dysfunction contribute to renal dysfunction and CKD

via various mechanisms. Renal adipose tissue and parenchymal lipid droplet accumulation contribute to alterations in renal hydrostatic pressure, inflammation and fibrosis and are key characteristics of CKD. Elevated uremic toxin concentrations resulting from insufficient urea clearance may exacerbate adipose tissue inflammation and intestinal permeability, contributing to systemic metabolic and renal dysfunction, thus potentially forming a cycle of worsening disease severity. Genetic risk factors, such as the *PNPLA3*-I148M variant, may directly affect renal function, which could include (amongst other things) altering renal lipid droplet composition that may also drive kidney dysfunction and CKD.

Abbreviations: SCFAs; short-chain fatty acids, LPS; lipopolysaccharide, BAs; bile acids, ROS; reactive oxygen species, eGFR; estimate glomerular filtration rate, PUFA; poly-unsaturated fatty acid.

Figure 3 – Putative mechanisms underlying the increased risk of CKD associated with the *PNPLA3*-I148M genetic variant. The presence of the *PNPLA3*-I148M variant is known to contribute to increased hepatic LD accumulation, inflammation and fibrosis via disrupting TAG lipolysis and activating inflammatory and hepatic stellate cells – such effects of the *PNPLA3*-I148M variant could drive CKD indirectly via the exacerbation of systemic metabolic dysfunction subsequently resulting in renal dysfunction. Additionally, the *PNPLA3*-I148M variant likely directly affects the kidney, especially renal podocytes. This genetic variant is known to reduce the hydrolytic and retinyl-palmitate lipase activity of the PNPLA3 protein, which, in turn, may reduce the release of PUFAs, retinol and glycerol, increasing LD accumulation and renal inflammation. While speculative, the increased renal podocyte LD accumulation partially driven by the *PNPLA3*-I148M variant may result in LD-induced nucleus indentation, contributing to cellular dysfunction and the production of reactive oxygen species, which may contribute to renal dysfunction and CKD.

Abbreviations: LD; lipid droplet, TAG; triglyceride, PUFA; polyunsaturated fatty acid, ROS; reactive oxygen species.

Figure 4 – Potential drug treatments for MASLD with CKD: potential direct and indirect actions of treatments on processes relevant to liver disease, cardiovascular risk factors, and CKD. Potential pharmacotherapies for MAFLD and CKD include sodium-glucose cotransporter 2 (SGLT2) inhibitors, incretin receptor agonists (e.g., glucagon-like peptide-1 [GLP-1] receptor agonists, glucose-dependent insulinotropic polypeptide [GIP] agonists, or dual GLP-1 and GIP receptor co-agonists), peroxisome proliferator-activated receptor (PPAR)-gamma agonists (pioglitazone), angiotensin II receptor blockers (AT-II), renin-angiotensin system (RAS) inhibitors or mineralocorticoid receptor antagonists. Although not all these drug classes have been shown to benefit steatotic liver disease in MASLD, these drugs have been shown to benefit kidney disease and cardiovascular risk factors (e.g., hypertension) that is very relevant to a holistic approach to

treating MASLD as a multisystem disease. GLP-1 receptor agonists have proven efficacy to benefit T2DM, CVD and CKD. GLP-1 receptor agonists are effective in the brain by decreasing appetite and inducing satiety, and by reducing dietary calorie intake. These effects can facilitate weight loss, which in turn benefits MASLD as well as T2DM and cardiovascular risk factors. Dual GLP-1 and GIP receptor co-agonists might be more effective at promoting weight loss than GLP-1 receptor agonists alone. Thus, dual GLP-1 and GIP receptor co-agonists might prove to be very effective treatments for MASLD, as well as the extrahepatic complications of MASLD as a multisystem disease.

Abbreviations: MASLD; metabolic dysfunction-associated steatotic liver disease, GIP; glucose-dependent insulinotropic polypeptide, GLP-1; glucagon-like peptide-1, TNF-α; tumour necrosis factor-α.

References

[1] Wong VW, Ekstedt M, Wong GL, Hagstrom H. Changing epidemiology, global trends and implications for outcomes of NAFLD. J Hepatol 2023;79(3):842-52.

[2] Karlsen TH, Sheron N, Zelber-Sagi S, Carrieri P, Dusheiko G, Bugianesi E, et al. The EASL-Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. Lancet 2022;399(10319):61-116.

[3] Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. JAMA 2019;322(13):1294-304.

[4] Byrne CD, Targher G. NAFLD as a driver of chronic kidney disease. J Hepatol 2020;72(4):785-801.

[5] Mantovani A, Petracca G, Beatrice G, Csermely A, Lonardo A, Schattenberg JM, et al. Non-alcoholic fatty liver disease and risk of incident chronic kidney disease: an updated meta-analysis. Gut 2022;71(1):156-62.

[6] Theofilis P, Vordoni A, Kalaitzidis RG. Interplay between metabolic dysfunction-associated fatty liver disease and chronic kidney disease: Epidemiology, pathophysiologic mechanisms, and treatment considerations. World J Gastroenterol 2022;28(39):5691-706.

[7] Zhou XD, Targher G, Byrne CD, Somers V, Kim SU, Chahal CAA, et al. An international multidisciplinary consensus statement on MAFLD and the risk of CVD. Hepatol Int 2023;17(4):773-91.

