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Review

METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE AND CHRONIC KIDNEY DISEASE

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ABSTRACT
The nomenclature of non-alcoholic fatty liver disease (NAFLD) has recently undergone substantial revision to better reflect its underlying pathophysiological link with metabolic dysfunction. In 2023, the designation *metabolic dysfunction-associated steatotic liver disease* (MASLD) was formally adopted, superseding NAFLD. The updated definition incorporates the requirement for at least one cardiometabolic risk factor, thereby refining diagnostic accuracy and emphasizing the systemic nature of the condition.
Emerging evidence consistently demonstrates a strong association between MASLD and chronic kidney disease (CKD). This interrelation appears to be mediated through shared pathogenic mechanisms, including insulin resistance, chronic subclinical inflammation, endothelial dysfunction, and activation of the renin–angiotensin–aldosterone system. Notably, individuals with MASLD exhibit an elevated risk of developing CKD compared with those without metabolic hepatic steatosis, independent of conventional risk factors.

Keywords: hepatic steatosis, kidney damage**,** NAFLD, MASLD, CKD, metabolic syndrome.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) are two major global public health challenges, affecting nearly 30% of the adult population in many regions worldwide (1–3). Both chronic conditions are expected to increase substantially in the near future and are strongly associated with adverse prognosis, premature mortality, reduced quality of life, and significant socioeconomic burden (1–3). An increasing body of clinical evidence supports the notion that NAFLD may serve as an identifier of individuals at elevated risk for the development of CKD, who may benefit from more intensive monitoring and therapeutic intervention aimed at reducing the risk of kidney damage (4). A meta-analysis of 13 prospective cohort studies (encompassing over 1.2 million individuals) demonstrated that NAFLD is associated with a 1.5-fold increased risk of incident CKD over a mean follow-up period of approximately 10 years (5).

The aim of this narrative review is to summarize and critically appraise current evidence on the relationship between metabolic dysfunction–associated steatotic liver disease (MASLD) and chronic kidney disease (CKD), with a particular focus on shared epidemiological patterns, underlying pathophysiological mechanisms, and therapeutic implications. By highlighting MASLD as a systemic condition with renal consequences, this review seeks to emphasize the importance of early identification and integrated management of patients at increased risk of kidney disease.

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MATERIALS AND METHODS

A narrative literature review was conducted using the PubMed, Scopus, and Web of Science databases. Peer-reviewed original articles, reviews, meta-analyses, and international clinical practice guidelines published in English were selected based on their relevance to the association between metabolic dysfunction–associated steatotic liver disease (MASLD) and chronic kidney disease (CKD), with particular emphasis on epidemiology, underlying pathophysiological mechanisms, and clinical implications. No formal systematic review methodology was applied.

From NAFLD to MAFLD and MASLD: Evolution of Terminology and Diagnostic Criteria

In the early 1980s, Ludwig et al. introduced the terms non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) (6). These authors described fatty liver disease in moderately obese individuals, most of whom had type 2 diabetes mellitus (T2DM), occurring in the absence of excessive alcohol consumption or other competing causes of hepatic steatosis. Since then, significant advances have been made in understanding the pathophysiological mechanisms of this highly prevalent liver disorder (7). In 2020, a large panel of international experts proposed a revision of the terminology and definition of NAFLD in adults, introducing the term metabolic dysfunction-associated fatty liver disease (MAFLD) (8). In 2023, three major multinational liver associations, in collaboration with numerous national hepatology societies and patient advocacy groups, endorsed the replacement of the term NAFLD with metabolic dysfunction-associated steatotic liver disease (MASLD) (9). MASLD is defined as the presence of excessive hepatic triglyceride accumulation in conjunction with at least one cardiometabolic risk factor (such as elevated BMI or waist circumference, prediabetes or T2DM, elevated blood pressure, elevated triglycerides, or low HDL cholesterol in patients with documented steatosis). The term MASLD encompasses various conditions, including isolated hepatic steatosis (metabolic dysfunction-associated steatotic liver, MASL), metabolic dysfunction-associated steatohepatitis (MASH), as well as liver fibrosis and cirrhosis. In addition to MASLD, the broader category of steatotic liver disease (SLD) also includes MASLD with moderate (elevated) alcohol intake (MetALD), alcoholic liver disease (ALD), SLD of specific etiology (e.g., drug-induced, monogenic disorders), and cryptogenic SLD (of unknown cause) (10).

