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Review Article

Metabolic Dysfunction-associated Steatotic Liver Disease and Chronic Kidney Disease: From Epidemiology and Pathophysiology to Clinical Prediction and Treatment Options

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) and chronic kidney disease (CKD) have shown a significant increase in comorbidity on a global scale due to the prevalence of metabolic syndrome. In 2023, a number of academic societies formally proposed the concept of MASLD, superseding the previous terminology of "non-alcoholic fatty liver disease" and "metabolic dysfunction-associated fatty liver disease". The diagnostic criteria have been revised to place greater emphasis on the association between hepatic steatosis and cardiometabolic risk factors. MASLD constitutes an independent risk factor for CKD, with this risk potentially increasing in line with the severity of fatty degeneration and the progression of hepatic fibrosis. CKD may represent a potential risk factor for the progression of fibrosis in patients with MASLD. The interaction between the two conditions may accelerate the occurrence of cardiovascular events and increase the risk of all-cause mortality. MASLD and CKD may share core pathophysiological mechanisms, including genetic variants, insulin resistance, lipid metabolism disorders, chronic inflammation, oxidative stress, and gut microbiota dysbiosis. However, the bidirectional causal relationship between the two conditions and the molecular dialogue between organs remains unclear. Furthermore, there are significant gaps in clinical prediction tools and targeted treatment strategies for comorbidities. This paper reviews common pathophysiological mechanisms in MASLD and CKD, the epidemiological and clinical evidence linking MASLD to the risk of CKD, biomarkers and clinical prediction models for coexisting conditions, and potential therapeutic strategies. Our aim is to provide a theoretical basis for early identification, mechanism exploration, and clinical treatment of comorbidities.

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Introduction

In 2020, the international expert consensus renamed non-alcoholic fatty liver disease (NAFLD) as metabolic dysfunction-associated fatty liver disease (MAFLD). The diagnosis of MAFLD is based on the presence of hepatic steatosis (detected by liver histology, non-invasive biomarkers, and imaging) while fulfilling at least one of the following three criteria: overweight or obesity, T2DM, or clinical evidence of metabolic dysfunction in lean individuals. The new nomenclature shifts the focus from "excluding other diseases" to "proactively identifying metabolic risk", emphasizing that metabolic dysfunction is a key driver of MAFLD and can coexist with other liver diseases. This standard enables more precise identification of at-risk populations, promotes personalized management, and facilitates multidisciplinary collaboration.[1–3] In 2023, the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the Latin American Association for the Study of the Liver jointly proposed the concept of metabolic dysfunction-associated steatotic liver disease (MASLD). This framework underscores hepatic steatosis in conjunction with at least one cardiometabolic risk factor, and it provides a precise delineation of the MetALD subtype to elucidate the integrated impact of metabolic and alcoholic factors.[4–7]

Despite these operational differences in the definitions of MAFLD and MASLD, both concepts pivot on the central role of metabolic health in liver disease. For the purpose of this review discussing the link with chronic kidney disease (CKD) (a condition strongly tied to metabolic syndrome (MetS)), the terms MAFLD and MASLD are used interchangeably to refer to fatty liver disease primarily driven by metabolic dysfunction, as the core pathophysiological mechanisms and clinical implications regarding CKD risk are considered broadly similar under both frameworks. A comparison among diagnostic criteria for NAFLD, MAFLD, and MASLD is shown in Figure 1.

Globally, both MASLD and CKD are highly prevalent, affecting approximately billions and hundreds of millions of

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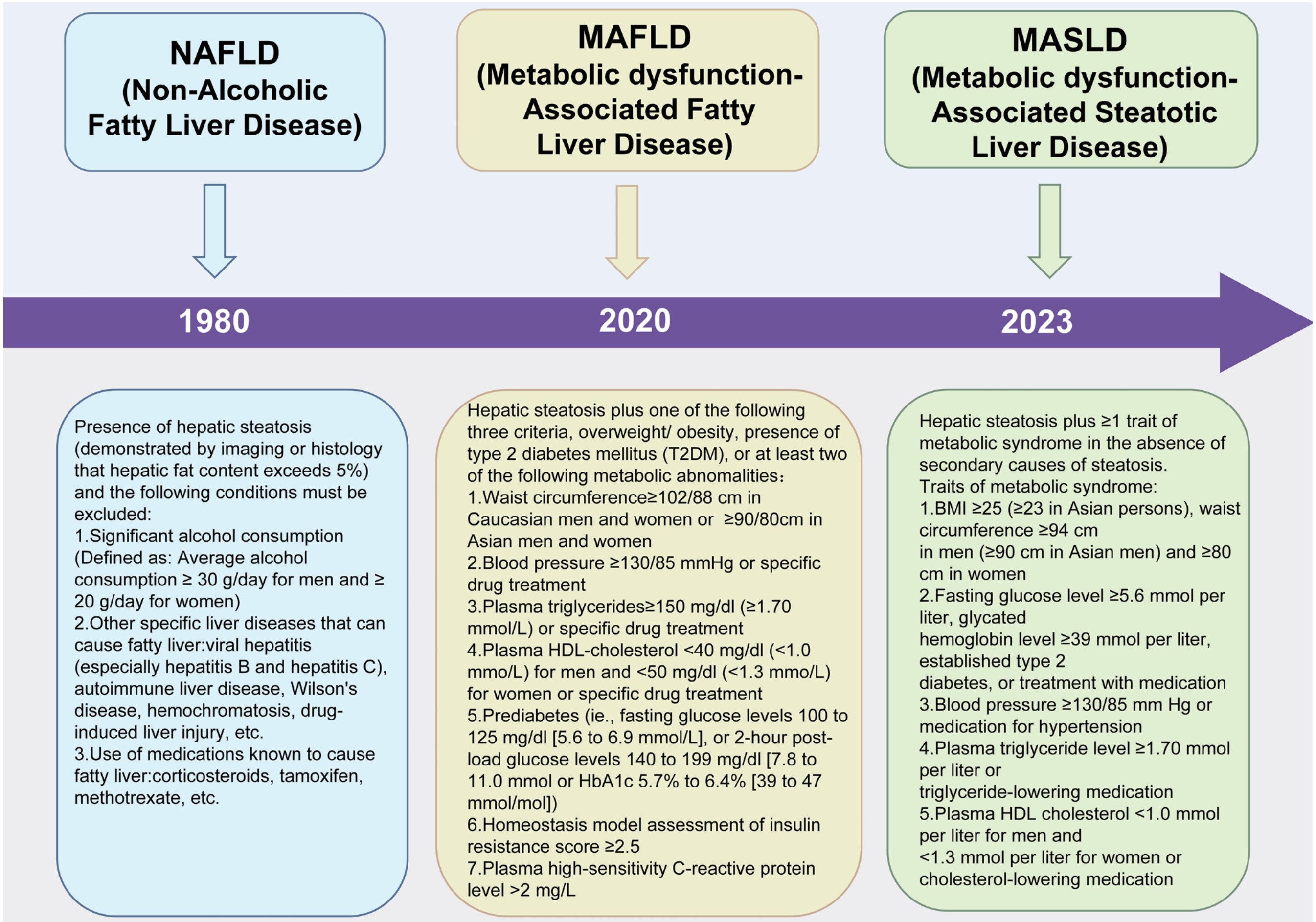

Fig. 1. Comparison among diagnostic criteria for NAFLD, MAFLD, and MASLD. This figure shows the evolution of terminology and diagnostic criteria from NAFLD to MAFLD and MASLD, with a focus shifting from "excluding other diseases" to "proactively identifying metabolic risk", emphasizing metabolic dysfunction as a core driver of disease. In current clinical practice, the terms MAFLD and MASLD are used interchangeably. NAFLD, non-alcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; BMI, body mass index; T2DM, type 2 diabetes mellitus; HDL, high-density lipoprotein; HbA1c, glycosylated hemoglobin.

individuals, respectively, and together they constitute a substantial public health burden. MASLD has a high global disease burden and has seen a significant increase in prevalence in recent years. It is a leading cause of liver cirrhosis and liver cancer and is associated with an increased risk of mortality from cardiovascular disease (CVD).[8,9] In 2021, the number of people affected by MASLD was double the number in 1990, and the prevalence increased by more than 50%. The prevalence of MASLD is more pronounced in countries and regions with a medium socio-demographic index, particularly in those located in North Africa and the Middle East.[10] In 2021, it was estimated that there were approximately 1.27 billion cases of MASLD globally, with an age-standardized prevalence rate of 15,018 per 100,000 people. There were also an estimated 138,328 deaths due to MASLD and 97,403 deaths due to MASLD-associated cirrhosis.[11] Overall, the prevalence and incidence are usually significantly higher in men than in women.[12] CKD is highly prevalent worldwide, and the disease burden due to dietary risk factors has increased rapidly in recent years.[13] End-stage renal disease (ESRD) is associated with a high risk of death and expensive treatment. From 1990 to 2021, there was a significant increase in the incidence, mortality, and disability-adjusted life year burden of CKD. Population growth and ageing are leading to a further increase in the burden of CKD.[14] In 2023, it was estimated that there were 788 million adults aged 20 years and older worldwide with CKD, a marked increase from 378 million in 1990. The global age-standardized prevalence rate of CKD among adults was 14.2% (13.4%–15.2%), representing a relative rise of 3.5% (2.7%–4.1%) compared to 1990.[15]

MASLD is an independent risk factor for CKD. This risk may increase with the severity of steatosis and the progression of liver fibrosis.[16] CKD may be a potential risk factor for the progression of fibrosis in patients with MASLD.[17] CKD is also an independent risk factor for death in patients with MASLD combined with T2DM.[18] The presence of CKD has been demonstrated to have a significant impact on the prognosis of patients with cirrhosis, due to the increased risk of acute kidney injury, the necessity for dialysis treatment, and the exacerbation of chronic liver disease.[19] Moreover, patients with CKD and MASLD are at a higher risk of cardiovascular events (CVEs). The NAFLD fibrosis score (NFS) is associated with an elevated risk of CVE and worse survival.[20,21] The concomitant presence of MASLD and CKD may offer a more precise prognosis for the likelihood of developing ischemic heart disease when compared with the prediction derived from the individual diagnoses of MASLD or CKD.[22]

CKD is more prevalent in patients with MASLD than in non-MASLD populations, and oxidative stress and the uremic environment may accelerate liver injury in patients with CKD. Both MASLD and CKD are associated with a number of risk factors, including abdominal obesity, insulin resistance (IR), dyslipidaemia, hypertension, and dysglycaemia. "Metabolic dysfunction" is an important pathogenic mechanism linking MASLD and CKD. Further studies are required to investigate the mechanisms of comorbidity and clinical diagnosis and treatment in order to provide guidance for the early prevention and clinical management of these two common and interrelated diseases.[23] This review systematically summarizes the molecular mechanisms of liver–kidney interactions, the epidemiological features and risk factors of comorbidities of MASLD and CKD, the clinical prediction tools of comorbidities, and the potential therapies. Our aim is to provide a theoretical basis for the early identification of comorbidities and precise intervention.