[8] Sun DQ, Targher G, Byrne CD, Wheeler DC, Wong VW, Fan JG, et al. An international Delphi consensus statement on metabolic dysfunction-associated fatty liver disease and risk of chronic kidney disease. Hepatobiliary Surg Nutr 2023;12(3):386-403.

[9] Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980;55(7):434-8.

[10] Schaffner F, Thaler H. Nonalcoholic fatty liver disease. Prog Liver Dis 1986;8:283-98.

[11] Gofton C, Upendran Y, Zheng MH, George J. MAFLD: How is it different from NAFLD? Clin Mol Hepatol 2023;29(Suppl):S17-S31.
[12] Targher G, Corey KE, Byrne CD, Roden M. The complex link between NAFLD and type 2 diabetes mellitus - mechanisms and treatments. Nat Rev Gastroenterol Hepatol 2021;18(9):599-612.
[13] Lim S, Kim JW, Targher G. Links between metabolic syndrome and metabolic dysfunction-associated fatty liver disease. Trends Endocrinol Metab 2021;32(7):500-14.
[14] Targher G, Byrne CD. From nonalcoholic fatty liver disease to metabolic dysfunction-associated fatty liver disease: is it time for a change of terminology? Hepatoma Research 2020;6:64.
[15] George J. Adding to the confusion in more than just the name. Clin Mol Hepatol 2023;29(4):973-6.
[16] Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73(1):202-9.
[17] Eslam M, Sarin SK, Wong VW, Fan JG, Kawaguchi T, Ahn SH, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatol Int 2020;14(6):889-919.
[18] Shiha G, Alswat K, Al Khatry M, Sharara AI, Ormeci N, Waked I, et al. Nomenclature and definition of metabolic-associated fatty liver disease: a consensus from the Middle East and north Africa. Lancet Gastroenterol Hepatol 2021;6(1):57-64.
[19] Nan Y, An J, Bao J, Chen H, Chen Y, Ding H, et al. The Chinese Society of Hepatology position statement on the redefinition of fatty liver disease. J Hepatol 2021;75(2):454-61.
[20] Mendez-Sanchez N, Bugianesi E, Gish RG, Lammert F, Tilg H, Nguyen MH, et al. Global multi-stakeholder endorsement of the MAFLD definition. Lancet Gastroenterol Hepatol 2022;7(5):388-90.
[21] Eslam M, Ratziu V, George J. Yet more evidence that MAFLD is more than a name change. J Hepatol 2021;74(4):977-9.
[22] Lin S, Huang J, Wang M, Kumar R, Liu Y, Liu S, et al. Comparison of MAFLD and NAFLD diagnostic criteria in real world. Liver Int 2020;40(9):2082-9.
[23] Sung KC, Yoo TK, Lee MY, Byrne CD, Zheng MH, Targher G. Comparative Associations of Nonalcoholic Fatty Liver Disease and Metabolic Dysfunction-Associated Fatty Liver Disease With Coronary Artery Calcification: A Cross-Sectional and Longitudinal Cohort Study. Arterioscler Thromb Vasc Biol 2023;43(3):482-91.
[24] Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023.
[25] Ciardullo S, Carbone M, Invernizzi P, Perseghin G. Exploring the landscape of steatotic liver disease in the general US population. Liver Int 2023;43(11):2425-33.
[26] Yang A, Zhu X, Zhang L, Ding Y. Transitioning from NAFLD to MAFLD and MASLD: Consistent prevalence and risk factors in a Chinese cohort. J Hepatol 2023.
[27] Perazzo H, Pacheco AG, Griep RH, Collaborators. Changing from NAFLD through MAFLD to MASLD: Similar prevalence and risk factors in a large Brazilian cohort. J Hepatol 2023.
[28] Zhao Q, Deng Y. Comparison of mortality outcomes in individuals with MASLD and/or MAFLD. J Hepatol 2023.
[29] Targher G, Chonchol M, Bertolini L, Rodella S, Zenari L, Lippi G, et al. Increased risk of CKD among type 2 diabetics with nonalcoholic fatty liver disease. J Am Soc Nephrol 2008;19(8):1564-70.

