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Title

Metabolic dysfunction-associated fatty liver disease: association with kidney disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is defined as hepatic fat accumulation in more than 5% of hepatocytes without significant alcohol consumption and other secondary causes of hepatic steatosis. In 2020, the more inclusive term metabolic (dysfunction)-associated fatty liver disease (MAFLD) with broader and "positive" diagnostic criteria was proposed to replace the old term NAFLD. The new terminology and definition of MAFLD better emphasize the pathogenic role of metabolic dysfunction and the use of "positive" criteria for diagnosing this common liver disease. In fact, the diagnosis of MAFLD is based on the evidence of hepatic steatosis (as assessed by liver biopsy, imaging techniques or blood biomarkers and scores) in persons who have overweight or obesity, type 2 diabetes or have metabolic dysregulation, regardless of the coexistence of other liver diseases or excessive alcohol consumption. It is known that NAFLD is associated with an increased risk of chronic kidney disease (CKD) and CKD may also be induced by metabolic dysfunction. Thus, compared to the NAFLD definition, the newly-proposed MAFLD definition is more likely to identify subjects with fatty liver and metabolic comorbidities, who are at greater risk of CKD. In this Perspectives article, we discuss the clinical associations between MAFLD and CKD, the pathophysiological mechanisms by which MAFLD may increase risk of CKD and the potential drug treatments that may benefit both conditions.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is histologically defined as hepatic fat accumulation in more than 5% of hepatocytes without excessive alcohol consumption or other competing causes for hepatic steatosis[1,2]. To date, it has been estimated that this liver disease affects approximately 25% of the global adult population [3] and nearly 30% of Chinese adults with a prevalence that is higher in urban than rural areas; in men than women, and in the eastern coastal areas than inland. Furthermore in China, NAFLD also affects approximately 2% of schoolchildren with sedentary lifestyles and an unhealthy diet [4,5].

NAFLD shares multiple cardiometabolic risk factors with chronic kidney disease (CKD), such as obesity, hypertension, insulin resistance, type 2 diabetes (T2DM) or prediabetes and atherogenic dyslipidemia [6-8]. The prevalence of CKD in people with NAFLD ranges from approximately 20% to 55% compared to 5% to 35% in the non-NAFLD population. Several studies have shown that the severity of NAFLD is closely associated with increasing stages of CKD [8-13]. For example, a previous meta-analysis that included 33 cross-sectional and longitudinal studies showed that there was a higher prevalence and incidence of CKD in patients with NAFLD and advanced fibrosis (odds ratio [OR] 5.20, 95% CI 3.14- 8.61) and hazard ratio [HR] 3.29, 95% CI 2.30- 4.71, respectively) compared to patients with NAFLD without advanced fibrosis [9]. The presence of nonalcoholic steatohepatitis (NASH) on liver histology was also independently associated with a higher prevalence (odds ratio 2.53, 95% CI 1.58-

4.05) and incidence (hazard ratio 2.12, 95% CI 1.42-3.17) of CKD than simple steatosis [9]. Similar results were also found in two more recent meta-analyses published in 2018 [13] and 2020 [14]. Patients with NAFLD were also observed to have an increased risk of abnormal albuminuria in 19 observational studies with 24804 participants (odds ratio 1.67, 95% CI 1.32-2.11, $P<0.05$) [15]. These data suggest that NAFLD may be an independent risk factor for CKD. Additionally, the severity of CKD may adversely affect long-term clinical outcomes from NAFLD by increasing the risk for all-cause mortality[16]. An observational study of 87 adults with biopsy-proven NAFLD, reported that NAFLD with microalbuminuria was associated with higher fibrosis scores than those patients with NAFLD without microalbuminuria [17]; implying that the presence of microalbuminuria may help identify those patients with more severe NAFLD. Another study of 120 patients with biopsy-proven NAFLD diagnosed in 1978-2006 reported that NAFLD patients with long-term CKD had increased mortality risk because of the associated metabolic comorbidities, rather than CKD per se [16]. That said, whether there is a causal association between NAFLD and CKD is unclear and achieving a better understanding of the link between NAFLD and CKD represents an important area of research.

In response to criticisms regarding the use of the adjective “non-alcoholic”, and in recognition of the fact that NAFLD is a purely metabolic liver disease, in 2020 an international panel of experts recommended the renaming of NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD). With the new term, different diag-