Epidemiological Evidence Linking MASLD and the Risk of Chronic Kidney Disease (CKD)

In 2008, two prospective studies reported that NAFLD (assessed by ultrasound) was associated with an increased risk of incident CKD in patients both with (11) and without type 2 diabetes (12), independent of traditional renal risk factors. Following these initial reports, numerous other studies have confirmed the strong association between NAFLD and the risk of developing CKD. In 2022, a comprehensive meta-analysis of 13 longitudinal studies (published up to August 2020), including approximately 1.2 million middle-aged individuals—28.1% of whom had NAFLD—demonstrated that NAFLD was associated with a moderately increased risk of developing stage ≥3 CKD (defined as an estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m², with or without concomitant proteinuria) over a mean follow-up period of 9.7 years (5). This risk was independent of age, sex, obesity, hypertension, type 2 diabetes, and other conventional CKD risk factors. Interestingly, the meta-analysis also showed that the risk of CKD increased further with more advanced liver disease, particularly in the presence of significant hepatic fibrosis (5). In a longitudinal study involving 3,627 Chinese individuals with type 2 diabetes, Wei et al. reported that MAFLD, diagnosed by ultrasound, was associated with an increased risk of incident CKD over a 10-year follow-up period, independent of age, sex, obesity, hypertension, dyslipidemia, liver enzyme levels, and baseline eGFR (13). Similarly, in another longitudinal study of 6,873 Chinese participants, Liang et al. found that ultrasound-diagnosed MAFLD was independently associated with a higher risk of developing CKD over a median follow-up of 4.6 years (14). In a further longitudinal study of 21,713 South Korean adults who underwent at least two consecutive health check-ups, Kwon et al. reported that individuals with MAFLD (diagnosed via ultrasound) had a significantly higher risk of incident CKD over a 5.3-year follow-up period (15). An association between MAFLD and the risk of end-stage renal disease (ESRD) has also been recently reported. In a longitudinal study involving 337,783 individuals from the UK Biobank, Chen et al. found that patients with MAFLD had nearly a twofold increased risk of developing ESRD compared to those without MAFLD over a median

follow-up period of 12.8 years (16). Therefore, multiple epidemiological studies suggest that both NAFLD and MAFLD definitions effectively identify subgroups of individuals at increased risk of developing stage ≥3 CKD over time. Moreover, advanced hepatic fibrosis appears to be associated with an even higher risk of CKD (7).

Proposed Mechanisms Linking MASLD and CKD

The exact pathophysiological mechanisms connecting these conditions remain incompletely understood and are likely to involve interactions between the liver and various extrahepatic organs. CKD is a multisystem disorder that shares several cardiometabolic risk factors with NAFLD/MASLD, making it difficult to establish clear causal relationships between the two conditions. A complex interplay of metabolic and hemodynamic alterations, lipotoxic nephrotoxicity, and genetic predisposition is believed to contribute to CKD development in individuals with NAFLD/MASLD (7).