[30] Chang Y, Ryu S, Sung E, Woo HY, Oh E, Cha K, et al. Nonalcoholic fatty liver disease predicts chronic kidney disease in nonhypertensive and nondiabetic Korean men. Metabolism 2008;57(4):569-76.
[31] Sanyal AJ, Van Natta ML, Clark J, Neuschwander-Tetri BA, Diehl A, Dasarathy S, et al. Prospective Study of Outcomes in Adults with Nonalcoholic Fatty Liver Disease. N Engl J Med 2021;385(17):1559-69.
[32] Zuo G, Xuan L, Xin Z, Xu Y, Lu J, Chen Y, et al. New Nonalcoholic Fatty Liver Disease and Fibrosis Progression Associate With the Risk of Incident Chronic Kidney Disease. J Clin Endocrinol Metab 2021;106(10):e3957-e68.
[33] Li M, Zhao Z, Qin G, Chen L, Lu J, Huo Y, et al. Non-alcoholic fatty liver disease, metabolic goal achievement with incident cardiovascular disease and eGFR-based chronic kidney disease in patients with prediabetes and diabetes. Metabolism 2021;124:154874.
[34] Liang Y, Chen H, Liu Y, Hou X, Wei L, Bao Y, et al. Association of MAFLD With Diabetes, Chronic Kidney Disease, and Cardiovascular Disease: A 4.6-Year Cohort Study in China. J Clin Endocrinol Metab 2022;107(1):88-97.
[35] Hashimoto Y, Hamaguchi M, Okamura T, Nakanishi N, Obora A, Kojima T, et al. Metabolic associated fatty liver disease is a risk factor for chronic kidney disease. J Diabetes Investig 2022;13(2):308-16.
[36] Jung CY, Koh HB, Park KH, Joo YS, Kim HW, Ahn SH, et al. Metabolic dysfunction-associated fatty liver disease and risk of incident chronic kidney disease: A nationwide cohort study. Diabetes Metab 2022;48(4):101344.
[37] Wei S, Song J, Xie Y, Huang J, Yang J. Metabolic dysfunction-associated fatty liver disease can significantly increase the risk of chronic kidney disease in adults with type 2 diabetes. Diabetes Res Clin Pract 2023;197:110563.
[38] Kwon SY, Park J, Park SH, Lee YB, Kim G, Hur KY, et al. MAFLD and NAFLD in the prediction of incident chronic kidney disease. Sci Rep 2023;13(1):1796.
[39] Chen S, Pang J, Huang R, Xue H, Chen X. Association of MAFLD with end-stage kidney disease: a prospective study of 337,783 UK Biobank participants. Hepatol Int 2023;17(3):595-605.
[40] Tanaka M, Mori K, Takahashi S, Higashiura Y, Ohnishi H, Hanawa N, et al. Metabolic dysfunction-associated fatty liver disease predicts new onset of chronic kidney disease better than fatty liver or nonalcoholic fatty liver disease. Nephrol Dial Transplant 2023;38(3):700-11.
[41] Mantovani A, Csermely A, Petracca G, Beatrice G, Corey KE, Simon TG, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2021;6(11):903-13.
[42] Miyamori D, Tanaka M, Sato T, Endo K, Mori K, Mikami T, et al. Coexistence of Metabolic Dysfunction-Associated Fatty Liver Disease and Chronic Kidney Disease Is a More Potent Risk Factor for Ischemic Heart Disease. J Am Heart Assoc 2023;12(14):e030269.
[43] Hydes TJ, Kennedy OJ, Buchanan R, Cuthbertson DJ, Parkes J, Fraser SDS, et al. The impact of non-alcoholic fatty liver disease and liver fibrosis on adverse clinical outcomes and mortality in patients with chronic kidney disease: a prospective cohort study using the UK Biobank. BMC Med 2023;21(1):185.
[44] Terasaka Y, Takahashi H, Amano K, Fujisaki K, Kita S, Kato K, et al. Change in Liver Fibrosis Associates with Progress of Diabetic Nephropathy in Patients with Nonalcoholic Fatty Liver Disease. Nutrients 2023;15(14).
[45] Noels H, Lehrke M, Vanholder R, Jankowski J. Lipoproteins and fatty acids in chronic kidney disease: molecular and metabolic alterations. Nat Rev Nephrol 2021;17(8):528-42.