nostic criteria for defining MAFLD were also proposed [18]. The diagnostic criteria for MAFLD are based on the evidence of hepatic steatosis (detected either by liver biopsy, imaging techniques or blood biomarkers and scores), and the coexistence of overweight or obesity, T2DM or metabolic dysregulation[18]. The term "MAFLD" represents this disease not as a single or "exclusive" condition, but also embraces metabolic disorders, and may coexist with excessive alcohol consumption or other chronic liver diseases that may have additive or synergistic effects to increase the severity of the liver condition (e.g. chronic viral hepatitis) [19,20]. Thus, the two terms of NAFLD and MAFLD cannot be considered fully interchangeable or simply equivalent. Although there is excellent concordance (with a Cohen's kappa statistic >0.90) between the NAFLD and MAFLD definitions in "real-world" data, there will be some individuals fulfilling the diagnostic criteria for MAFLD but not NAFLD (i.e., persons with MAFLD who have other coexisting chronic liver diseases), and some individuals fulfilling the criteria for NAFLD but not MAFLD (i.e. lean persons with NAFLD who do not have any coexisting metabolic dysfunction) [21]. Notably, evidence is now accumulating to suggest that subjects with MAFLD are more likely to have multiple metabolic comorbidities and to be at greater risk of advanced liver fibrosis or CKD, compared to those with NAFLD[22]. In this Perspectives article, we discuss the clinical associations and the pathophysiological mechanisms underpinning MAFLD with CKD and how this differs from our understanding of the relationship between NAFLD and CKD. We also briefly discuss targeted pharmacological treatments for NAFLD and MAFLD and how these might affect CKD.

From NAFLD to MAFLD

The terms of NAFLD and its progressive necro-inflammatory form, NASH, were first coined in 1980 and 1986 to characterize a liver disease histologically similar to alcoholic fatty liver disease but without a prior history of significant alcohol intake [23,24]. NAFLD includes a histopathological spectrum of progressive liver conditions, ranging from nonalcoholic fatty liver (NAFL, simple steatosis without evidence of any hepatocellular injury) to NASH (hepatic steatosis *plus* inflammation and hepatocellular injury, with or without varying levels of fibrosis) and cirrhosis [1,25-27]. Most individuals with NAFLD or NASH are overweight or obese, and many of them have obesity-associated diseases, such as T2DM, hypertension and atherogenic dyslipidemia. A link between liver damage and obesity had been recognized since 1950s [28] and in 1999 [29], an analysis of subjects with biopsy-proven NAFLD reported a strong association with the typical features of the metabolic syndrome such as hyperinsulinemia, dysglycemia, hypertension and dyslipidemia. Similar results were also reported [30] in a study of 551 severely obese individuals undergoing bariatric surgery. Since that time, various reasons for renaming and redefining NAFLD have been presented and debated (**Figure 1**) [31-36]. Firstly, the definition of NAFLD has exclusiveness and does not allow for the presence of other coexisting liver diseases. Indeed, the coexistence of NAFLD with another chronic liver disease is not rare in clinical practice [19]. Secondly, the question of the thresholds of "healthy or unhealthy" alcohol consumption and the risk of stigmatizing and misleading individuals make the compound adjective

"non-alcoholic" inappropriate. Some studies have suggested that modest alcohol consumption (less than 20 g/day) may exert a protective effect on NAFLD [37-39], but other large studies have found the opposite result [40,41]. The assessment of daily alcohol consumption is still not standard and accurate, and may be misinterpreted as stigmatization, especially in adolescents, while alcohol consumption may also be taboo for religious or cultural reasons [42,43]. The compound adjective "non-alcoholic" may mislead some persons into thinking that they can drink alcohol and that this disease is not severe ("non"-alcoholic), compared with alcoholic cirrhosis. Thirdly, there are varying degrees of disease progression and severity, such as Asian people with NAFLD are leaner but have more severe liver histopathology compared with their counterparts of Caucasian ethnicity. Additionally, pre-menopausal women often have a lower prevalence of NAFLD, while post-menopausal women have a higher prevalence of NAFLD than men of similar age. The high heterogeneity of NAFLD is mainly related to the diversity of pathogenesis of the condition (involving, for example, genetic predisposition, estrogen exposure and presence of underlying metabolic dysfunction). Fourthly, the term "NAFLD" can be misunderstood as it emphasizes only "non-alcoholic" factors and does not highlight the key pathogenic role of metabolic dysfunction. Finally, the high heterogeneity of NAFLD may also affect the reliability of clinical trial results and the non-invasive assessment of liver fibrosis (by using the scores of advanced fibrosis, such as the NAFLD fibrosis score (NFS) and fibrosis 4 (FIB-4), or vibration-controlled transient elastography) [44-46]. These issues eventually prompted a panel of international experts from 22 countries to propose that NAFLD

be renamed and re-classified as MAFLD [18,20] with new diagnostic and "positive" criteria better emphasizing the dysmetabolic pathophysiology of this common liver disease and its systemic adverse effects on both liver-related and extra-hepatic outcomes (including CKD) [47]. The details of the diagnosis and the specific features of NAFLD and MAFLD definitions have been summarized (**Figure 2A and Supplementary Table 1**). Moreover, we have utilized a "Venn diagram" to illustrate the overlap between NAFLD and MAFLD definitions according to a recent study undertaken by our group in biopsy-proven individuals from Wenzhou [48] (**Figure 2B**).