Common pathophysiological mechanisms in MASLD and CKD

MASLD is characterized by a pathological spectrum that begins with hepatic steatosis and can progress to steatohepatitis, marked by inflammation and liver cell injury. This process often leads to hepatic fibrosis, which is the central driver of liver-related complications.[24] CKD is defined by a sustained decline in kidney function, primarily evidenced by a reduced estimated glomerular filtration rate (eGFR). Its hallmark features include the presence of albuminuria and the development of renal fibrosis, which culminates in the progressive loss of kidney function.[25]

The pathophysiological mechanisms shared between MASLD and CKD remain incompletely understood. Metabolic dysfunction is an important pathogenic mechanism linking MASLD and CKD. Genetic variations, metabolic dysfunction (obesity, IR, hypertension, dyslipidaemia), chronic inflammation, oxidative stress, gut microbiota dysbiosis, and portal hypertension may collectively contribute to the development of CKD in patients with MASLD.[23]

Hereditary factor

Genetic mutations and epigenetic factors both play significant roles in the pathogenesis of MASLD. Single nucleotide polymorphisms in specific genes, such as *PNPLA3, TM6SF2, MBOAT7, MARC1, HSD17B13, IFNL3/4, and FGF21*, are closely associated with the onset and progression of MASLD.[26] Among them, the *PNPLA3* gene is expressed in both the liver and kidney and plays an important role in the association of MASLD with CKD. The *PNPLA3* rs738409 (I148M protein variant) G allele is associated with MASLD, as well as with reduced eGFR levels and an accelerated decline in eGFR.[27,28] Previous studies have demonstrated that the *PNPLA3* I148M variant is associated with reduced eGFR and an increased risk of CKD in patients with NAFLD complicated by T2DM. This association is independent of common renal risk factors and the severity of NAFLD. Furthermore, *PNPLA3* exhibits high expression levels in renal podocytes.[29] Patients with NAFLD and persistent normal alanine aminotransferase (ALT) who carry the *PNPLA3* rs738409 G allele face a higher risk of early glomerular and tubular injury.[30] The *PNPLA3* p.I148M variant has an adverse effect on eGFR levels in middle-aged individuals with metabolic dysfunction. Silencing the *PNPLA3* p.I148M variant can prevent the progression of kidney injury in carriers.[31] In addition, eGFR levels are higher in patients carrying the rare A allele of *HSD17B13*. This effect is observed in both patients with and without NAFLD and is independent of *PNPLA3* and *TM6SF2* gene polymorphisms. This variant protects renal function and reduces its decline with age.[32] The main studies of hereditary factors in MASLD/MAFLD/NAFLD and CKD are shown in Table 1.[28–32]

Metabolic dysfunction

MetS is the underlying pathological basis for the development of both MASLD and CKD. It mainly mediates organ damage through core components such as IR, lipid metabolism disorders, hypertension, and hyperglycaemia.[33,34]

Insulin resistance: Insulin resistance is an important feature of MetS and a common driver of MASLD and CKD.

Systemic IR promotes the release of free fatty acids (FFAs) from visceral adipose tissue into the bloodstream. An increase in the uptake of FFAs by the liver, alongside enhanced hepatic synthesis of its own lipids and decreased lipid oxidation and export, leads to the accumulation of lipids within the liver. Insulin resistance also promotes increased hepatic gluconeogenesis, exacerbating systemic IR. Hepatocyte lipid overload and IR activate inflammatory pathways (such as IKKβ/NF-κB and JNK) and stress pathways (such as endoplasmic reticulum stress and oxidative stress), thereby promoting steatohepatitis and fibrosis.[35–38]

Similarly, IR damages the kidney through a variety of pathways, including hemodynamic alterations, direct cellular damage, promotion of inflammation, and fibrosis. Insulin resistance activates the renin–angiotensin–aldosterone system (RAAS) via sympathetic excitability and vascular endothelial dysfunction. This affects renal haemodynamics and intraglomerular pressure, as well as having a modulating effect on the glomerular filtration rate. Insulin resistance interferes with the insulin signaling pathway in podocytes, which can lead to podocyte damage and disruption of the glomerular filtration barrier. This increases protein filtration, resulting in proteinuria. The chronic low-grade inflammation, adipokine imbalance, mitochondrial dysfunction, and oxidative stress associated with IR can activate renal inflammatory and fibrotic pathways.[39–41] In addition, obesity, overnutrition, lipotoxicity, chronic inflammation, and CKD–mineral bone metabolism disorder further aggravate IR.[42] The Metabolic Score of Insulin Resistance can be used to stratify the risk of CKD in non-diabetic populations.[43]

Disorders of lipid metabolism and lipotoxicity: Disorders of lipid metabolism and lipotoxicity constitute a common pathological basis for the development of MASLD and CKD.[44]

Patients with MASLD have elevated plasma concentrations of triglycerides and total and low-density lipoprotein (LDL) cholesterol, as well as reduced high-density lipoprotein. The liver synthesizes various intrahepatic lipids, such as triacylglycerols, diacylglycerols, ceramides, and sterols, by re-esterifying FFAs. Accumulation of hepatic lipids produces lipotoxicity, which can induce mitochondrial dysfunction, oxidative stress, and inflammatory factor release. These factors, in turn, drive the progression of MASLD.[45,46]

In CKD patients, uremic toxins cause endoplasmic reticulum and oxidative stress, which enhances lipolysis and increases the release of FFAs, resulting in lipotoxicity and IR. Altered lipid metabolism, lipotoxicity, and the accumulation of uremic toxins can cause macrophages to adopt a pro-inflammatory phenotype, resulting in an increased release of inflammatory factors. The expansion of adipose tissue due to hypertrophy and hyperplasia is both a consequence and a driver of this metabolic-inflammatory dysregulation. Specifically, adipocyte hypertrophy drives adipose tissue dysfunction and a pro-inflammatory state, which in turn further

Table 1. Major studies of hereditary factors in MASLD/MAFLD/NAFLD and CKD

Author, Year[Refs.]	Study characteristics	Main findings	Conclusion
Alessandro Mantovani *et al*., 2020[29]	157 patients with non-insulin -treated T2DM were enrolled to diagnose NAFLD and to detect CKD (defined as eGFR < 60 mL/min/1.73 m^2 or abnormal albuminuria)	The prevalence of CKD was significantly higher in *PNPLA3* I148M pure heterozygote (M/M) patients (63.6%, $P = 0.028$) and was independent of the severity of liver disease (liver stiffness ≥ 7kPa) and other risk factors	The *PNPLA3* I148M variant is associated with an increased risk of CKD in patients with T2DM combined with NAFLD and is independent of traditional renal risk factors and NAFLD severity
Dan-Qin Sun *et al*., 2020[30]	A total of 217 patients with histologically-proven NAFLD were enrolled, including 75 with persistently normal ALT (nALT, ALT < 40U/L for ≥3 months) and 142 with abnormal ALT (abnALT)	In nALT patients, the *PNPLA3* rs738409 GG genotype carriers had higher CKD risk (adjusted OR = 3.42), abnormal albuminuria risk (adjusted OR = 2.87) than CC/CG carriers, independent of kidney risk factors and NAFLD histologic severity	*PNPLA3* genotyping may help identify NAFLD patients at higher risk of renal tubular injury
Anna Di Sessa *et al*., 2020[32]	A study consecutively included 684 obese children with a diagnosis of NAFLD to assess the association of the HSD17B13 variant with eGFR	The rare A allele of *HSD17B13* rs72613567: TA variant is associated with higher eGFR levels in obese children, independent of *PNPLA3* and *TM6SF2* polymorphisms, and regardless of NAFLD	The *HSD17B13* gene variant has a protective effect on kidney function and provides new evidence for a genetic association between NAFLD and CKD
Alessandro Mantovani *et al*., 2023[31]	The study included 1,144 middle-aged individuals with metabolic dysfunction from the Liver-Bible-2022 cohort	The *PNPLA3* p.I148M variant was associated with lower eGFR (−1.24 mL/min/1.73 m^2 per allele, 95% CI: −2.32 to −0.17, $P = 0.023$), independent of age, sex, PRS-CKD, and other confounders	The *PNPLA3* p.I148M variant exerts a detrimental impact on eGFR in middle-aged individuals with metabolic dysfunction
Alessandro Mantovani *et al*., 2024[28]	A narrative minireview synthesized epidemiological (cross-sectional and prospective) and experimental studies	The *PNPLA3* rs738409 G allele was significantly associated with impaired renal function as evidenced by reduced eGFR, abnormal albuminuria, and increased risk of CKD in adults and children, independently of traditional renal risk factors and MASLD severity	The *PNPLA3* rs738409 G allele is strongly associated with kidney disease and may serve as a biomarker for identifying people at high risk for CKD and progression of MASLD

NAFLD, non-alcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; CKD, chronic kidney disease; T2DM, type 2 diabetes mellitus; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; PRS-CKD, polygenic risk score for chronic kidney disease; OR, odds ratio; CI, confidence interval; PNPLA3, patatin-like phospholipase domain-containing protein 3; TM6SF2, transmembrane 6 superfamily member 2; HSD17B13, hydroxysteroid 17-beta dehydrogenase 13.

exacerbates systemic metabolic disturbances. This can lead to haemodynamic changes that promote glomerular hyperfiltration. In addition, the expression levels of adipokines, including lipocalin and leptin, are significantly altered in patients with CKD. These factors promote renal microvascular injury, inflammation, thrombosis, and fibrosis when acting together.[47–49]

Hypertension: Hypertension, which is prevalent in MetS, is an independent risk factor for CKD and may also accelerate MASLD progression through systemic vascular injury.