[46] Charlton A, Garzarella J, Jandeleit-Dahm KAM, Jha JC. Oxidative Stress and Inflammation in Renal and Cardiovascular Complications of Diabetes. Biology 2020;10(1).
[47] Lonardo A, Mantovani A, Targher G, Baffy G. Nonalcoholic Fatty Liver Disease and Chronic Kidney Disease: Epidemiology, Pathogenesis, and Clinical and Research Implications. Int J Mol Sci 2022;23(21).
[48] Baffy G, Bosch J. Overlooked subclinical portal hypertension in non-cirrhotic NAFLD: Is it real and how to measure it? J Hepatol 2022;76(2):458-63.
[49] Yang M, Luo S, Yang J, Chen W, He L, Liu D, et al. Crosstalk between the liver and kidney in diabetic nephropathy. European journal of pharmacology 2022;931:175219.
[50] Cheung A, Ahmed A. Nonalcoholic Fatty Liver Disease and Chronic Kidney Disease: A Review of Links and Risks. Clin Exp Gastroenterol 2021;14:457-65.
[51] Post A, Dam WA, Sokooti S, Groothof D, Gloerich J, van Gool AJ, et al. Circulating FGF21 Concentration, Fasting Plasma Glucose, and the Risk of Type 2 Diabetes: Results From the PREVEND Study. J Clin Endocrinol Metab 2023;108(6):1387-93.
[52] Salgado JV, Goes MA, Salgado Filho N. FGF21 and Chronic Kidney Disease. Metabolism: clinical and experimental 2021;118:154738.
[53] Tucker B, Li H, Long X, Rye KA, Ong KL. Fibroblast growth factor 21 in non-alcoholic fatty liver disease. Metabolism: clinical and experimental 2019;101:153994.
[54] Velingkar A, Vuree S, Prabhakar PK, Kalashikam RR, Banerjee A, Kondeti S. Fibroblast growth factor 21 as a potential master regulator in metabolic disorders. American Journal of Physiology-Endocrinology and Metabolism 2023;324(5):E409-E24.
[55] Mitrofanova A, Merscher S, Fornoni A. Kidney lipid dysmetabolism and lipid droplet accumulation in chronic kidney disease. Nat Rev Nephrol 2023;19(10):629-45.
[56] Hammoud SH, AlZaim I, Al-Dhaheri Y, Eid AH, El-Yazbi AF. Perirenal Adipose Tissue Inflammation: Novel Insights Linking Metabolic Dysfunction to Renal Diseases. Front Endocrinol (Lausanne) 2021;12:707126.
[57] D'Marco L, Salazar J, Cortez M, Salazar M, Wettel M, Lima-Martínez M, et al. Perirenal fat thickness is associated with metabolic risk factors in patients with chronic kidney disease. Kidney Res Clin Pract 2019;38(3):365-72.
[58] Jiang Z, Wang Y, Zhao X, Cui H, Han M, Ren X, et al. Obesity and chronic kidney disease. American journal of physiology Endocrinology and metabolism 2023;324(1):E24-e41.
[59] Qi X-Y, Qu S-L, Xiong W-H, Rom O, Chang L, Jiang Z-S. Perivascular adipose tissue (PVAT) in atherosclerosis: a double-edged sword. Cardiovasc Diabetol 2018;17(1):134.
[60] Loneker AE, Alisafaei F, Kant A, Li D, Janmey PA, Shenoy VB, et al. Lipid droplets are intracellular mechanical stressors that impair hepatocyte function. Proc Natl Acad Sci U S A 2023;120(16):e2216811120.
[61] Martin-Taboada M, Vila-Bedmar R, Medina-Gómez G. From Obesity to Chronic Kidney Disease: How Can Adipose Tissue Affect Renal Function? Nephron 2021;145(6):609-13.
[62] Arabi T, Shafqat A, Sabbah BN, Fawzy NA, Shah H, Abdulkader H, et al. Obesity-related kidney disease: Beyond hypertension and insulin-resistance. Front Endocrinol (Lausanne) 2022;13:1095211.
[63] Bilson J, Sethi JK, Byrne CD. Heterogeneity of white adipocytes in metabolic disease. Curr Opin Clin Nutr Metab Care 2023.
[64] Duerre DJ, Galmozzi A. Deconstructing Adipose Tissue Heterogeneity One Cell at a Time. Front Endocrinol (Lausanne) 2022;13:847291.
[65] Whytock KL, Sun Y, Divoux A, Yu G, Smith SR, Walsh MJ, et al. Single cell full-length transcriptome of human subcutaneous adipose tissue reveals unique and heterogenous cell populations. iScience 2022:104772.

[66] Chen H, Tan H, Wan J, Zeng Y, Wang J, Wang H, et al. PPAR-γ signaling in nonalcoholic fatty liver disease: Pathogenesis and therapeutic targets. Pharmacology & Therapeutics 2023;245:108391.
[67] Ma Y, Shi M, Wang Y, Liu J. PPARγ and Its Agonists in Chronic Kidney Disease. Int J Nephrol 2020;2020:2917474.
[68] Tsuchida T, Friedman SL. Mechanisms of hepatic stellate cell activation. Nature Reviews Gastroenterology & Hepatology 2017;14(7):397-411.
[69] Krukowski H, Valkenburg S, Madella AM, Garssen J, van Bergenhenegouwen J, Overbeek SA, et al. Gut microbiome studies in CKD: opportunities, pitfalls and therapeutic potential. Nat Rev Nephrol 2023;19(2):87-101.
[70] Bilson J, Sethi JK, Byrne CD. Non-alcoholic fatty liver disease: a multi-system disease influenced by ageing and sex, and affected by adipose tissue and intestinal function. The Proceedings of the Nutrition Society 2022;81(2):146-61.
[71] Beker BM, Colombo I, Gonzalez-Torres H, Musso CG. Decreasing microbiota-derived uremic toxins to improve CKD outcomes. Clinical Kidney Journal 2022;15(12):2214-9.
[72] Salguero MV, Al-Obaide MAI, Singh R, Siepmann T, Vasylyeva TL. Dysbiosis of Gram-negative gut microbiota and the associated serum lipopolysaccharide exacerbates inflammation in type 2 diabetic patients with chronic kidney disease. Exp Ther Med 2019;18(5):3461-9.
[73] Kim DH, Park JS, Choi HI, Kim CS, Bae EH, Ma SK, et al. The role of the farnesoid X receptor in kidney health and disease: a potential therapeutic target in kidney diseases. Exp Mol Med 2023;55(2):304-12.
[74] Wang X, Yang S, Li S, Zhao L, Hao Y, Qin J, et al. Aberrant gut microbiota alters host metabolome and impacts renal failure in humans and rodents. Gut 2020;69(12):2131-42.
[75] Zhang YL, Li ZJ, Gou HZ, Song XJ, Zhang L. The gut microbiota-bile acid axis: A potential therapeutic target for liver fibrosis. Front Cell Infect Microbiol 2022;12:945368.
[76] Miyazaki-Anzai S, Masuda M, Shiozaki Y, Keenan AL, Chonchol M, Kremoser C, et al. Free Deoxycholic Acid Exacerbates Vascular Calcification in CKD through ER Stress-Mediated ATF4 Activation. Kidney360 2021;2(5):857-68.
[77] Mutengo KH, Masenga SK, Mweemba A, Mutale W, Kirabo A. Gut microbiota dependant trimethylamine N-oxide and hypertension. Front Physiol 2023;14:1075641.
[78] Chen Y-m, Liu Y, Zhou R-f, Chen X-l, Wang C, Tan X-y, et al. Associations of gut-flora-dependent metabolite trimethylamine-N-oxide, betaine and choline with non-alcoholic fatty liver disease in adults. Scientific Reports 2016;6(1):19076.
[79] Magliocca G, Mone P, Di Iorio BR, Heidland A, Marzocco S. Short-Chain Fatty Acids in Chronic Kidney Disease: Focus on Inflammation and Oxidative Stress Regulation. Int J Mol Sci 2022;23(10).
[80] Yang T, Richards EM, Pepine CJ, Raizada MK. The gut microbiota and the brain-gut-kidney axis in hypertension and chronic kidney disease. Nat Rev Nephrol 2018;14(7):442-56.
[81] Stavropoulou E, Kantartzi K, Tsigalou C, Konstantinidis T, Romanidou G, Voidarou C, et al. Focus on the Gut-Kidney Axis in Health and Disease. Front Med (Lausanne) 2020;7:620102.
[82] Wang TY, Wang RF, Bu ZY, Targher G, Byrne CD, Sun DQ, et al. Association of metabolic dysfunction-associated fatty liver disease with kidney disease. Nat Rev Nephrol 2022;18(4):259-68.
[83] Mantovani A, Zusi C. PNPLA3 gene and kidney disease. Exploration of Medicine 2020;1(1):42-50.