1. Metabolic Syndrome and Liver-Mediated Mechanisms of Injury

Many cardiometabolic features of MASLD represent shared risk factors for both cardiovascular disease (CVD) and chronic kidney disease (CKD). These factors may contribute to the progression of both hepatic and renal diseases by promoting vascular and metabolic dysfunction alongside low-grade chronic inflammation (7). The proatherogenic dyslipidemia commonly observed in individuals with obesity and/or metabolic syndrome also contributes to renal vascular pathology and reduced estimated glomerular filtration rate (eGFR), thereby potentially increasing the risk of CKD (17, 37). In addition to alterations in plasma lipoprotein concentrations characteristic of MASLD and CKD, changes in the composition of small molecules, proteins, and fatty acids within lipoproteins have also been proposed to further promote renal injury, inflammation, and fibrosis (17). Other systemic factors associated with MASLD, such as arterial hypertension and chronic hyperglycemia, typically cluster into a group of metabolic risk factors that, together with abdominal obesity, are well-known contributors to the increased risk of CKD and the development of macro- and microvascular renal complications (4). These systemic metabolic risk factors may induce renal oxidative stress as well as infiltration and activation of pro-inflammatory immune cells that modify the renal microenvironment, potentially leading to albuminuria and reduced eGFR (18, 37). Altered hepatokine secretion in MASLD may also contribute to CKD development. Indeed, several hepatokines have been implicated in the pathogenesis of CKD (19).

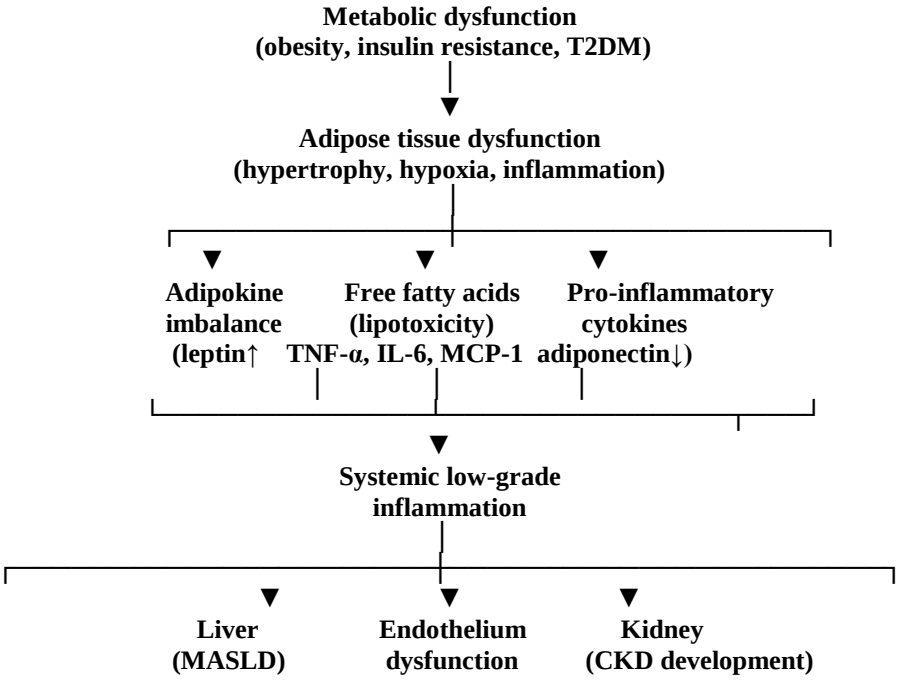

Figure 1. Pathophysiological links between metabolic dysfunction–associated steatotic liver disease (MASLD), adipose tissue dysfunction, and chronic kidney disease.
The figure was created by the authors based on current evidence from the literature.