Hypertension leads to high glomerular capillary pressure and endothelial damage. This causes glomerular hyperfiltration and proteinuria, as well as promoting glomerulosclerosis. RAAS hyperactivation is a key factor. Angiotensin II (hereinafter referred to as Ang II) increases glomerular capillary pressure by constricting small outgoing glomerular arterioles and by stimulating the proliferation of cells and the deposition of extracellular matrix. Sustained high blood pressure can also cause renal microvascular ischaemia and the activation of RAAS, creating a vicious cycle of "hypertension–renal injury–RAAS activation" that drives immune inflammation and fibrosis.[50–53]

Systemic endothelial dysfunction mediated by vasoactive substances promotes hepatic sinusoidal capillarization and portal hypertension.[54] The latter can affect the homeostasis of the gut–hepatic axis, disrupting intestinal barrier function and altering the composition of intestinal flora. This can lead to an increase in bacterial and endotoxin translocation, as well as the activation of hepatic immune cells to produce pro-inflammatory mediators that can amplify renal inflammation and fibrosis.[55] In addition, hypertension can create a positive feedback loop with IR, whereby IR exacerbates sodium retention and volume load, while hypertension exacerbates hepatic lipid accumulation and inflammation through sympathetic excitation. This forms a vicious triangle of "hypertension–IR–MASLD".[39]

Hyperglycaemia and glycotoxicity: Hyperglycaemia in MetS is an important risk factor for MASLD and CKD.

Hyperglycaemia contributes to the development of MASLD by increasing IR in the body, causing lipid metabolism disorders that produce excessive lipotoxins, affecting the normal function of mitochondria, and altering the levels of inflammatory and adipokine factors, which in turn damage liver cells and exacerbate liver inflammation and steatosis.[56,57] MASLD significantly influences the risk of diabetes and the development of microvascular and macrovascular complications. Diabetes accelerates the progression of liver fibrosis in MASLD and promotes the development of hepatocellular carcinoma.[58]

Metabolic changes induced by hyperglycaemia are a major driver of diabetic kidney disease, leading to glomerular hypertrophy, glomerulosclerosis, and inflammation and fibrosis of the glomeruli.[59,60] Hyperglycaemia activates RAAS, leading to glomerular hyperfiltration. Hyperglycaemia triggers endoplasmic reticulum stress, leading to cellular dysfunction and damage. Hyperglycaemia induces mitochondrial fission and increases ROS production, leading to proteinuria. Hyperglycaemia promotes the production of inflammatory cytokines such as IL-6, TNF-α, and MCP-1, thereby exacerbating renal inflammation and fibrosis.[61]

Immunomodulation and inflammatory response

Immune regulation and inflammatory response are important pathophysiological bridges between MASLD and CKD.

Hepatic macrophages (such as Kupffer cells and monocyte-derived macrophages), neutrophils, lymphocytes, and other cells participate in the inflammatory and fibrotic progression of MASLD, forming a pro-inflammatory hepatic immune microenvironment. Histone modifications, non-coding RNA regulation (such as microRNA (miRNA)), chromatin remodeling, and RNA modifications (such as m^6A modifications) influence the reprogramming and activity of immune cells in MASLD. Signaling pathways including Notch, cGAS–STING, and CD47–SIRPα are activated in immune cells within MASLD, regulating cellular differentiation and inflammatory responses.[62–67] Interestingly, this pro-inflammatory and pro-fibrotic immune microenvironment can also contribute to the development of CKD. A key factor in the development of fibrosis is the shift in macrophage phenotype from an early pro-inflammatory (M1) state to a mid- to late pro-fibrotic (M2) state. Decreased renal function due to CKD can also cause changes to the immune system, including persistent systemic inflammation and acquired immunosuppression.[68]

Pro-inflammatory factors can directly damage hepatocytes and renal cells, triggering an inflammatory response that activates hepatic and renal stellate cells and fibroblasts. This leads to the deposition of extracellular matrix and fibrosis.[69–71] In addition, altered hepatic cytokine release in MASLD may contribute to the development of CKD through close hepatic–renal crosstalk, such as FGF21.[72,73]

Intestinal flora imbalance

Intestinal flora imbalance plays a key role in the development of MASLD and CKD by impacting bile acid metabolism, generating abnormal metabolites, and altering the composition of the microbiota.[74]

Intestinal flora is involved in bile acid homeostatic changes and metabolic transformations. Patients with MASLD have altered bile acid profiles, such as elevated serum levels of total bile acids and primary and secondary bile acids.[75,76] Patients with CKD also have imbalances in bile acid homeostasis, such as elevated serum bile acids and decreased urinary bile acids.[77] Abnormal bile acid metabolism due to intestinal flora dysbiosis interferes with the farnesoid X receptor (FXR) and TGR5 signaling pathways and affects the normal function of the liver and kidney.[78–81]

Metabolites such as short-chain fatty acids (SCFAs) and trimethylamine-N-oxide (TMAO), which are produced by intestinal flora, play an important role in the development of MASLD in patients with CKD. Decreased levels of SCFAs lead to increased synthesis of uremic toxins and induce renal dysfunction.[82] High levels of TMAO promote the progression of hepatic fibrosis and renal dysfunction.[83,84]

The composition of the intestinal microbiota is altered in patients with both MASLD and CKD. Patients with MASLD exhibit an increased relative abundance ofthe genus *Bacteroides* and the genus *Aspergillus* along with a decreased abundance of Firmicutes in their faeces.[85,86] Patients with CKD show a reduced abundance of Actinobacteria in their faeces, as well as an increased abundance of Verrucomicrobia and *Lactobacillus* spp.[87] In patients with MASLD and CKD, there are changes in *Aspergillus* spp., *Lactobacillus* spp., the *Escherichia–Shigella* group, and Firmicutes. These flora changes may be involved in the pathogenesis of MASLD and CKD by influencing metabolite production and immune responses.[74]

In addition, recent studies have shown that the gut microbiota of patients with MASLD and CKD differs from that of healthy individuals. Patients with CKD have lower levels of bacteria that produce SCFAs and faecal acetyl-CoA transferase, as well as higher levels of plasma intestinal fatty acid-binding protein. The composition of the gut microbiota can effectively distinguish between the two conditions, with patients exhibiting mixed characteristics of both.[88]

Portal hypertension

The main cause of portal hypertension in patients with MASLD is increased intrahepatic vascular resistance, which stems from perisinusoidal fibrosis and microcirculatory damage. The molecular basis of the adverse effects of portal hypertension is the activation of signaling pathways and mechanical forces. Disruption of the mechanical homeostasis of hepatic sinusoids is a key factor in the pathogenesis of MASLD. This disruption results from the accumulation of intracellular lipids, enhanced extracellular matrix stiffness, and altered contractile cytoskeletal function. Ultimately, this leads to fibrosis accumulation and cell shrinkage. Fibrosis narrows the sinusoidal gap, distorting the microvascular network and inducing the local secretion of vasoactive mediators. This leads to abnormal vasoregulation and endothelial dysfunction, exacerbating intrahepatic vascular resistance and elevating portal pressure.[54,89–91] Animal studies have shown that a sudden increase in portal pressure can trigger a hepatic–renal reflex, leading to a decreased glomerular filtration rate and oliguria.[92] Early-stage MASLD may present with subclinical portal hypertension. As the disease progresses, sustained increases in intrahepatic vascular resistance, as well as inflammation and fibrosis of the liver, can trigger a pathological hepatico–renal reflex. This reflex affects renal blood flow and exacerbates renal injury.[93]

Common pathophysiological mechanisms in MASLD and CKD are shown in Figure 2.

Epidemiological and clinical evidence linking MASLD to the risk of CKD

Both epidemiological studies and clinical evidence confirm that MASLD is closely associated with the onset and progression of CKD. The major systematic reviews and meta-analyses linking MASLD to CKD risk are detailed in Table 2.[94–102]

MASLD or MAFLD better identifies patients at risk of CKD than NAFLD

The diagnosis of traditional NAFLD relies on exclusion criteria, potentially overlooking individuals with fatty liver disease who exhibit significant metabolic disorders and a risk of CKD. The diagnostic criteria for MASLD or MAFLD, which are based on overweight/obesity, diabetes, or metabolic dysfunction, have superior predictive power for CKD risk. Studies have shown that the MAFLD criteria identify a wider at-risk population and detect more individuals who are at risk

Table 2. Systematic reviews and meta-analyses linking MASLD/MAFLD/NAFLD to CKD risk