[84] Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nature Genetics 2008;40(12):1461-5.
[85] Meroni M, Longo M, Tria G, Dongiovanni P. Genetics Is of the Essence to Face NAFLD. Biomedicines 2021;9(10).
[86] Mantovani A, Taliento A, Zusi C, Baselli G, Prati D, Granata S, et al. PNPLA3 I148M gene variant and chronic kidney disease in type 2 diabetic patients with NAFLD: Clinical and experimental findings. Liver international : official journal of the International Association for the Study of the Liver 2020;40(5):1130-41.
[87] Mantovani A, Pelusi S, Margarita S, Malvestiti F, Dell'Alma M, Bianco C, et al. Adverse effect of PNPLA3 p.I148M genetic variant on kidney function in middle-aged individuals with metabolic dysfunction. Aliment Pharmacol Ther 2023;57(10):1093-102.
[88] Musso G, Cassader M, Gambino R. PNPLA3 rs738409 and TM6SF2 rs58542926 gene variants affect renal disease and function in nonalcoholic fatty liver disease. Hepatology 2015;62(2):658-9.
[89] Targher G, Mantovani A, Alisi A, Mosca A, Panera N, Byrne CD, et al. Relationship Between PNPLA3 rs738409 Polymorphism and Decreased Kidney Function in Children With NAFLD. Hepatology 2019;70(1):142-53.
[90] Mantovani A, Zusi C, Sani E, Colecchia A, Lippi G, Zaza GL, et al. Association between PNPLA3rs738409 polymorphism decreased kidney function in postmenopausal type 2 diabetic women with or without non-alcoholic fatty liver disease. Diabetes & metabolism 2019;45(5):480-7.
[91] Oniki K, Saruwatari J, Izuka T, Kajiwara A, Morita K, Sakata M, et al. Influence of the PNPLA3 rs738409 Polymorphism on Non-Alcoholic Fatty Liver Disease and Renal Function among Normal Weight Subjects. PloS one 2015;10(7):e0132640.
[92] Pingitore P, Pirazzi C, Mancina RM, Motta BM, Indiveri C, Pujia A, et al. Recombinant PNPLA3 protein shows triglyceride hydrolase activity and its I148M mutation results in loss of function. Biochim Biophys Acta 2014;1841(4):574-80.
[93] Luukkonen PK, Nick A, Hölttä-Vuori M, Thiele C, Isokuortti E, Lallukka-Brück S, et al. Human PNPLA3-I148M variant increases hepatic retention of polyunsaturated fatty acids. JCI insight 2019;4(16).
[94] Mondul A, Mancina RM, Merlo A, Dongiovanni P, Rametta R, Montalcini T, et al. PNPLA3 I148M Variant Influences Circulating Retinol in Adults with Nonalcoholic Fatty Liver Disease or Obesity. The Journal of nutrition 2015;145(8):1687-91.
[95] Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023;77(5):1797-835.
[96] ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2023. Diabetes Care 2023;46(Suppl 1):S158-S90.
[97] Coelho FDS, Borges-Canha M, von Hafe M, Neves JS, Vale C, Leite AR, et al. Effects of sodium-glucose co-transporter 2 inhibitors on liver parameters and steatosis: A meta-analysis of randomized clinical trials. Diabetes Metab Res Rev 2021;37(6):e3413.
[98] Mantovani A, Petracca G, Csermely A, Beatrice G, Targher G. Sodium-Glucose Cotransporter-2 Inhibitors for Treatment of Nonalcoholic Fatty Liver Disease: A Meta-Analysis of Randomized Controlled Trials. Metabolites 2020;11(1).