Consequences for clinical practice

Although some experts have endorsed the newly-proposed term and definition of MAFLD [43,49], others have been less enthusiastic, arguing that this change in nomenclature is premature. The primary reasons are the ongoing debate about diagnostic criteria of "metabolic health" and the ambiguity around the aetiological root cause. The adjective "metabolic" they suggest is too simple and broad to cover all disease phenotypes and aetiological attributions [50]. For example, some lean and metabolically healthy individuals can have hepatic steatosis, emphasizing that other factors (e.g. genetic factors) may be dominant in some phenotypes [51-53]. What's more, other rarer "metabolic" diseases may also cause hepatic steatosis, such as Wilson's disease and short gut syndrome-associated fatty liver, but these are not included under the term "MAFLD" [50]. Renaming and re-classifying this common metabolic liver disease may also have unintended consequences for some stakeholders. For example, with ongoing

drug trials, reclassification of this liver disease may affect trial outcomes that are focussed on histological resolution of NASH as a primary efficacy endpoint [50,54].

In our opinion, a growing body of data largely supports the nomenclature change from NAFLD to MAFLD. For example, a 2020 study of 765 Japanese individuals showed that the newly proposed definition of MAFLD identified more accurately subjects with advanced liver fibrosis (assessed by non-invasive tests) compared with the NAFLD definition. In addition, the presence of MAFLD with coexisting mild alcohol consumption (less than 20 g/day) was also associated with a higher prevalence of liver fibrosis than the presence of MAFLD alone (without coexisting alcohol intake) (25.0% vs. 15.5%, P=0.018) [55], suggesting that even mild alcohol consumption may increase the prevalence of liver fibrosis; so further emphasizing the inappropriateness of the term "non-alcoholic". In a study of 922 adults from Hong Kong, there was no difference in the prevalence of MAFLD and NAFLD (25.9% and 25.7%, respectively), but the incidence of MAFLD (2.8 per 100 person-years) was lower than that of NAFLD (3.7 per 100 person-years) and almost 25% of participants with fatty liver (on ultrasound examinations) were classified as not having MAFLD [56], confirming that the MAFLD and NAFLD definitions can identify different groups of subjects. However, the aforementioned difference in incidence rates of MAFLD appears to be more marked among lean individuals without metabolic dysfunction. Overall, therefore, the current evidence suggests that the definition of MAFLD can more accurately identify subjects at higher risk of progressive liver disease than the NAFLD definition. This

has important implications not only for clinical practice but also for recruitment of patients to clinical trials testing new pharmacotherapies for this liver disease. That said, as discussed above the currently available 'real-world' studies clearly suggest that the diagnostic criteria for MAFLD are more useful in clinical practice than those for NAFLD [18,55]. Another useful change in clinical practice with the implementation of the newly proposed definition of MAFLD is the semiquantitative evaluation of the grade of inflammatory activity and stage of liver fibrosis to replace the dichotomous stratification into NASH and non-NASH [18]. The diagnosis of NASH can be affected by sampling variability [57] and ballooning of hepatocytes on histology (as a cardinal feature of NASH) can fluctuate over short timeframes in the same subject [57]. Furthermore, studies have demonstrated that liver fibrosis, rather than other histologic features, may predict the most important clinical outcomes of NAFLD [58,59]. Consequently, we consider that a terminology change from NAFLD to MAFLD will have little effect on ongoing clinical trials where they evaluate "improvement of liver fibrosis"; and thus far, no drug has received regulatory approval for the treatment of NASH [57]. Overall, the newly proposed definition of MAFLD may facilitate much-needed improvements in the prevention, diagnosis, treatment and management of this common and burdensome liver disease.

MAFLD is more closely related to CKD

As previously mentioned, metabolic dysregulation is a key feature of MAFLD, and individuals with MAFLD are not only more likely to have metabolic comorbidities,

but also have a greater prevalence of advanced liver fibrosis than those with NAFLD[22,55]. As NAFLD with advanced liver fibrosis is closely associated with CKD (and T2DM) [60], it is reasonable to infer that MAFLD may be more closely related to CKD than NAFLD. Our recent re-examination of the National Health and Nutrition Examination Survey (NHANES)-III database 1988–1994, involving 12,571 individuals, who underwent liver ultrasound examinations and who did not have viral hepatitis, reported that the overall prevalence of MAFLD and NAFLD was 30.2% and 36.6%, respectively. Notably, individuals with MAFLD had lower values of estimated glomerular filtration rate (eGFR: 74.9±18.2 vs. 76.5±18.2 ml/min/1.73 m^2, P<0.001) and a higher prevalence of CKD stages 3-5 (20.3% vs. 17.8%, P=0.005), compared to those with NAFLD[22] (**Figure 3**). Furthermore, in this population-based study, the ultrasonographic severity of MAFLD was associated with a nearly 1.3-fold increased risk of prevalent CKD, even after adjustment for sex, age, ethnicity, alcohol intake and pre-existing diabetes.These results suggested that MAFLD definition can identify patients with CKD more accurately than the NAFLD definition[22]. Another study based on the NHANES database 1999–2016 also found that subjects with MAFLD had a higher risk of both CKD and abnormal albuminuria than subjects who did not have MAFLD. Also, subjects with MAFLD had a higher risk of cardiovascular events (evaluated by the Framingham or the American College of Cardiology and American Heart Association Atherosclerotic Cardiovascular Disease risk equations) than those with NAFLD [61]. Thus, MAFLD may be associated with a greater risk of cardiovascular disease and CKD than NAFLD. However, in contrast to these aforementioned data,