Author, Year[Refs.]	Number of studies	Number of subjects	Main findings
Giovanni Musso *et al*., 2014[98]	33	63,902	Cross-sectional study: the prevalence of CKD was significantly higher in patients with NAFLD (OR = 2.12, 95% CI 1.69–2.66, $P < 0.00001$); Longitudinal study: the prevalence of CKD was significantly higher in patients with NAFLD (HR = 1.79, 95% CI 1.65–1.95, $P < 0.00001$)
Alessandro Mantovani *et al*., 2018[99]	9	96,595	Patients with NAFLD had a significantly higher risk of chronic kidney disease (CKD, stage ≥ 3) than the non-NAFLD population, with a hazard ratio of 1.37 (95% CI 1.20–1.53, $I^2 = 33.5\%$) in the random-effects model; Patients with severe NAFLD (assessed by ultrasound and non-invasive fibrosis markers) had a higher risk of CKD (2 studies, HR = 1.50, 95% CI 1.25–1.74, $I^2 = 0\%$)
Alessandro Mantovani *et al*.,2022[100]	13	1,222,032	NAFLD was associated with a moderately increased risk of incident CKD stage ≥ 3 (random-effects HR 1.43, 95% CI 1.33 to 1.54; $I^2 = 60.7\%$)
Yueqiao Chen *et al*., 2023[101]	19	1,111,046	The incidence of CKD is highly significant in NAFLD subjects compared with controls (OR: 1.95; 95% CI: 1.65–2.31). The diabetic non-NAFLD subjects showed a significantly increased incidence of CKD compared to the non-diabetic subjects with NAFLD (OR: 1.79; 95% CI: 1.35–2.38)
Jianghua Zhou *et al*., 2023[94]	17	845,753	In 7 cohort studies, the combined random effect HR for incident CKD in patients with MAFLD was 1.29 (95% CI 1.17–1.41, $I^2 = 87.0\%$); In 10 cross-sectional studies, the combined random effect OR for prevalent CKD in patients with MAFLD was 1.35 (95% CI 1.11–1.64, $I^2 = 92.6\%$)
Nenny Agustanti *et al*., 2023[95]	11	355,886	Cross-sectional study: significantly higher prevalence of CKD in patients with MAFLD (OR = 1.50, 95% CI [1.02–2.23], $P = 0.04$); Cohort study: significantly higher prevalence of CKD in patients with MAFLD (corrected HR = 1.35, 95% CI [1.18–1.52], $P < 0.001$)
Wanghao Liu *et al*., 2024[96]	8	598,531	MAFLD is significantly associated with increased CKD risk (Pooled HR: 1.38, 95% CI: 1.24–1.53, $I^2 = 95\%$), independent of sex, BMI, and other traditional CKD risk factors
Grazia Pennisi *et al*., 2024[97]	21	7,666,916	There was a non-significant trend towards a higher risk of CKD in patients with MAFLD (OR = 1.06, 95% CI:1.00–1.12, $P = 0.058$)
Yixian You *et al*., 2024[102]	15	122,874	Patients with non-obese NAFLD had a comparable risk of developing CKD compared to patients with obese NAFLD (OR 0.92, 95% CI 0.72–1.19)

NAFLD, non-alcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; CKD, chronic kidney disease; BMI, body mass index; CI, confidence interval; HR, hazard ratio; OR, odds ratio.

of CKD.[103,104] They include groups that were excluded by the NAFLD criteria but were at an elevated risk of CKD, such as MAFLD patients who consumed excessive amounts of alcohol or had comorbid viral hepatitis.[104] MAFLD is an independent risk factor for new-onset CKD, and compared with fatty liver disease and NAFLD, MAFLD demonstrates superior predictive capability for the risk of CKD development.[105] The strength of the overall association between MAFLD and CKD is higher than that between NAFLD and CKD.[106] The MAFLD criteria may prove more accurate than the MASLD criteria in identifying patients with concurrent liver injury, metabolic disorders, and CKD.[107]

The MASLD or MAFLD criteria are more closely linked to the pathophysiology of CKD. Patients with MAFLD exhibit poorer renal function indicators, such as a lower eGFR and a higher prevalence of CKD, compared with patients with NAFLD. Furthermore, the definition is more consistent with CKD-related mechanisms, such as genetic polymorphisms and intestinal flora.[108] In addition, patients with MAFLD are at a higher risk of hypertension, dyslipidaemia, and diabetes than those with NAFLD. MAFLD is a better representation of the metabolic and CVD burden of fatty liver disease.[109] The severity of MAFLD exhibits a significant graded association with CKD and abnormal albuminuria. Patients diagnosed with MAFLD who exhibit elevated liver fibrosis scores are predisposed to an increased risk of developing CKD and abnormal albuminuria.[110] Studies have indicated that the definition of MASLD is also more effective than the definition of NAFLD in identifying individuals at high risk of developing CKD or abnormal albuminuria.[111]

In summary, the superior ability of MAFLD or MASLD criteria to identify patients at risk for CKD stems, in part, from a fundamental alignment of their diagnostic frameworks. By definition, MAFLD and MASLD positively select for individuals with cardiometabolic risk factors, such as obesity, dyslipidaemia, hypertension, and IR, which are themselves well-established drivers of CKD pathogenesis. Using MASLD or MAFLD criteria can help with the early screening of people with fatty liver disease who need to be monitored for kidney injury and can provide a framework for targeted interventions. The comparison of MASLD/MAFLD versus NAFLD in identifying CKD risk is shown in Table 3.[103–107,110,111]

MASLD is an independent risk factor for the development of CKD

Preliminary studies have indicated a significant correlation between MAFLD and the increased prevalence and incidence of CKD.[34] A meta-analysis incorporated data from 17 observational studies, encompassing a total of 845,753 par-

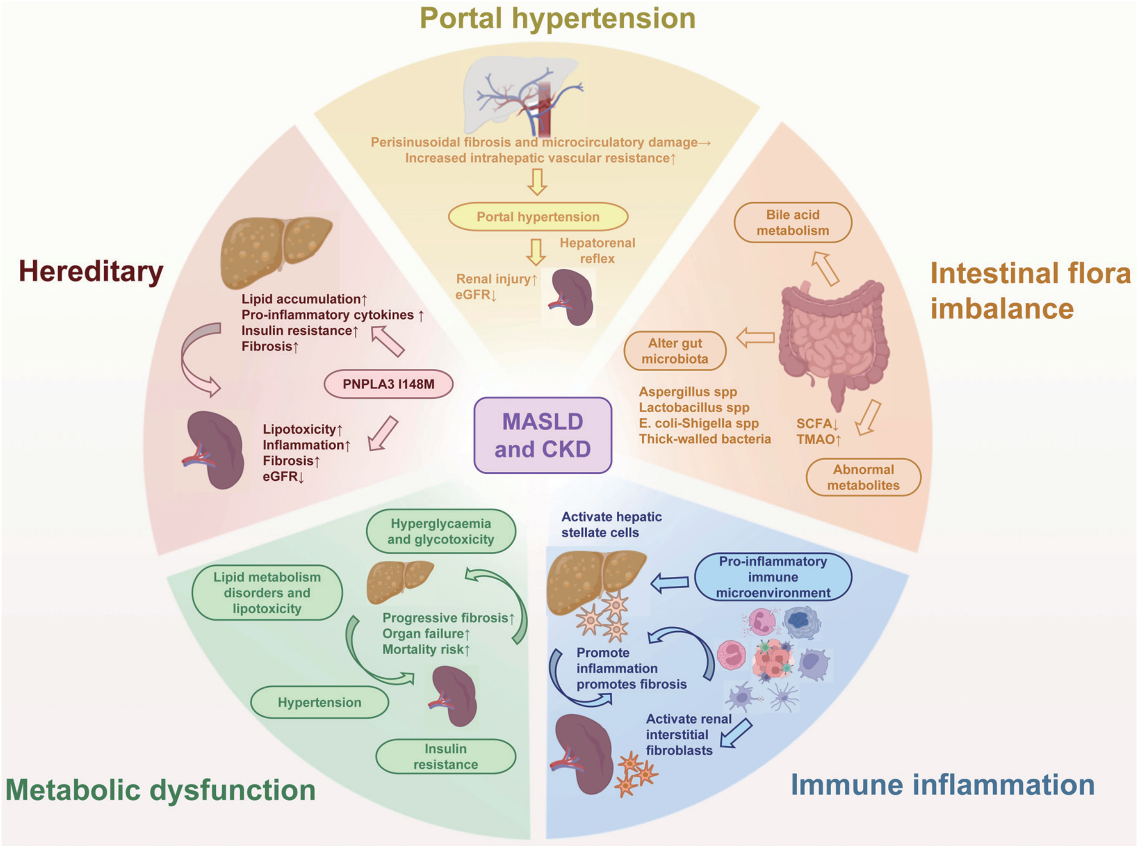

Fig. 2. Common pathophysiological mechanisms in MASLD and CKD. This figure demonstrates the core pathophysiological mechanisms of genetic variants, metabolic dysfunction (insulin resistance, dyslipidaemia, hypertension, glucose metabolism disorders), immune-inflammatory response, dysbiosis of intestinal flora, and portal hypertension that may be shared by MASLD and CKD. This schematic diagram was created using Microsoft PowerPoint. The graphic elements depicting organs and cells are adapted from publicly available scientific image libraries and comply with licensing terms permitting academic use and publication. MASLD, metabolic dysfunction-associated steatotic liver disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TMAO, trimethylamine oxide; SCFAs, short-chain fatty acid; PNPLA3, patatin-like phospholipase domain-containing 3.

ticipants. In the seven cohort studies, the pooled random-effects hazard ratio (HR) for incident CKD in patients with MAFLD was 1.29 (95% CI 1.17–1.41, I^2 = 87.0%). In the ten cross-sectional studies, the pooled random-effects odds ratio (OR) for prevalent CKD in patients with MAFLD was 1.35 (95% CI 1.11–1.64, I^2 = 92.6%).[94] Another meta-analysis incorporating 11 studies involving 355,886 participants, with follow-up periods ranging from 4.6 to 6.5 years, demonstrated that MAFLD was associated with a higher prevalence (OR 1.50, 95% CI 1.02–2.23) and incidence (HR 1.35, 95% CI 1.18–1.52) of CKD, and that this association did not vary by age, sex, comorbidities, study region, or follow-up duration.[95] MAFLD is an independent predictor of CKD (HR 1.38, 95% CI 1.24–1.53, I^2 = 95%), and this association is unaffected by sex, BMI, and other confounding factors.[96] A retrospective cohort study enrolled 41,246 participants in China, of whom 11,860 (28.8%) were diagnosed with MAFLD. Over the course of the 14-year follow-up (median 10.0 years), 5,347 (13%) participants experienced a new incident of CKD (135.73 per 10,000 person-years). MAFLD-related CKD risk was higher in men under 60 years of age with combined dyslipidaemia.[112] Further investigations revealed that patients with MASLD exhibited a higher risk of CKD compared with those without MASLD (HR 1.12, 95% CI 1.09–1.16), with this risk increasing alongside the severity of hepatic steatosis ($P < 0.001$). Moreover, even after disease remission, individuals with a history of moderate-to-severe hepatic steatosis retained an elevated CKD risk (HR 1.15, 95% CI 1.03–1.27).[16] It is also notable that CKD may be a potential risk factor for the development of liver fibrosis in patients with MAFLD.[17]