[99] Borisov AN, Kutz A, Christ ER, Heim MH, Ebrahimi F. Canagliflozin and Metabolic Associated Fatty Liver Disease in Patients With Diabetes Mellitus: New Insights From CANVAS. J Clin Endocrinol Metab 2023;108(11):2940-9.
[100] Xu R, Lian D, Xie Y, Chen Z, Wang Y, Mu L, et al. SGLT-2 Inhibitors for Non-Alcoholic Fatty Liver Disease: A Review. Frontiers in bioscience (Landmark edition) 2023;28(7):134.
[101] Zelniker TA, Bonaca MP, Furtado RHM, Mosenzon O, Kuder JF, Murphy SA, et al. Effect of Dapagliflozin on Atrial Fibrillation in Patients With Type 2 Diabetes Mellitus. Circulation 2020;141(15):1227-34.
[102] Neal B, Perkovic V, Mahaffey KW, De Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. New England Journal of Medicine 2017;377(7):644-57.
[103] Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. New England Journal of Medicine 2020;383(15):1425-35.
[104] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine 2015;373(22):2117-28.
[105] Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine 2018;380(4):347-57.
[106] Sarafidis P, Ferro CJ, Morales E, Ortiz A, Malyszko J, Hojs R, et al. 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. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2019;34(2):208-30.
[107] Zhao Y, Xu L, Tian D, Xia P, Zheng H, Wang L, et al. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: A meta-analysis of randomized controlled trials. Diabetes Obes Metab 2018;20(2):458-62.
[108] Scheen AJ, Esser N, Paquot N. Antidiabetic agents: Potential anti-inflammatory activity beyond glucose control. Diabetes Metab 2015;41(3):183-94.
[109] Vallon V, Gerasimova M, Rose MA, Masuda T, Satriano J, Mayoux E, et al. SGLT2 inhibitor empagliflozin reduces renal growth and albuminuria in proportion to hyperglycemia and prevents glomerular hyperfiltration in diabetic Akita mice. American journal of physiology Renal physiology 2014;306(2):F194-204.
[110] Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366(9493):1279-89.
[111] DeFronzo RA, Inzucchi S, Abdul-Ghani M, Nissen SE. Pioglitazone: The forgotten, cost-effective cardioprotective drug for type 2 diabetes. Diabetes & vascular disease research 2019;16(2):133-43.
[112] EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64(6):1388-402.
[113] Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67(1):328-57.

[114] Francque SM, Bedossa P, Ratziu V, Anstee QM, Bugianesi E, Sanyal AJ, et al. A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH. N Engl J Med 2021;385(17):1547-58.
[115] Mantovani A, Byrne CD, Scorletti E, Mantzoros CS, Targher G. Efficacy and safety of anti-hyperglycaemic drugs in patients with non-alcoholic fatty liver disease with or without diabetes: An updated systematic review of randomized controlled trials. Diabetes Metab 2020;46(6):427-41.
[116] Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al. Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial. Ann Intern Med 2016;165(5):305-15.
[117] Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and Advanced Liver Fibrosis in Nonalcoholic Steatohepatitis: A Meta-analysis. JAMA internal medicine 2017;177(5):633-40.
[118] Yoshihara D, Kurahashi H, Morita M, Kugita M, Hiki Y, Aukema HM, et al. PPAR-gamma agonist ameliorates kidney and liver disease in an orthologous rat model of human autosomal recessive polycystic kidney disease. American journal of physiology Renal physiology 2011;300(2):F465-74.
[119] Zuo Y, Yang HC, Potthoff SA, Najafian B, Kon V, Ma LJ, et al. Protective effects of PPARγ agonist in acute nephrotic syndrome. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2012;27(1):174-81.
[120] Francque S, Szabo G, Abdelmalek MF, Byrne CD, Cusi K, Dufour JF, et al. Nonalcoholic steatohepatitis: the role of peroxisome proliferator-activated receptors. Nat Rev Gastroenterol Hepatol 2021;18(1):24-39.
[121] Targher G, Mantovani A, Byrne CD. Mechanisms and possible hepatoprotective effects of glucagon-like peptide-1 receptor agonists and other incretin receptor agonists in non-alcoholic fatty liver disease. The lancet Gastroenterology & hepatology 2023;8(2):179-91.
[122] Mantovani A, Byrne CD, Targher G. Efficacy of peroxisome proliferator-activated receptor agonists, glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors for treatment of non-alcoholic fatty liver disease: a systematic review. The lancet Gastroenterology & hepatology 2022;7(4):367-78.
[123] Mima A, Nomura A, Fujii T. Current findings on the efficacy of incretin-based drugs for diabetic kidney disease: A narrative review. Biomed Pharmacother 2023;165:115032.
[124] Brown E, Heerspink HJL, Cuthbertson DJ, Wilding JPH. SGLT2 inhibitors and GLP-1 receptor agonists: established and emerging indications. Lancet 2021;398(10296):262-76.
[125] A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes (SURPASS-CVOT). ClinicalTrialsgovID NCT04255433.
[126] Sattar N, McGuire DK, Pavo I, Weerakkody GJ, Nishiyama H, Wiese RJ, et al. Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis. Nature medicine 2022;28(3):591-8.
[127] Georgescu EF. Angiotensin receptor blockers in the treatment of NASH/NAFLD: could they be a first-class option? Advances in therapy 2008;25(11):1141-74.
[128] Vos MB, Van Natta ML, Blondet NM, Dasarathy S, Fishbein M, Hertel P, et al. Randomized placebo-controlled trial of losartan for pediatric NAFLD. Hepatology 2022;76(2):429-44.
[129] Perakakis N, Bornstein SR, Birkenfeld AL, Linkermann A, Demir M, Anker SD, et al. Efficacy of finerenone in patients with type 2 diabetes, chronic kidney disease and altered markers of liver steatosis and fibrosis: A FIDELITY subgroup analysis. Diabetes Obes Metab 2023.