the latest cross-sectional analyses of the NHANES database 2017–2018 (involving 4869 subjects) showed that MAFLD was not independently associated with the presence of CKD, although higher FIB-4 score (i.e., a non-invasive score for liver fibrosis, adjusted-odds ratio [OR] 1.23, 95% CI 1.05-1.01), hyperuricemia (adjusted-OR 1.91, 95% CI 1.55- 2.36), hypertension (adjusted-OR 1.66, 95% CI 1.38- 2.00), and T2DM (adjusted-OR 2.21, 95% CI 1.89- 3.11) were independently associated with CKD [62]. That said, these latter results are somewhat inconsistent with previously published studies[9,13,22], but further studies are needed to better clarify the association between MAFLD (or NAFLD) and CKD progression over time. However, from the perspective of integrated care, the newly proposed criteria for MAFLD are easily applied by clinicians across different healthcare settings, including in most resource-limited parts of the world [18].

Mechanisms linking MAFLD and CKD

Preclinical reports, observational studies, genome-wide association studies and epigenome-wide association studies are useful to define the "crosstalk" existing between CKD and this metabolic liver disease and better decipher the complex underlying mechanisms linking both conditions [63-65]. To date, the pathophysiological mechanisms linking NAFLD and CKD involve metabolic disorders (e.g. abdominal obesity, insulin resistance, hypertension, atherogenic dyslipidemia and dysglycemia), low-grade inflammation and, more recently, a possible involvement of the liver-gut-kidney axis. Presently, the precise pathophysiological mechanisms linking

MAFLD and CKD are uncertain, although the putative pathophysiological mechanisms that link MAFLD to CKD are likely to be similar to those underlying the association between NAFLD and CKD. Herein, we briefly discuss the main putative underlying mechanisms linking MAFLD and CKD, focusing on genetic predisposition, environmental risk factors and metabolic dysfunction.

Genetic predisposition

Emerging studies suggest that some genetic polymorphisms affecting patatin-like phospholipase domain-containing 3 (*PNPLA3*), 17β-hydroxysteroid dehydrogenase type 13 (*HSD17B13*), trans-membrane 6 superfamily member 2 (*TM6SF2*), membrane-bound O-acyltransferase domain-containing 7 (*MBOAT7*), and glucokinase regulator (*GCKR*) genes play an important role in the development and progression of NAFLD [66-68]. Some of these NAFLD-associated genetic polymorphisms are also associated with kidney abnormalities although some inconsistencies in study findings exist (**Table 1**). A meta-analysis of 23 case-control studies (involving 6071 subjects with NAFLD and 10366 controls) showed that individuals who carried a *PNPLA3* G allele had a higher risk of NAFLD (additive model: OR 3.41, 95%CI 2.57-4.52) and NASH (additive model: OR 4.44, 95%CI 3.39-5.82) [69]. Notably, an increasing number of studies showed that this gene variant is also associated with lower eGFR levels, abnormal albuminuria and higher prevalence of CKD in both children and adults with either biopsy-confirmed or imaging-defined NAFLD, independent of age, sex, adiposity measures, hypertension, diabetes, and severity of NAFLD [68,70-72]. Similarly, we

observed that the *PNPLA3* GG genotype was not only associated with higher risk of glomerular dysfunction, but was also with higher levels of urinary neutrophil gelatinase-associated lipocalin (a biomarker of kidney tubular injury) in individuals with biopsy-proven NAFLD [67]. *PNPLA3* mRNA is highly expressed in the liver, and also in adipose tissue and kidney [73], and this gene variant affects the lipid droplet architecture and retinol metabolism of hepatic stellate cells, as well as the release of multiple pro-inflammatory and pro-fibrogenic factors which may contribute to increased hepatic fibrogenesis [73-75]. Furthermore, the G allele of *PNPLA3* rs738409 may increase ectopic lipid accumulation in both renal mesangial and tubular cells under conditions of lipid excess, potentially leading to lipid nephrotoxicity. In fact, *PNPLA3* mRNA levels were found to be highly expressed in renal podocytes compared to renal tubular cells [76]. Kidney damage may activate renal podocytes leading to increased angiogenesis, dysregulation of both renal medullary and cortical blood flows, and increased kidney fibrosis [76-78]. Thus, it can be implied that *PNPLA3* mRNA may adversely affect renal podocytes leading to renal dysfunction **(Figure 4)**.

HSD17B13 rs72613567, a loss-of-function variant, may be a protective factor and a therapeutic target in NAFLD by affecting the regulation of hepatic lipid metabolism [79,80]. In an Italian study of 684 obese children with ultrasound-defined NAFLD, carriers of the A allele of rs72613567 had higher eGFR levels than homozygous subjects [81]. However, in another study involving 215 Chinese adults with biopsy-proven NAFLD, the A/- or A/A *HSD17B13* genotypes were associated with a lower risk of abnormal

albuminuria, but not with altered levels of eGFR or urinary neutrophil gelatinase-associated lipocalin [82].