Degree of hepatic fibrosis may be a stratifier of MASLD-associated CKD risk

The degree of liver fibrosis in patients with MAFLD, rather than simple hepatic steatosis, is a significant hepatic factor in predicting the risk of CKD.[95] Another study indicates that MAFLD with liver fibrosis constitutes an independent risk factor for abnormal proteinuria, whereas MAFLD without liver fibrosis is unrelated to abnormal proteinuria. MAFLD is associated with a lower risk of reduced eGFR, whereas liver fibrosis is unrelated to eGFR decline.[113] Liver stiffness measured by vibration-controlled transient elastography is significantly associated with an increased risk of CKD and albuminuria in patients with NAFLD.[114] Significant liver fibrosis is associated with an increased risk of early kidney dysfunction in patients with MAFLD. Transient elastography can be used to screen for early kidney dysfunction, and a liver stiffness measurement (LSM) cut-off value of 6.1 kPa is the most accurate predictor of early kidney dysfunction.[115] Improving MAFLD could be an effective way to prevent or slow the progression of CKD. A large-scale prospective cohort study involving 337,783

Table 3. MASLD/MAFLD vs. NAFLD in identifying CKD risk

Author, Year[Refs.]	Study characteristics	Outcome indicator	Main findings
Dan-Qin Sun *et al*., 2020[110]	A cross-sectional study using data from NHANES-III (1988–1994) included 12,571 adults aged 20–74 years. Subjects were categorized into MAFLD, NAFLD, and non-metabolic dysregulation (MD) NAFLD group	Incident CKD was defined as eGFR < 60 mL/min/1.73 m^2 or urinary ACR ≥ 3mg/mmol	The prevalence of CKD was significantly higher in MAFLD than NAFLD (29.60% vs. 26.56%, $P < 0.05$), with lower eGFR (74.96±18.21 vs. 76.46±18.24 mL/min/1.73 m^2, $P < 0.001$). MAFLD identifies CKD better than NAFLD
Chan-Young Jung *et al*., 2022[103]	A nationwide cohort study with a median follow-up of 5.1 years included 268,946 adults aged 40–64 years with a diagnosis of FLD based on FLI (≥30) and was divided into non-MD NAFLD, MAFLD-but-not-NAFLD, and overlapping FLD	Incident CKD was defined as eGFR < 60 mL/min/1.73 m^2 or proteinuria (≥trace) on two consecutive health examinations	MAFLD identified a higher proportion of individuals at risk of incident CKD than NAFLD (aHR = 1.39 vs. 1.33, both $P < 0.001$). MAFLD better identifies individuals at risk of incident CKD compared to NAFLD
So Yoon Kwon *et al*., 2023[104]	A retrospective cohort study with a median follow-up of 5.3 years included 21,713 adults. Categorized into 5 groups based on FLD and MD: non-FLD without MD, non-FLD with MD, MAFLD-only, NAFLD-only, and both-FLD	Incident CKD defined as eGFR < 60 mL/min/1.73 m^2 or urine albumin-to- creatinine ratio (uACR) ≥ 30 mg/g	Compared to the control group, the risk of incident CKD was significantly higher in MAFLD-only (HR 1.97, 95% CI 1.49–2.60), both-FLD (HR 1.50, 95% CI 1.19–1.89), and non-FLD with MD (HR = 1.23, 95% CI 1.00–1.53). No significant association was observed in NAFLD-only (HR 1.06, 95% CI 0.63–1.79). MAFLD criteria identify more individuals at risk for CKD
Marenao Tanaka *et al*., 2023[105]	A prospective cohort study with a 10-year follow-up included 13,159 Japanese subjects with a mean age of 48 years. Subjects were categorized into FL, NAFLD, and MAFLD groups	New onset of CKD, defined as eGFR < 60 mL/min/1.73 m^2 or positive for urinary protein	MAFLD was an independent risk factor for CKD (HR 1.12, 95% CI 1.02–1.26, $P = 0.027$), whereas FL or NAFLD were not significantly and independently associated with CKD ($P > 0.05$). MAFLD predicts the risk of CKD better than FL or NAFLD
Yixiao Zhang *et al*., 2023[106]	A prospective cohort study used two independent cohorts (TCLSIH and UK Biobank), including 25,974 adults from Tianjin, China (TCLSIH) and 113,954 adults from the UK (UK Biobank)	Incident CKD was defined as eGFR < 60 mL/min/1.73 m^2, proteinuria, or clinical diagnosis	Both MAFLD and NAFLD are associated with higher CKD risk, with stronger association for MAFLD (TCLSIH:HR = 1.47; UKB:HR = 1.73)
Ziyan Pan *et al*., 2024[107]	A cross-sectional study using data from the U.S. NHANES (2017–2020) including 5,492 adults. Subjects were categorized into "MAFLD-only" (3.5%), "MASLD-only" (1.1%), and overlapping groups (43.4%)	Prevalence of CKD (eGFR ≤ 60 mL/min/1.73 m^2 or albuminuria), albuminuria (uACR ≥ 3 mg/mmol)	MAFLD criteria are superior to MASLD criteria in predicting CKD risk. After adjusting for confounders, the MAFLD-only group had a 4.73-fold higher risk of CKD than the MASLD-only group ($P < 0.03$)
Ji Hye Heo *et al*., 2024[111]	A retrospective cohort study included 214,145 Korean adults with a median follow-up duration of 6.1 years. Subjects were categorized into No-SLD group, NAFLD-only group, MASLD-only group, both NAFLD and MASLD group, SLD not categorized as NAFLD or MASLD	Incident CKD (eGFR < 60 mL/min/1.73 m^2). Incident abnormal albuminuria (uACR ≥ 30 mg/g)	Both MASLD and NAFLD groups were associated with a higher risk of incident CKD, with MASLD showing a slightly stronger association (adjusted HR: 1.21 vs. 1.18). The MASLD-only group had the strongest association with incident abnormal albuminuria (adjusted HR = 1.96). The NAFLD-only group had no independent association with CKD or abnormal albuminuria. MASLD criteria identify more individuals at risk for CKD and abnormal albuminuria than NAFLD

NAFLD, non-alcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; uACR, urinary albumin-to-creatinine ratio; FLD, fatty liver disease; FLI, fatty liver index; SLD, steatotic liver disease; aHR, adjusted hazard ratio; HR, hazard ratio; CI, confidence interval; TCLSIH, Tianjin Chronic Low-grade Systemic Inflammation and Health Cohort; uACR, urinary albumin-to-creatinine ratio; UKB, UK Biobank.

participants with a median follow-up of 12.8 years found that MAFLD was significantly associated with the development of end-stage kidney disease (ESKD)(HR 2.03, 95% CI 1.68–2.46, $P < 0.001$). Elevated liver fibrosis scores and increased genetic risk scores were associated with a higher risk of ESKD in patients with MAFLD.[116]

MetS components are important mediators of the association between MASLD and CKD

In patients with NAFLD, obesity, hypertension, and hyperuricaemia are all independent predictors of CKD. This supports the idea that common cardiometabolic risk factors may be the link between NAFLD and CKD.[117] The association between MAFLD and CKD may be substantially mediated by coexisting metabolic abnormalities. While MAFLD is strongly associated with CKD risk in models adjusted for basic demographics, this association often attenuates when further accounting for individual components of MetS. This suggests that the metabolic dysfunction intrinsic to MAFLD is a primary driver of the heightened CKD risk observed in this population.[118] Hypertension, hyperuricaemia, remnant cholesterol, and the NFS are independent risk factors for the prevalence of CKD in individuals with diabetes or prediabetes and MAFLD.[119] The coexistence of abdominal obesity and MAFLD increases the prevalence and mortality of CKD. Abdominal obesity mediates the association between MAFLD and CKD, with waist circumference, waist-to-hip ratio, and lipid accumulation product demonstrating superior mediating effects compared with BMI.[120] Elevated triglyceride-to-glucose ratios in patients with MAFLD may increase the incidence of CKD, particularly among younger individuals.[121] MAFLD independently increases the risk of CKD alongside eGFR and urine albumin-to-creatinine ratio, with T2DM status playing a key driving role. The worsening of blood glucose levels in MAFLD exhibits a dose-dependent relationship with CKD risk.[122] Notably, the co-occurrence of MAFLD significantly increases the risk of progression to CKD in patients with T2DM, particularly in those under 60 years of age. This highlights the importance of preventing MAFLD early to reduce complications associated with T2DM.[123] Advanced liver fibrosis in patients with NAFLD is associated with an increased risk of CKD in patients with T2DM.[124] Among MASLD patients, the presence of hypertension, T2DM, and MetS characteristics, along with the extent of liver fibrosis, increases the risk of developing CKD, whereas the presence of MetS elevates the risk of progression to ESRD.[33]