[130] Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. N Engl J Med 2020;383(23):2219-29.

Table 1. Principal longitudinal studies assessing the association between steatotic liver disease and the risk of incident chronic kidney disease.

Author, Year, [Ref.]	**Study characteristics**	**Definition of** steatotic **liver disease; prevalence at baseline**	**Definition of** CKD**; incident cases**	Covariate a**djustments**	Main findings
Mantovani et al. 2022 [5]	Systematic review and meta-analysis: 13 longitudinal studies (published from inception date to August 2020) for a total of 1,222,032 adult individuals followed for a median of 9.7 years	NAFLD was diagnosed by blood-based biomarkers/scores, ICD codes, imaging methods or liver biopsy; 28.1% with NAFLD at baseline	eGFR <60 mL/min/1.73 m^2, with or without proteinuria; 33,840 cases of incident CKD	Age, sex, obesity, hypertension, diabetes, and other conventional CKD risk factors	NAFLD was associated with an increased risk of incident CKD (random-effect HR 1.43, 95%CI 1.33-1.54; I^2 =60.7%). The CKD risk appeared to be higher in those with advanced NAFLD
Sanyal et al 2021 [31]	A multicenter cohort of 1773 United States adult patients with NASH and different stages of liver fibrosis from the NASH Clinical Research Network. Median follow-up: 4 years	NASH was diagnosed by liver biopsy	Decrease of more than 40% in eGFR from baseline	Age, sex, race, diabetes status, and baseline histologic liver severity	As compared with patients with stage F0 to F2 fibrosis, patients with stage F4 fibrosis had a decrease of more than 40% in the eGFR (2.98 vs. 0.97 events per 100 person-years; HR 1.9; 95% 1.1-3.4)
Zuo et al. 2021 [32]	Community-based prospective study: 4042 adult individuals free of CKD at baseline. Mean follow-up: 4.4 years.	Changes in NAFLD status was diagnosed by ultrasonography and NAFLD fibrosis score (NFS) was used to evaluate fibrosis stage and progression; at baseline, 29.4% had NAFLD	eGFR <60 mL/min/1.73 m^2 or abnormal albuminuria; 355 cases of incident CKD	Age, sex, smoking status, drinking status, physical activity, BMI, systolic blood pressure, HbA1c, white blood cell count, lipids, baseline eGFR, and medications changes for incident diabetes, hypertension or obesity status	NAFLD development and fibrosis progression were associated with an increased risk of incident CKD (adjusted-HR 1.44; 95%CI, 1.01-2.06). The risk of incident CKD was not significantly different between

					NAFLD resolution and persistent NAFLD. Fibrosis progression from low NFS to intermediate or high NFS was associated with a significantly increased risk of incident CKD compared with those with stable fibrosis in low NFS
Li et al. 2021 [33]	Population-based prospective cohort study: 101,296 Chinese patients with prediabetes or diabetes from the China Cardiometabolic Disease and Cancer Cohort (notably, only 64,533 were included in the analysis of incident CKD). Mean follow-up: 3.8 years	NAFLD was diagnosed by FLI ≥60; at baseline, 20.1% had NAFLD	eGFR <60 mL/min per 1.73 m^2 and/or a >50% decrease in eGFR from baseline, renal replacement therapy and/or CKD-related death; 1943 cases of incident CKD	Age, sex, education level, smoking status, alcohol consumption, physical activity, HbA1c goal achievement (<6.5% or ≥6.5%), blood pressure goal achievement (<130/80 mmHg or not), and LDL-cholesterol goal achievement (<100 mg/dL or ≥100 mg/dL)	Compared with those without NAFLD, patients with NAFLD and pre-diabetes (adjusted-HR 1.42; 95% CI 1.22–1.66) and those with NAFLD and type 2 diabetes (adjusted-HR 1.25; 95% CI 1.08–1.44) had a higher risk of incident CKD
Liang et al 2022 [34]	Longitudinal study: 6873 Chinese adult individuals from the Shanghai Nicheng Cohort Study. Median follow-up: 4.6 years	NAFLD and MAFLD were diagnosed by ultrasonography. Patients were categorized in NAFLD or MAFLD; at baseline, 40.3% had NAFLD and 46.7% had MAFLD	eGFR <60 mL/min/1.73 m^2 and/or abnormal albuminuria; 1606 cases of incident CKD	Age, sex, educational level, smoking, and leisure-time exercise at baseline	MAFLD was associated with a higher risk of incident CKD (adjusted-HR 1.64; 95%CI 1.39-1.94). Similar association for NAFLD was observed (adjusted-HR 1.70, 95%CI 1.43-2.01). The change from NAFLD to MAFLD did not significantly affect the associations with CKD
Hashimoto et al. 2022 [35]	Cross-sectional and longitudinal study: 16,938 of 27,371 participants	MAFLD was diagnosed by ultrasonography; at baseline, 19.6% had MAFLD	eGFR <60 mL/min/1.73 m^2 and/or proteinuria	Age, sex, physical activity, smoking status, and alcohol use	Compared with the non-FLD without metabolic dysfunction, MAFLD