TM6SF2 rs58542926 is associated with a greater susceptibility to NAFLD, but a lower risk of cardiovascular disease [83]. This may be explained by diverting toxic cholesterol away from the vessels into the liver and adipose tissue [84]. A small cross-sectional study of 61 individuals with biopsy-proven NAFLD also reported that the *TM6SF2* T allele was associated with higher eGFR levels and a lower prevalence of abnormal albuminuria and CKD [85]. In another study involving 532 obese children with normal kidney function, the *TM6SF2* rs58542926 T allele was associated with higher eGFR levels, regardless of the presence or absence of NAFLD [86].

MBOAT7 rs641738 has also been reported to increase the risk of NAFLD and other chronic liver diseases [87,88]. In a cohort of Asian individuals with biopsy-proven NAFLD, the *MBOAT7* rs641738 variant was associated with worsening stages of CKD, irrespective of NASH [89].

The T allele of *GCKR* rs1260326 increases the risk of NAFLD, possibly via enhancing hepatic *de novo* lipogenesis [90] and may be related to a greater risk of CKD or end-stage kidney disease [91]. In the Japan Multi-Institutional Collaborative Cohort Study, the authors reported that the *GCKR* rs1260326 T allele was associated with a higher risk of CKD [92]. Conversely, another study of 195 individuals found that *GCKR*

rs1260326 T allele was associated with higher eGFR levels, but these may be offset by an adverse effect on risk of coronary artery disease (OR 1.02 per risk allele, 95%CI 1.00-1.04, *P*=0.01) [93]. Finally, a study of 230 Italian overweight or obese children reported that *TM6SF2*, *GCKR*, and *MBOAT7* risk alleles did not show any significant association with kidney function parameters[94].

All these studies were performed before the newly proposed change in nomenclature from NAFLD to MAFLD. However, given the close relationship between these genetic variants and metabolic dysfunction, it is plausible that these genetic variants will have equal relevance in people with MAFLD. More importantly, a recent cohort study of 4653 middle-aged and elderly Chinese adults showed that *PNPLA3* or *TM6SF2* gene variants are associated with higher liver fat content, especially in individuals with at least one metabolic disorder, based on the MAFLD definition; whilst no differences in liver fat content were observed in those without any metabolic disorder [95]. These results support the conclusion that *PNPLA3* rs738409 and *TM6SF2* rs58542926 gene variants are associated with the development of MAFLD in Chinese adults.

Environmental risk factors

Emerging studies suggest that the gut microbiota and intestinal barrier integrity may be linked to NAFLD and CKD (i.e. the so-called gut-liver-kidney axis) **(Figure 5)** [96]**.** Gut microbiota is a highly versatile ecosystem contributing to multiple host physiological processes [97]. Prebiotics, synbiotics and food components (including polyphe-

nols, sugars and proteins) may alter the gut microbiota diversity and the production of uraemic toxins [98]. Gut microbiota-derived metabolites (for example, indoxyl sulfate and p-cresyl sulfate), which are produced by several obligate or facultative anaerobes, are harmful to the host and require active elimination by the kidney and this may influence both kidney and liver damage [96,97,99].

The intestinal microbiome also generates trimethylamine N-oxide (TMAO), endogenous alcohol and short-chain fatty acids (SCFAs). TMAO production results from a multistep process that is affected by dietary ingredients, such as choline and carnitine, which undergo microbial processing, mainly related to lipid metabolism [100]. In a cohort of 512 patients with CKD followed for 5 years, plasma levels of TMAO were higher in patients with CKD than in non-CKD control subjects, and were associated with a nearly 3-fold increased risk of mortality [101]; in a preclinical study, dietary TMAO supplementation also resulted in progressive renal tubulo-interstitial dysfunction and fibrosis [101]. Likewise, plasma levels of TMAO were increased in subjects with NAFLD and associated with higher serum bile acid concentrations. TMAO administration in high fat diet fed mice also exacerbated hepatic steatosis by inhibiting hepatic nuclear receptor farnesoid X receptor (FXR) signaling, thus up-regulating hepatic *de novo* lipogenesis [99]. It is known that FXR is a major nuclear receptor for bile acids, which is expressed in a variety of tissues, including the liver and kidney [102]. FXR is involved in the regulation of lipid and glucose metabolism as well as multiple inflammation pathways [103] and it is also implicated in the pathogenesis of NAFLD [104].

Some preliminary evidence also supports the view that FXR activation has the potential to repair renal tissue damage and prevent renal pathogenic processes [102].