Poor prognosis of MASLD and CKD coexistence

Patients with MAFLD combined with CKD are at higher risk of CVE. Research indicates that the coexistence of MAFLD and CKD better predicts new-onset ischaemic heart disease than either condition occurring in isolation. Liver and kidney dysfunction may increase CVD risk through inter-organ interactions.[22] A UK prospective cohort study enrolled 18,073 participants (eGFR < 60 mL/min/1.73 m^2 or proteinuria > 3 mg/mmol), with a median follow-up duration of 13 years. The study demonstrated that, among individuals with CKD, NAFLD was associated with increased risks of CVEs (HR 1.49, 95% CI 1.38–1.60), all-cause mortality (HR 1.22, 95% CI 1.14–1.31), and ESRD (HR 1.26, 95% CI 1.02–1.54).[21] A meta-analysis incorporating 21 cohort studies revealed that patients with MAFLD exhibited significantly higher rates of overall mortality (random-effects OR 1.12, 95% CI 1.04–1.21) and cardiovascular mortality (random-effects OR 1.15, 95% CI 1.04–1.26) than those with NAFLD. They also exhibited higher rates of CKD (random-effects OR 1.06, 95% CI 1.00–1.12) and extrahepatic cancer (random-effects OR 1.11, 95% CI 1.00–1.23) compared with patients with NAFLD. This highlights the critical role of metabolic comorbidities in disease progression and prognosis.[97]

Impact of intervention for MASLD on CKD risk

Patients with MAFLD who successfully reduce hepatic fat content through dietary and lifestyle interventions may experience improvements in renal parameters.[125] The resolution of MASLD is associated with a reduced risk of developing CKD. Monitoring the risk of CKD in patients with MASLD and implementing early screening and intervention can lower the risk of CKD in individuals with hepatic steatosis.[16] In addition, improving MAFLD status is considered an effective preventive and therapeutic approach for stopping or slowing the progression of CKD.[116] Reducing MAFLD and its risk factors helps to improve glomerular hyperfiltration and delay age-related eGFR decline.[126] This benefit is primarily mediated through the reversal of shared pathogenic pathways. Improving MAFLD alleviates systemic IR, which in turn normalizes glomerular haemodynamics by reducing renin–angiotensin system activation and intraglomerular pressure. Concurrently, the reduction in chronic inflammation, oxidative stress, and lipotoxicity associated with MAFLD amelioration protects renal cells from injury and fibrosis, thereby preserving eGFR.

Biomarkers and clinical predictive models for MASLD combined with CKD

Novel biomarkers

Traditional renal biomarkers for predicting MASLD with CKD primarily include albuminuria (typically assessed via the random urine albumin-to-creatinine ratio), eGFR, N-acetyl-β-D-glucosaminidase, neutrophil gelatinase-associated lipocalin, liver-type fatty acid-binding protein, kidney injury molecule-1, and non-albuminuric proteinuria.[127] Liver biomarkers include ALT, aspartate aminotransferase, gamma-glutamyl transferase, Fibrosis-4 index (FIB-4), NFS, PRO-C3, enhanced liver fibrosis, CK-18, TIMP-1, and FGF21. Inflammatory mediators include C-reactive protein, IL-6, IL-8, and TNF-α. Lipid metabolic products include adiponectin and leptin.[71,128,129] Specific circular miRNAs may also serve as non-invasive biomarkers for MASLD.[130]

Changes in bioactive metabolites and gut microbiota can influence the development of both MASLD and CKD. In patients with both MASLD and CKD, there are consistent patterns of alteration in plasma levels of taurocholic acid, glycocholic acid, tauroursodeoxycholic acid, and glycochenodeoxycholic acid. Patients with MASLD and CKD exhibit altered gut microbiota composition, with metabolites such as SCFAs and TMAO influencing disease progression. This suggests that bile acids and microbial profile characteristics may serve as non-invasive diagnostic markers.[74]

In addition, studies have shown that higher grip strength is significantly associated with a lower prevalence and incidence of CKD and abnormal albuminuria in MASLD populations. This suggests that skeletal muscle strength could be used as a biomarker to predict combined CKD in MASLD.[131]

Clinical predictive models

Early studies indicated that high FIB-4 correlated with an increased risk of CKD in patients with NAFLD. With a cut-off value of 1.100 for FIB-4, it is useful in excluding the presence of CKD in patients with NAFLD.[132] Studies have shown that non-invasive fibrosis markers (FIB-4, NFS, APRI, and BARD scores) are associated with CKD prevalence in patients with NAFLD. Of these markers, FIB-4 and NFS can independently predict the risk of CKD in patients with NAFLD, with FIB-4 being the most effective predictor of an increased risk of CKD. New cut-off values of 1.0148 for FIB-4 and −1.1711 for NFS have been proposed to identify NAFLD patients with CKD, achieving negative predictive values of 98.4% and 97.9%, respectively. This enables CKD to be excluded in NAFLD patients in clinical practice.[133] Routine measurement of these non-invasive liver fibrosis markers can better stratify the risk of CKD and enable early detection, especially in the NAFLD patient population.[128]

FIB-4 can also be used to independently predict the development of CKD in patients with T2DM and MAFLD.[134] Studies have shown that an increased risk according to the NFS is strongly associated with the onset and progression of CKD in elderly T2DM patients. FIB-4 is better than NFS in predicting the risk of CKD onset and progression.[135,136]

Moreover, NAFLD and NAFLD with advanced liver fibrosis independently influence CVE, ESRD, and all-cause mortality in CKD patients. Using the NFS to assess NAFLD and NAFLD fibrosis in CKD patients can aid in risk stratification and intervention.[21]

A high Fatty Liver Disease Index score is significantly associated with an increased risk of ESRD in patients with T2DM, especially those with CKD at baseline. This association is more pronounced in women, older patients, and patients with ≥5 years of diabetes duration.[137] Studies have shown that liver fibrosis in MASLD patients is an independent risk factor for CKD, and an LSM of ≥8 kPa can be used as a screening threshold for CKD.[138] PRO-C3 is a biomarker of advanced fibrosis in MASLD and may be involved in renal fibrosis. The new algorithm, the PERIOD score, is a non-invasive score used to identify patients at high risk of CKD in MASLD and combines measurements of PRO-C3, PRO-C6, as well as factors such as BMI, hypertension, and diabetes mellitus. It is a more accurate predictor of MASLD combined with CKD than the traditional FIB-4 and NFS. Additionally, combining the PRO-C3-based ADAPT score with the Agile 3+ score improved the accuracy with which advanced liver fibrosis could be identified in patients with MASLD and CKD.[139,140]

Potential clinical management strategies for MASLD combined with CKD

For MASLD, lifestyle intervention (encompassing dietary modification and increased physical activity) remains the foundational therapy, primarily aimed at weight loss and metabolic improvement. Pharmacological agents with proven efficacy in improving hepatic steatosis, inflammation, and/or fibrosis include glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and incretin-based dual or triple agonists, sodium-glucose cotransporter-2 inhibitors (SGLT-2is), thyroid hormone receptor β agonists (e.g., resmetirom), PPAR agonists, FGF21 analogs, FXR agonists, as well as other investigational agents directed against novel targets.[24] For CKD, standard care focuses on slowing disease progression and managing complications through the use of RAAS inhibitors, SGLT-2is, and stringent control of blood pressure, glycemia, and lipids.[25] The convergence of metabolic, inflammatory, and fibrotic pathways in MASLD and CKD provides a rationale for drugs that may simultaneously target both organs.

There are no specific treatments for patients with MASLD combined with CKD, and for potential therapeutic strategies that may be clinically beneficial for MASLD combined with CKD, there is a need to focus on medications that can both reduce hepatic steatosis, inflammation, and fibrosis, as well as ameliorate CKD or risk factors for CKD, in addition to performing lifestyle interventions. The potential drug treatments include GLP-1 RAs, SGLT-2is, statins, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), finerenone (a novel non-steroidal mineralocorticoid receptor antagonist (MRA)), pemafibrate (a PPARα agonist), pioglitazone (a PPARγ agonist), and vonafexor (a FXR agonist), and other medications.[141–143] Potential clinical management strategies for MASLD combined with CKD are shown in Figure 3.

GLP-1 RAs

Representative GLP-1 RAs include liraglutide, dulaglutide, and semaglutide. GLP-1 RAs may play a dual protective role in patients with MASLD combined with CKD. They improve steatosis, inflammation, and fibrosis, slow the decline of eGFR, and reduce proteinuria and the risk of ESKD. They have hypoglycaemic, weight-loss, and cardiorenal protective properties. By reducing weight and improving systemic IR, they promote liver and kidney health, thereby breaking the cycle of metabolic inflammation and fibrosis.[141,144–146]

A meta-analysis included 13 studies involving a total of 704 patients. Compared with the control treatment, GLP-1 RAs treatment induced a greater resolution of steatohepatitis (RR 2.87, 95% CI 0.89–9.23), delayed the progression of liver fibrosis (RR 3.83, 95% CI 0.91–16.07), and reduced liver fat deposition (MD −1.40, 95% CI −2.75 to −0.05). It is also beneficial for MetS, reducing BMI, waist circumference, and hyperlipidaemia.[147] A meta-analysis incorporating 11 phase II randomized controlled trials demonstrated that treatment with GLP-1 RAs for 26 weeks (median duration) reduced hepatic fat content and was associated with a higher likelihood of achieving metabolic dysfunction-associated steatohepatitis (MASH) remission and no worsening of fibrosis compared with placebo.[148] A multicenter retrospective longitudinal study investigated liver steatosis and fibrosis markers in patients with T2DM treated with GLP-1 RAs. Results demonstrated that MAFLD was highly prevalent among T2DM outpatients (approximately 70%), with GLP-1 RAs treatment significantly improving MAFLD.[149] GLP-1 RAs can improve long-term outcomes for patients with MAFLD and diabetes. Furthermore, they can reduce mortality, stroke, heart failure, and atrial fibrillation in patients with MAFLD/MASH who do not have diabetes or a history of alcohol abuse.[150] Recently, the first part of the Phase 3 ESSENCE trial demonstrated that, of 800 obese adults with MASH confirmed by liver biopsy and moderate-to-severe liver fibrosis, those who received semaglutide (2.4 mg weekly) for 72 weeks were more likely to achieve both endpoints than those who received placebo: histological remission of MASH without worsening fibrosis and improvement in liver fibrosis without worsening MASH.[151] In August 2025, semaglutide received formal approval from the US Food and Drug Administration, becoming the second treatment after resmetirom for adults with non-cirrhotic MASH complicated by moderate-to-severe fibrosis.