	(included in the cross-sectional analysis) were followed for a median period of 4.6 years				was associated with the risk of incident CKD (adjusted-HR 1.24, 95%CI 1.14-1.36). MAFLD was associated with a higher risk of CKD, whereas FLD without MD was not
Jung et al. 2022 [36]	Longitudinal study: 268,946 Korean participants aged 40-64 years, who underwent National Health Insurance Service health examinations between 2009 and 2015. Median follow-up: 5.1 years	NAFLD and MAFLD were diagnosed by FLI ≥30. Patients were categorized in NAFLD or MAFLD; at baseline, 27.4% participants had NAFLD and 33% had MAFLD	eGFR <60 mL/min/1.73m^2 or proteinuria on two consecutive health examinations; 8,335 cases of incident CKD	Age, sex, income level, hypertension, diabetes mellitus, heart failure, cerebrovascular disease, ischemic heart disease, exercise frequency, alcohol intake, smoking, use of lipid-lowering agents, NSAIDs or anti-platelet drugs, LDL-cholesterol, serum transaminases, and baseline creatinine	Compared to non-NAFLD participants, those with NAFLD had an increased risk of incident CKD (adjusted-HR 1.33, 95%CI 1.27-1.39). Compared to non-MAFLD participants, those with MAFLD had an increased risk of incident CKD (adjusted-HR 1.39, 95% CI 1.33-1.46). MAFLD identified a numerically greater proportion of individuals at risk of developing CKD than NAFLD
Wei et al. 2023 [37]	Longitudinal study: 3,627 Chinese individuals with T2DM who had received at least three health examinations between 2008 and 2015. Median follow-up: 10 years	MAFLD was diagnosed by ultrasonography; 61.6% with MAFLD at baseline	eGFR <60 mL/min/1.73 m^2 or proteinuria; 837 cases of incident CKD	Age, sex, obesity, hypertension, dyslipidemia, LDL-cholesterol, serum transaminases, and baseline eGFR	MAFLD was associated with an increased risk of incident CKD (adjusted-HR 1.28, 95%CI 1.09-1.50), especially in those aged <60 years
Kwon et al. 2023 [38]	Longitudinal retrospective study: 21,713 South Korean adults who underwent at least two serial health examinations.	NAFLD and MAFLD were diagnosed by ultrasonography. Patients were categorized in NAFLD or MAFLD; at baseline, 2.2% participants had NAFLD-only, 8.2% had	eGFR <60 mL/min/1.73 m^2 and/or abnormal albuminuria at the time of first health examination; 912 cases of incident CKD	Age, sex, BMI, baseline eGFR, smoking, physical activity, prediabetes, diabetes, hypertension, cardiovascular disease, and NAFLD fibrosis score	Both-FLD group (adjusted-HR 1.50, 95%CI 1.19–1.89), and MAFLD-only group (adjusted-HR 1.97, 95%CI 1.49–2.60), but not NAFLD-only group

	Median follow-up: 5.3 years	MAFLD-only and 22.3% had both conditions			(adjusted-HR 1.06, 95%CI 0.63–1.79), had a higher risk of incident CKD. The switch from NAFLD to MAFLD criteria may identify a greater number of individuals at CKD risk
Chen et al. 2023 [39]	Longitudinal study: 337,783 participants from the UK Biobank. Median follow-up: 12.8 years	MAFLD was diagnosed by FLI ≥60; at baseline, 38.7% had MAFLD	ESRD: patients treated with chronic dialysis; 618 cases of incident ESRD	Age, sex, systolic blood pressure, assessment center, deprivation index, smoking status, alcohol intake, fasting glucose, lipids, and serum transaminases	MAFLD was associated with incident ESRD (adjusted-HR 2.03; 95%CI 1.68-2.46). There were graded associations between non-invasive liver fibrosis scores and the risk of ESRD in MAFLD cases. Furthermore, the risking alleles of PNPLA3 rs738409, TM6SF2 rs58542926, GCKR rs1260326 and MBOAT7 rs641738 amplified the MAFLD effect on ESRD risk
Tanaka et al. 2023 [40]	Longitudinal study: 13,159 Japanese adult individuals who received annual health examinations. Mean follow-up: 6.3 years	NAFLD and MAFLD were diagnosed by ultrasonography. Patients were categorized in NAFLD or MAFLD; at baseline, the prevalence rates of NAFLD and MAFLD were 32.8% and 32.3%, respectively	eGFR <60 mL/min/1.73 m^2 or proteinuria; 2163 cases of incident CKD	Age, sex, baseline eGFR, smoking, ischemic heart disease, diabetes mellitus, overweight/obesity, hypertension, and dyslipidemia	MAFLD (adjusted-HR 1.12; 95%CI 1.02–1.26), but not NAFLD, was associated with a higher risk of incident CKD. The addition of MAFLD to traditional renal risk factors significantly improved the discriminatory capacity to predict CKD

1069

Abbreviations: CI, confidence interval, eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FLD, fatty liver disease; FLI, fatty liver index; HR, hazard ratio; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score.