SCFAs (e.g. acetate, sodium butyrate, and propionate), which are generated from the degradation of indigestible carbohydrates via anaerobic bacteria, may activate G-protein coupled receptors in various cells and regulate blood pressure through the renin-angiotensin system [105-107]. SCFAs may also inhibit histone deacetylases (HDACs), which regulate epigenetic modification through changes of histone tails [108]. Thus, decreased SCFAs may lead to an increase in blood pressure further impairing kidney function [109,110]. Animal and clinical studies also support the notion that SCFAs may have anti-hypertensive properties, but the exact underlying mechanisms have not been completely identified [110-112]. A recent small study also showed that individuals with NAFLD had higher faecal SCFA levels and faecal bacteria, such as *Prevotella copri, Megashpaera, Fusobacterium, Ruminococcus torques* and *Eubacterium biforme* [113]. Notably, SCFAs, such as sodium butyrate which is a bacterial fermentation product, may increase the secretion of glucagon-like peptide (GLP)-1 (that enhances glucose-induced pancreatic insulin secretion) from intestinal epithelial cells and increase the expression of hepatic GLP-1 receptors [114]. Thus, it has been speculated that sodium butyrate supplementation might prevent the progression of NAFLD to NASH [114]. Additionally, treatment with sodium butyrate may improve insulin resistance, serum urea concentrations and urinary protein excretion, possibly via improving 5'-adenosine monophosphate-activated protein kinase phosphorylation, increasing

GLP-1 secretion and/or promoting colonic mucin and tight junction proteins in a nephrectomy-CKD model [115].

Disrupted intestinal barrier integrity is another mechanism potentially implicated in the gut-liver-kidney axis, which may cause the release of endotoxins and bacterial DNA into the circulation, thereby causing low-grade chronic inflammation. The progression of CKD and NAFLD may, in turn, contribute to further disrupting epithelial tight junctions and affecting intestinal barrier function [96,116,117].

The imbalance of diet and nutrition (e.g. high fructose intake and vitamin-D deficiency or insufficiency) may also contribute to the development of NAFLD and CKD. A high fructose intake increases hepatic *de novo* lipogenesis and uric acid production. In turn, uric acid further increases endogenous fructose production via stimulating aldose reductase in the polyol pathway [118]. One study suggested that hyperuricemia may be a risk factor for NAFLD, particularly in men, via inducing the suppression of silent information regulator-1 (SIRT1) signaling [119]. SIRT1 is a NAD(+)-dependent deacetylase and responds to oxidative stress and inflammation by inducing p53 mediated apoptosis, participating in the nuclear factor kappa-B (NF-κB) mediated inflammatory responses, forkhead box class O 3a (FOXO3a)-mediated autophagy and oxidative stress [120,121]. Meanwhile, SIRT1 activation may be beneficial for obesity and NAFLD through inhibiting hepatic *de novo* lipogenesis, increasing fatty acid β-oxidation, as well as reducing hepatic oxidative stress and improving hepatic glucose metabolism

[122,123]. SIRT1 is abundantly expressed in mouse kidneys and may exert a protective effect on the development of renal injury in these animals through the protection of podocyte function and reduction of renal medullary cell damage following oxidative stress [124,125]. There was also a strong inverse association between SIRT1 expression, serum uric acid levels and liver pathology in humans [119]. Observational studies also showed an association between higher serum uric acid levels and various CKD-related outcomes (e.g. lower eGFR and abnormal albuminuria) [126-129].

Metabolic dysfunction

The metabolic dysfunction in the MAFLD definition includes a cluster of metabolic risk factors such as abdominal overweight or obesity, hypertension, insulin resistance, prediabetes/diabetes, atherogenic dyslipidemia and low-grade inflammation (as reflected by increased plasma C-reactive protein levels)[18]. These metabolic risk factors have individually been associated with an increased risk of both NAFLD and CKD [130-132]. Using the NHANES-III database, the investigators reported that subjects with metabolic syndrome had a ~2.5-fold increased risk of CKD compared with those without metabolic syndrome [133].

Obesity also plays an important role in the development and progression of NAFLD and CKD. Ectopic lipid deposition triggers oxidative stress by two main intracellular transcription factor signaling pathways, i.e., the nuclear factor-κB (NF-κB) pathway and the c-Jun-amino-terminal kinase (JNK) pathway [134]. It is known that perivascular

fat may contribute to the impairment of endothelium-dependent vasodilatation, which is involved in CKD pathogenesis. Furthermore, a study of 146 individuals showed that increased renal sinus fat had an adverse effect on urinary albumin excretion and kidney function [135] [136]. Additionally, adipose tissue is an endocrine organ that secretes several adipokines (for example, leptin and adiponectin), which may regulate food intake, insulin sensitivity, low-grade chronic inflammation and even activate the renin-angiotensin system, thereby affecting the development of MAFLD and CKD [137].

Obesity, T2DM and MAFLD can promote systemic and hepatic insulin resistance and, in turn, insulin resistance can lead to hepatic macrophage activation, hepatic fat accumulation and impaired glucose metabolism[138]. This may further aggravate renal hemodynamics, leading to renal disease progression via activation of the sympathetic nervous system, sodium retention, and down-regulation of natriuretic peptide system[139].

As discussed above, CKD represents the final result of interactions of multiple factors, many of which have a close association with the metabolic dysfunction (for example, abdominal obesity, T2DM, insulin resistance, dyslipidaemia, hypertension, intestinal dysbiosis, high fructose intake and vitamin-D deficiency, etc). Since the MAFLD definition specifically includes individuals who have any metabolic dysfunction (which is not applicable to all subjects with NAFLD), it is reasonable to assume that metabolic dysfunction may be an important factor mediating the link between

MAFLD and CKD.