A meta-analysis including nine randomized controlled trials with 75,088 patients, of whom 17,568 had an eGFR < 60 mL/min/1.73 m^2, found that GLP-1 RAs reduced the incidence of major adverse CVEs (RR 0.84, 95% CI 0.74–0.95) and slowed CKD progression (RR 0.85, 95% CI 0.77–0.94) in patients with CKD.[152] The increasing prevalence of CKD is closely linked to overweight or obesity, T2DM, and hypertension. MetS is a major contributing factor to the development of both MASLD and CKD. GLP-1 RAs, particularly dual-target agonists, are safe and effective for treating obesity. They can improve dietary habits, reduce the risk of T2DM and cardiovascular disease, and promote weight loss, which may prevent the onset of CKD, slow its progression, and lower all-cause mortality. Thus, GLP-1 RAs have therapeutic potential in the liver-kidney-metabolic field.[153,154]

Recent studies have also shown that GLP-1 RAs can alter the structure of the gut microbiota and increase the abundance of Lactobacillus reuteri, which in turn enhances fat browning and energy expenditure and reduces obesity and related metabolic disorders. GLP-1 RAs reduce the proportion of pro-inflammatory bacteria such as Escherichia coli–Shigella, decrease intestinal permeability and endotoxin release, and attenuate the inflammatory response in the liver and

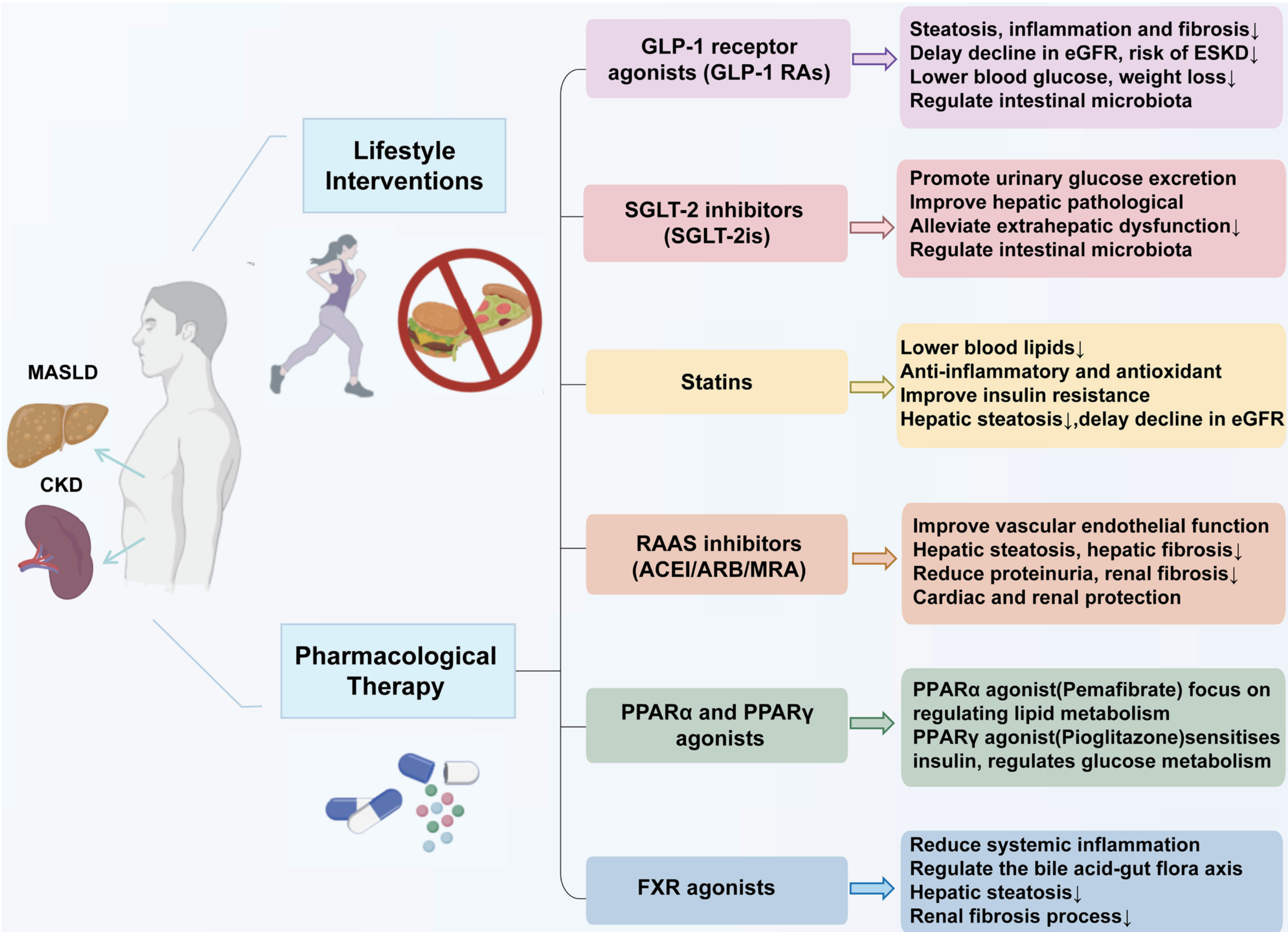

Fig. 3. Potential Clinical Management Strategies for MASLD combined with CKD. This figure illustrates potential treatment strategies that may be clinically beneficial for MASLD combined with CKD, including lifestyle interventions and potential pharmacological treatments. Pharmacological treatments may primarily include GLP-1 RAs, SGLT-2is, statins, ACEI/ARB analogues, finerenone, pemafibrate (PPARα agonist), pioglitazone (PPARγ agonist), and vonafexor (FXR agonist). This schematic diagram was created using Microsoft PowerPoint. The graphic elements depicting organs and cells are adapted from publicly available scientific image libraries and comply with licensing terms permitting academic use and publication. MASLD, metabolic dysfunction-associated steatotic liver disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end stage renal disease; SGLT-2is, sodium-glucose cotransporter-2 inhibitors; RAAS, renin-angiotensin-aldosterone system; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; PPAR, peroxisome proliferator-activated receptor; FXR, farnesoid X receptor.

kidney. GLP-1 RAs achieve synergistic therapeutic effects on MASLD and CKD by remodeling the structure of the intestinal flora, modulating metabolite signaling (e.g., bile acids, SCFAs, TMAO), and inhibiting inflammatory pathways. Therefore, GLP-1 RAs are expected to treat MASLD and CKD by modulating the gut microbiota.[74]

SGLT-2is

Representative SGLT-2is include empagliflozin, canagliflozin, dapagliflozin, etc. The interaction between oxidative stress, biogenesis, dynamics and autophagy in mitochondrial dysfunction plays a crucial role in the progression of MASLD combined with CKD. Research shows that SGLT-2is may have potential benefits in the treatment of MASLD combined with CKD by regulating mitochondrial function.[155]

T2DM is a prevalent contributing factor to CKD and MASLD. SGLT-2is and GLP-1 RAs exert cardiorenal protective effects by significantly reducing the risk of CKD and CVD through improved glucose homeostasis.[156] SGLT-2is have beneficial effects on patients with MAFLD/MASH and T2DM, as they inhibit glucose reabsorption in the proximal tubules and increase urinary glucose excretion.[157]

In addition, SGLT-2is exert its effects in MASLD through multiple cellular and molecular mechanisms. It has beneficial effects on MASLD and its progression to MASH, improving hepatic pathological features and extrahepatic dysfunction. The latter primarily includes CVD, CKD, and hepatorenal syndrome. The specific mechanisms include regulating liver fat metabolism, oxidative stress, endoplasmic reticulum stress, cell apoptosis and inflammation, regulating ferroptosis, cell senescence and miRNA signaling, and maintaining a healthy gut microbiota. These mechanisms may be applicable to the treatment of MASLD combined with CKD.[158-161]

A meta-analysis of 12 randomized controlled phase 2 trials showed that treatment with SGLT-2is for 24 weeks reduced hepatic fat content (as measured by magnetic resonance imaging–proton density fat fraction; hereinafter referred to as MRI-PDFF) and serum liver enzyme levels.[162] A meta-analysis of observational cohort studies showed that SGLT-

2is were associated with a long-term reduction in the risk of liver-related events and mortality in patients with T2DM, compared with other glucose-lowering medications (excluding GLP-1 RAs).[163]

Recent studies have shown that SGLT-2is increase the abundance of beneficial intestinal bacteria such as Akkermansia and Lachnoclostridium, reduces uremic toxins and TMAO produced by intestinal flora, improves intestinal barrier function, reduces the role of endotoxin release, modulates inflammatory responses, and thus reduces hepatic lipid accumulation and inflammation, and delays the deterioration of renal function. SGLT-2is are expected to treat MASLD and CKD by modulating the gut microbiota.[74]

Statins

Statins are a first-line lipid-lowering therapy for cardiovascular risk reduction. Their potential repurposing for MASLD and CKD is based on pleiotropic effects beyond cholesterol lowering. Statins reduce lipid toxicity and glomerular damage in the liver by lowering lipids, reducing inflammation, and improving vascular endothelial and insulin function. This breaks the vicious cycle of the "liver–kidney axis" and may be beneficial in the treatment of MASLD combined with CKD.