2. Adipose Tissue, Lipid Deposition, and PPAR-γ Dysfunction as Linking Mechanisms Between MASLD and CKD

Adipose tissue dysfunction, rather than obesity per se, is likely to contribute to CKD development in the context of MASLD through both direct and indirect mechanisms, including the exacerbation of cardiometabolic risk factors. Adipocyte hypertrophy, associated with obesity and/or insulin resistance, leads to adipokine imbalance, which may affect not only adipose tissue itself but also the liver and kidneys. Indeed, numerous studies have shown that lipid droplet accumulation in the kidneys is a hallmark of CKD (20). In the kidney, lipids typically accumulate in the perirenal space, renal sinus, and renal parenchyma. Accumulation of perirenal adipose tissue is strongly associated with CKD and may directly contribute to renal dysfunction, although the underlying mechanisms are not fully elucidated (21). Excess perirenal adipose tissue may compress renal vessels and parenchyma, increasing interstitial hydrostatic pressure, stimulating renin secretion, and reducing eGFR (22). Similarly, increased adipose tissue volume in the renal sinus—considered a type of perivascular fat—lies in close proximity to renal vasculature and can produce a variety of biologically active molecules, including adipokines (e.g., leptin and adiponectin), pro-inflammatory mediators, nitric oxide, and reactive oxygen species (23). As a result, dysfunction and accumulation of sinus fat may contribute to inflammation, fibrosis, and hypertension, thereby facilitating CKD progression (7). Further impairing kidney function is the deposition of lipids in the renal parenchyma—specifically the cortical and medullary regions—which has been associated with tubular injury, glomerulosclerosis, interstitial fibrosis, and proteinuria (20). Beyond promoting ectopic lipid infiltration, dysfunctional adipose tissue in obesity may also drive systemic low-grade inflammation, which is closely linked to both CKD and MASLD (7). Interestingly, the interaction between adipose tissue and the kidneys appears to be bidirectional. Elevated systemic levels of uremic toxins resulting from renal dysfunction can induce adipose tissue inflammation and alter the adipokine profile, thereby creating a "vicious cycle" (24). The peroxisome proliferator-activated receptor gamma (PPAR-γ) plays a central role in lipid storage, metabolic homeostasis, and adipogenesis. Impairment of PPAR-γ signaling compromises adipose tissue function and plasticity, leading to both local and systemic insulin resistance—considered a key driver in the pathogenesis of both MASLD and CKD (25, 26).

3. Gut Dysfunction and Dysbiosis in MASLD and CKD

Gut dysbiosis is a hallmark of both NAFLD/MASLD and chronic kidney disease (CKD), and disturbances in intestinal function are believed to contribute to the development of both chronic conditions (27, 28). Alterations in gut microbiota composition in MASLD and CKD commonly involve reduced microbial diversity and a deficiency of beneficial bacteria, such as *Lactobacillus* and *Bifidobacterium*. In contrast, there is an overrepresentation of potentially pathogenic taxa, such as *Enterobacteria* and *Enterococci* in affected individuals (29). This dysbiotic state facilitates the translocation of microbial components, particularly lipopolysaccharides (LPS), into the systemic circulation. LPS are potent activators of nuclear factor kappa B (NF-κB) and signaling pathways associated with Toll-like receptors (TLR)-2 and TLR-4. Their presence in distant organs, including the liver and kidneys, can amplify tissue inflammation and accelerate the development of hepatic and renal fibrosis (30). Additionally, dysbiosis-induced reduction in the production of short-chain fatty acids (SCFAs) has been associated with the progression of both CKD and NAFLD/MASLD through mechanisms such as increased systemic inflammation, oxidative stress, and compromised gut barrier integrity (31). Moreover, gut dysbiosis may contribute to the development of arterial hypertension via the gut–brain–kidney axis, which has been implicated in the impairment of renal microcirculation and the progression of CKD (32).

4. Genetic Predisposition to MASLD and CKD

The role of genetic polymorphisms associated with NAFLD/MASLD as risk factors for renal dysfunction and CKD has garnered increasing attention in recent literature (33, 34). Despite some inconsistencies across studies, several MASLD-related polymorphisms—including those in *PNPLA3*, *TM6SF2*, *HSD17B13*, *MBOAT7*, and *GCKR*—have also been linked to an increased risk of CKD onset and progression (33). Notably, the *PNPLA3* I148M variant,

which affects a protein involved in hepatic lipid droplet metabolism, has been associated with reduced kidney function and an elevated risk of renal impairment in both adult and pediatric populations (35, 36). This polymorphism is thought to contribute to lipid accumulation and fibrogenesis in both hepatic and renal tissues, thereby promoting the co-progression of MASLD and CKD.

Treatment of MASLD and CKD

1. Lifestyle Interventions

Lifestyle modification remains foundational in the management of MASLD and CKD. A hypocaloric diet (500–1,000 kcal/day deficit) combined with moderate-intensity exercise (≥150 min/week) improves hepatic steatosis, inflammation, and insulin sensitivity, while reducing albuminuria and slowing eGFR decline, as supported by both liver and kidney practice guidelines (10, 37). A weight loss of 7–10% is associated with significant regression of steatosis and inflammation; ≥10% weight loss may lead to regression of MASH and improvement of fibrosis in 40–45% of patients (10, 38).