It is also worth noting that MAFLD can coexist with other chronic liver diseases (e.g. viral hepatitis), but a definition of NAFLD precludes the co-existence of other liver diseases. An observational study found that MAFLD patients with co-existing viral hepatitis had higher risk of cardiovascular disease, compared to their counterparts without viral infection [140]. Infections with hepatitis B virus (HBV) or hepatitis C virus (HCV) can both induce HBV-related or HCV-related glomerulonephritis, which usually manifests clinically with varying levels of proteinuria and microscopic hematuria [141]. These results suggest that HBV and HCV might also be directly involved in the pathogenic processes linking MAFLD and CKD, but further studies are needed.

Pharmacologic agents for CKD and NAFLD

Pharmacotherapy (e.g., lipid-lowering, blood pressure-controlling, glucose-lowering and weight loss) has become a major focus for management of NAFLD and CKD [142]. Based on the aforementioned links between these two conditions, the development of common drugs for NAFLD (or MAFLD) and CKD has become an important research area. A number of pharmacological treatments have the potential to benefit both CKD and NAFLD. In **Table 2,** we summarize the results of completed and ongoing trials, testing drugs that are relevant to the treatment of both NAFLD/NASH and CKD. In **Supplementary Table 2**, we have also listed other promising drugs and therapeutic targets for NAFLD/NASH and CKD that are in preclinical or early development for

NASH or CKD. However, to date, there are no definitive curative common treatments for both MAFLD (or NAFLD) and CKD. Drugs targeting environmental risk factors for MAFLD (or NAFLD) and CKD demonstrate the concept of "food as medicine" and of a "healthy diet". The most important treatment of environmental risk factors is to change eating habits, which is extremely hard to maintain. Drugs targeting redox regulation, inflammation and fibrosis but of unproven efficacy to date. Drugs targeting metabolic risk factors are considered to be the most promising to date. As discussed below, although the currently published controlled trials involved individuals with NAFLD (or NASH) and not MAFLD, it is plausible that drugs targeting metabolic risk factors may be even more effective in people with MAFLD.

Targeting of metabolic risk factors

Drugs targeting metabolic risk factors exert their actions mainly on regulation of lipid and glucose metabolism. Peroxisome proliferator-activated receptors (PPARs), as the key nuclear receptors involved in lipid and glucose metabolism, have three main isotypes: PPAR-α, PPAR-γ and PPAR-δ [143]. Glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors are two newer classes of glucose-lowering agents. GLP-1 as a gut-derived incretin hormone induces beta-cell insulin secretion and reduces glucagon secretion [144] Thus, GLP-1RAs have been developed for the treatment of type 2 diabetes through increasing insulin and decreasing glucagon levels. SGLT2 inhibitors (e.g. empagliflozin, dapagliflozin and canagliflozin) improve plasma glucose levels by preventing glucose reabsorption in

the proximal renal tubule[145]. We have listed the principal clinical trials that directly target CKD and NAFLD (or NASH) in **Table 2**. However, many clinical trials targeting metabolic dysfunction (e.g. in those T2DM) were not designed to study CKD or fatty liver disease. Semaglutide is an approved GLP-1RA for the treatment of type 2 diabetes. In the SUSTAIN-1 (Efficacy and Safety of Semaglutide Once-weekly Versus Placebo in Drug-naïve Subjects With Type 2 Diabetes, NCT02054897)[146] and SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes, NCT01720446) [147], semaglutide had a similar safety profile and no greater cardiovascular risk profile compared to placebo. The SUSTAIN-1 trial showed that semaglutide was better than placebo in reducing body weight [146]. The SUSTAIN-6 trial also found that treatment with semaglutide was associated with lower rates of new or worsening nephropathy [147]. Since obesity and T2DM are established risk factors for fatty liver disease, CKD and cardiovascular events, semaglutide is likely to become a suitable treatment option for both MAFLD and CKD. In the recent trial (Investigation of Efficacy and Safety of Three Dose Levels of Subcutaneous Semaglutide Once Daily Versus Placebo in Subjects With Non-alcoholic Steatohepatitis, NCT02970942) [148], semaglutide was associated with greater histologic resolution of NASH than placebo, but did not improve liver fibrosis stage. There were no changes of renal function in the PIONEER-5 (Efficacy and Safety of Oral Semaglutide Versus Placebo in Subjects With Type 2 Diabetes and Moderate Renal Impairment, NCT02827708) [149], thereby suggesting that semaglutide is safe in CKD. GLP1RAs and SGLT-2 inhibitors may be the most promising drugs

for treatment of both fatty liver disease and CKD, but well designed trials are needed to test the effects of these classes of drugs on both outcomes.

Conclusion

Increasing evidence suggests that the newly proposed definition of MAFLD is more closely related to CKD than the NAFLD definition. We strongly believe that a multidisciplinary and person-centred approach is needed to manage subjects with MAFLD and CKD as most of these individuals have common metabolic comorbidities, such as obesity, hypertension, atherogenic dyslipidemia or T2DM. Therefore, it is clinically important to assess kidney function in people with MAFLD. Lastly, emerging evidence suggests that some drug classes targeting metabolic risk factors, such as GLP1RAs and SGLT-2 inhibitors, may benefit both the liver and the kidney in individuals with MAFLD and CKD.