Statins can reduce hepatic steatosis, delay the progression of NASH, and prevent fibrosis. Studies have shown that the use of statins is associated with a lower incidence of advanced liver fibrosis (LSM ≥ 9.7 kPa) in patients with MAFLD (CAP ≥ 274 dB/m) who also have T2DM (OR 0.35, 95% CI 0.13–0.90).[164] Statins can reduce the risk of progression to cirrhosis or liver cancer in patients with MAFLD/MASH.[165] Recent studies have also shown that the combination of bifidobacteria and rosuvastatin is more effective than either bifidobacteria or rosuvastatin alone in regulating the gut microbiota of rats with MAFLD, promoting gastrointestinal emptying, and improving liver pathology and function.[166]

Statins have a protective effect on the kidneys, delaying the decline in eGFR and reducing the risk of CVD,[167,168] thereby indirectly reducing the risk of CKD–MASLD comorbidity.

RAAS inhibitors

RAAS inhibitors include ACEI/ARB/MRA drugs. RAAS inhibitors alleviate hepatic steatosis and glomerulosclerosis by blocking the inflammation–fibrosis cascade driven by the Ang II–mineralocorticoid receptor axis and are particularly suitable for MAFLD combined with CKD associated with hypertension or diabetes. Inhibiting the renal RAAS can reduce fibrosis in various organs, including the liver.[169]

Studies have shown that ACEIs are associated with a lower risk of liver-related events in patients with MAFLD, especially those with CKD.[170] ARBs have been found to significantly reduce plasma levels of LDL and total cholesterol in patients with NAFLD, which could be beneficial for treatment.[171] ACEIs/ARBs have been shown to reduce the risk of mortality in patients with CKD[172] and reduce the risk of replacement therapy in patients with advanced CKD.[173]

The MRA spironolactone may also have potential therapeutic effects on MAFLD.[174] Finerenone is a novel non-steroidal MRA. Finerenone can reduce proteinuria, alleviate renal fibrosis, lower the risk of CKD progression, and reduce the risk of CVE, thereby exerting cardiorenal protective effects. Finerenone may exert a dual protective effect in the liver and kidneys by blocking the binding of aldosterone to mineralocorticoid receptor and inhibiting inflammatory and fibrotic signaling and may be particularly suitable for patients with diabetes-related MASLD combined with CKD.[175–177]

PPARα and PPARγ agonists

Pemafibrate is a novel, highly selective PPARα agonist. Pioglitazone is a representative PPARγ agonist. PPAR agonists have therapeutic potential in the treatment of MASLD combined with CKD.

PPARα agonists focus on regulating lipid metabolism and are suitable for patients with severe hypertriglyceridaemic MAFLD. Studies have shown that pemafibrate combined with a low-carbohydrate diet can reduce weight in patients with MAFLD and improve ALT, magnetic resonance elastography, and MRI-PDFF.[178] Pemafibrate may be a safe and effective treatment for patients with MAFLD and hypertriglyceridaemia.[179] Pemafibrate also has a protective effect on the kidneys, inhibiting renal fibrosis and the progression of CKD.[180] Research shows that pemafibrate may be an effective and safe option for CKD patients with hypertriglyceridaemia.[181]

PPARγ agonists can increase insulin sensitivity, reduce hepatic steatosis, and improve metabolic disorders. They may therefore be particularly suitable for patients with diabetes and MAFLD.[182,183] PPARγ agonists protect the kidneys by inhibiting renal fibrosis, regulating renal glucose and lipid metabolism, and modulating immune cell function in the kidneys.[184]

FXR agonists

FXR agonists represent a novel, liver-targeted therapeutic class for MASH. Their investigation of patients with concurrent CKD explores the potential for systemic anti-inflammatory and anti-fibrotic effects to confer renal benefit. FXR agonists primarily exert their effects by modulating bile acid metabolism, leading to reduced hepatic lipogenesis and inflammation, and may confer renal benefits through systemic anti-fibrotic effects.[185,186] Vonafexor is a highly selective FXR agonist. Studies have shown that vonafexor has a beneficial effect on eGFR in NASH patients with mild to moderate CKD. Vonafexor reduces liver fat, liver enzymes, fibrosis biomarkers, body weight, and abdominal circumference in the short term and may improve renal function, while possible mild-to-moderate pruritus and elevated LDL cholesterol can be controlled with lower doses and statins.[186,187]

Existing potential therapies may be effective in improving clinical outcomes, but there is a lack of large-scale prospective studies. Future research should focus on the treatment and prognostic impact of MASLD in patients with CKD. Targeting liver- and kidney-specific disease-causing genes, metabolic pathways, and inflammatory pathways may be future research directions.

Discussion

From a pathophysiological perspective, the liver and kidneys share numerous intrinsically interconnected pathways. MetS is a key factor in the development of MASLD in conjunction with CKD. Hypertension, diabetes, and obesity are key components of MetS. These metabolic abnormalities are characterized by low-grade subclinical inflammation, increased oxidative stress, and increased synthesis of multiple pro-fibrotic growth factors. This triggers IR and compensatory hyperinsulinaemia and contributes to the development of CKD through various mechanisms, including endoplasmic reticulum stress, glomerular hyperfiltration, and endothelial dysfunction. This process intersects with the pathogenesis of MASLD. Additionally, specific genetic variants, such as those in the PNPLA3 gene, are associated with MASLD and renal function. Immune inflammation, dysbiosis of intestinal flora, and portal hypertension are also involved in the development of MASLD combined with CKD.[23,141,188,189] It is necessary to gain a deeper understanding of the role of these pathophysiological mechanisms in MASLD combined with CKD. Moreover, whether there are tissue-specific targets for liver–kidney interactions and the mechanism of action of gut–liver–kidney axis imbalance in MASLD combined with CKD still need to be further investigated.

Compared with individuals without MASLD, those with MASLD exhibit a higher prevalence of CKD. In patients with T2DM or non-T2DM, MASLD remains an independent risk factor for CKD even after correction for traditional risk factors. Compared with patients presenting with hepatic steatosis but no evidence of other systemic metabolic disorders, those with MASLD exhibit a heightened risk of developing CKD. MASLD can increase the prevalence of CKD, and CKD may increase the overall risk of death in patients with MASLD. Furthermore, MASLD patients with advanced fibrosis (stage F3/4) have a higher prevalence of CKD than those without advanced fibrosis (stage F0–2). Among patients with T2DM, those with MASLD and advanced hepatic fibrosis are at significantly increased risk of CKD.[23,98,99,189–192] Although epidemiological studies confirm a strong association between the two conditions, with MASLD driving CKD and CKD exacerbating MASLD, the bidirectional causality between them remains uncertain. Existing research predominantly consists of cross-sectional studies, lacking large-scale prospective cohort studies to validate temporal relationships. In addition, the impact of MASLD subtypes (obese/lean and diabetes-related) on CKD progression is understudied in terms of stratification. The interaction between CKD stage (early eGFR decline versus late proteinuria) and MASLD severity (simple steatosis versus fibrosis) has not yet been quantified.

MASLD can coexist with other causes of chronic liver disease, such as viral hepatitis. HBV and HCV infections can lead to virus-associated glomerulonephritis, which can cause renal impairment and lead to the development or exacerbation of CKD. Patients with MASLD who are co-infected with HBV or HCV may be at an increased risk of CKD. Furthermore, viral infections can promote the development of MASLD by triggering metabolic dysfunctions, such as disturbances in fat and glucose metabolism.[193,194]

Existing tools, such as scores based on FIB-4 and eGFR, have low sensitivity to early comorbidities and do not incorporate omics biomarkers.[127,128] A future research direction could involve integrating genomics, serum biomarkers (inflammatory and metabolic factors), disease clinical scores, and relevant imaging studies in order to perform precise classification of the MASLD–CKD population (e.g., MASLD subtypes with high renal impairment risk) and construct machine learning-driven dynamic prediction models.

Lifestyle interventions, such as low-calorie diets and regular exercise, can improve both MASLD and CKD, although the extent of the benefits may differ for each condition. Several drugs, including SGLT-2is, GLP-1 RAs, RAAS inhibitors, PPAR-α agonists, PPAR-γ agonists, FXR agonists, and gut microbiome modulation, may potentially benefit patients with MASLD complicated by CKD or those at high risk. In addition, both MASLD and CKD patients require active treatment of their cardiovascular risk factors. In MASLD patients, antihypertensive treatment is important for reducing the risk of CKD. In CKD patients, it is necessary to be vigilant for the presence of severe MASLD.[23,146,188,189,191] However, drug therapy for MASLD complicated by CKD faces several challenges, primarily due to the complexity of the disease mechanism, the hepatic and renal dependency of drug metabolism, potential conflicts in treatment objectives, and insufficient evidence-based medical data. Future research directions include conducting prospective intervention studies on MASLD combined with CKD to clarify the dual benefits of existing drugs on the liver and kidneys, implementing precision interventions based on phenotypic stratification (e.g., obese MASLD vs. lean MASLD). In addition, it is necessary to further explore the synergistic mechanisms of combination therapy and develop novel therapies targeting common pathological mechanisms.

Conclusions

MASLD and CKD exhibit a strong bidirectional association driven by shared pathophysiological mechanisms, including heredity,metabolic dysfunction, chronic inflammation, and gut dysbiosis. The severity of liver fibrosis, rather than steatosis alone, is a key determinant of CKD risk. The MAFLD/MASLD criteria, which actively incorporate cardiometabolic risk factors, outperform the traditional NAFLD definition in identifying patients at high risk for CKD. Lifestyle intervention remains fundamental, while certain pharmacotherapies (e.g., GLP-1 RAs, SGLT-2is) offer promising dual-organ benefits. Future efforts should focus on developing integrated prediction models and validating mechanism-based therapies to enable early, precise management of this comorbid population.

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Conflict of interest

HR has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2023. The other authors have no conflict of interests related to this publication.

Author contributions

Writing - original draft preparation (JL), writing - review and editing (HR, JL, CM, YW), design and Conceptualization (JL, CM, YW), visualization (JL), funding acquisition (HR), and supervision (HR). All authors commented on previous versions of the manuscript and contributed to the study conception and design. All authors read and approved the final manuscript.

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