2. Pharmacotherapy with Dual Hepatic and Renal Benefits Resmetirom (Rezdiffra)

An oral thyroid hormone receptor-β agonist approved by the FDA in March 2024 for non-cirrhotic MASH with moderate-to-advanced fibrosis. In the phase III MAESTRO-NASH trial, resmetirom achieved NASH resolution without worsening of fibrosis in approximately 26–30% of treated patients versus ~10% in the placebo group, with a ≥1-stage fibrosis improvement in 24–26% versus 14% (39, 40).

GLP-1 Receptor Agonists (e.g., Semaglutide)

In a 72-week randomized controlled trial (ESSENCE study), semaglutide led to NASH resolution in 62.9% of subjects versus 34.1% with placebo, and fibrosis improvement in 37% versus 22.5% (41). Furthermore, the phase III FLOW trial conducted in patients with type 2 diabetes and CKD reported a 24% reduction in risk of major kidney outcomes (HR 0.76; 95% CI 0.66–0.88; P=0.0003), along with an 18% reduction in major adverse cardiovascular events, 20% lower all-cause mortality, and slower eGFR decline compared to placebo over a median 3.4-year follow-up (42, 43).

SGLT-2 Inhibitors

Primarily studied for renal protection, SGLT-2 inhibitors also reduce hepatic fat content and inflammation, making them synergistic with GLP-1RAs in patients with coexisting MASLD and CKD (44).

Pioglitazone and Vitamin E

These off-label options for biopsy-confirmed MASH improve histological outcomes but have less direct evidence for renal benefit; their use is supported in non-diabetic patients (for vitamin E) and insulin-resistant individuals (for pioglitazone) (45, 46).

3. Emerging Therapies

New agents include pan-PPAR agonist lanifibranor, FXR agonist combinations (cilofexor + firsocostat), and RNAi therapy targeting HSD17B13—each demonstrating anti-fibrotic effects in MASH, with potential renoprotective implications via shared metabolic pathways (47, 48).

4. CKD Management in the Context of MASLD

Standard CKD management—tight blood pressure control through RAAS inhibition, glycemic management (metformin remains safe at eGFR ≥30 mL/min/1.73 m²), and albuminuria reduction—is consistent with KDIGO guidelines and supports both renal and hepatic outcomes (37, 49).

5. Integrated Treatment Strategy

1. **Lifestyle first**: structured weight loss, Mediterranean diet, physical activity.
2. **Pharmacotherapy based on disease severity**:
   - Resmetirom for MASH with fibrosis
   - GLP-1RAs for MASLD with obesity/diabetes and CKD
   - SGLT-2 inhibitors or pioglitazone/vitamin E if GLP-1RAs are contraindicated
3. **Optimize CKD risk factors**: RAAS inhibitors, glycemic control, albuminuria monitoring
4. **Monitor treatment**: imaging, non-invasive fibrosis scores, liver/renal biochemistry
5. **Enroll in trials**: novel agents especially for advanced fibrosis or progressive CKD.

CONCLUSION

MASLD is now understood as a systemic condition with consequences that extend well beyond the liver. Evidence consistently demonstrates that it confers an increased risk for incident and progressive CKD, independent of classical metabolic comorbidities. The

connection between these two diseases is likely driven by overlapping mechanisms such as insulin resistance, chronic low-grade inflammation, oxidative stress, and lipid-mediated toxicity, as well as shared genetic determinants. When MASLD and CKD coexist, the risk of adverse cardiovascular events and premature mortality rises substantially, emphasizing the need for integrated clinical care. Moving forward, priority should be given to clarifying the molecular basis of the MASLD–CKD link, validating noninvasive diagnostic tools, and testing interventions capable of addressing both hepatic and renal injury. Framing MASLD as a determinant of renal outcomes reinforces the importance of early detection, patient stratification, and multidisciplinary management strategies to improve prognosis.

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