Acknowledgements: None.

Author contributions: Dan-Qin Sun and Ming-Hua Zheng designed the study. Dan-Qin Sun and Ting-Yao Wang draft the manuscript and prepared the figures. Rui-Fang Wang and Zhi-Yin Bo were responsible for information retrieval. Giovanni Targher and Christopher D Byrne contributed to the writing, critical evaluation and proof reading of the manuscript. All authors contributed to the manuscript for important intellectual content and approved the submission.

Competing interests: None.

Funding Sources

This work was supported by grants from the National Natural Science Foundation of China (82070588, 82000690), High Level Creative Talents from Department of Public Health in Zhejiang Province, Project of New Century 551 Talent Nurturing in Wenzhou and Project of Science and Technology Development Fund in Wuxi (N20202001). Dan-Qin Sun is supported in part by grants from Youth Research Project Fund from Wuxi Municipal Health Commission (Q201932), Top-notch Talents from Young and Middle-Age Health Care in Wuxi (BJ2020026). GT is supported in part by grants from the University School of Medicine of Verona, Verona, Italy. CDB is supported in part by the Southampton NIHR Biomedical Research Centre (IS-BRC-20004), UK.

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LEGENDS TO THE TABLES AND FIGURES

Table 1. Genotypes associated with risk of both NAFLD and CKD.

Table 2. Potential pharmacologic agents and targets for CKD and NAFLD.

Supplementary table 1. Features of NAFLD and MAFLD.

Supplementary table 2. Other potential pharmacological options and therapeutic targets for NAFLD/NASH or CKD.

Figure 1. Timeline of key comments on the renaming of NAFLD to MAFLD.

Abbreviations: AASLD, the American association for the study of liver diseases; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steato-hepatitis; ALD, alcoholic liver disease; AFLD, alcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; CKD, chronic kidney disease; EASL, the European association for the study of the liver.

Figure 2. Framework for the diagnosis of NAFLD and MAFLD (A) and "Venn diagram" showing schematically the overlap between MAFLD and NAFLD in individuals with biopsy-proven fatty liver disease (B).

Figure 3. Mean levels of eGFR (A) and prevalence of CKD stage (B) in MAFLD and NAFLD populations.

Data are presented as mean with 95% confidence intervals (CI) (A) and percentages

(B), respectively. * P<0.05. Data were extrapolated from the study by Sun et al[22].

Figure 4. *PNPLA3* rs738409 polymorphism and related potential mechanisms between NAFLD and CKD.

The *PNPLA3* gene is highly expressed in the liver (mostly in hepatocytes and hepatic stellate cells), adipose tissue and kidney (mostly in renal podocytes and tubular cells). It has been found that the *PNPLA3* gene has a lipase activity but the G allele of *PNPLA3* rs738409 is associated with loss of this lipase activity. The G allele of *PNPLA3* rs738409 may affect lipid droplet architecture and retinol metabolism, and release multiple pro-inflammatory and pro-fibrogenic factors, thereby promoting the development and progression of NAFLD. The G allele of *PNPLA3* rs738409 also increases ectopic lipid accumulation in both renal mesangial and tubular cells, potentially leading to lipid nephrotoxicity. This genetic variant may also adversely affect the activation of renal podocytes causing kidney damage.

Abbreviations: *PNPLA3*, patatin-like phospholipase domain-containing 3; NAFLD, non-alcoholic fatty liver disease; CKD, chronic kidney disease.

Figure 5. Potential mechanisms implicated in the gut-liver-kidney axis.

An imbalance diet (e.g. high fructose and high fat) can result in intestinal dysbiosis (mainly increasing the Gram-negative bacteria), which may disrupt the intestinal barrier integrity and increase gut permeability. These intestinal disorders may further promote the release of lipopolysaccharide (LPS), small molecules and even bacteria

into the portal and systemic circulation, causing endotoxemia and low-grade inflammation. Intestinal dysbiosis also increases the production of endogenous alcohol, short-chain fatty acids, secondary bile acids, trimethylamine N-oxide, p-cresyl sulfate, indoxyl sulfate, and so on, which may affect the development of both NAFLD and CKD. Short-chain fatty acids (e.g. acetate, sodium butyrate, and propionate) provide up to 9% of the energy requirements. These molecules may also participate in the regulation of blood pressure, hepatic lipogenesis and gluconeogenesis, though the exact underlying mechanisms have not been fully elucidated. Thus, sodium butyrate supplementation might prevent the progression of NAFLD and CKD. Secondary bile acids and trimethylamine N-oxide can inhibit the activation of hepatic nuclear receptor farnesoid X receptor (FXR) signaling, but FXR activation can decrease lipid synthesis, gluconeogenesis, as well as renal inflammation and fibrosis. Trimethylamine N-oxide, p-cresyl sulfate and indoxyl sulfate, as the uremic toxins, can adversely affect the kidney by activating oxidative stress and renin-angiotensin system, and injuring vascular endothelium.