



Metabolically associated fatty liver disease: What hepatologists need to know about this systemic disease

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Abstract

Metabolically associated fatty liver disease, recently redefined from non-alcoholic fatty liver disease, has emerged as the most common chronic liver disease worldwide. The new nomenclature emphasizes the metabolic drivers and highlights its strong links to extrahepatic disorders such as diabetes, cardiovascular disease, and chronic kidney disease. Yet, controversies remain regarding terminology, diagnostic thresholds, and the lack of effective disease-modifying drugs. This review discusses the rationale for the new definition, summarizes current knowledge of pathogenesis and the clinical spectrum, and highlights critical research gaps, including the role of gut microbiota, the need for improved risk stratification, and the evaluation of novel therapeutic classes.

Key Words: Metabolic associated fatty liver disease; Non-alcoholic fatty liver disease; Metabolic dysfunction-associated steatotic liver disease; Metabolic associated steatotic liver disease; Metabolic dysfunction-associated steatohepatitis; Diabetes mellitus; Viral hepatitis; Hepatocarcinoma

Core Tip: Metabolically associated fatty liver disease (MAFLD) is the new term replacing non-alcoholic fatty liver disease. Today, it is the most common chronic liver disease worldwide, affecting approximately 38% of the world's population. This comprehensive review offers insight into the various aspects of MAFLD, focusing on terminology, epidemiology, new findings on pathophysiology, key clinical factors, and current treatment options.

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INTRODUCTION

Metabolically associated fatty liver disease (MAFLD) is now recognized as the most common chronic liver disease worldwide, affecting nearly 40% of the global population[1,2]. It encompasses a broad clinical spectrum, ranging from isolated hepatic steatosis (HS) to metabolic dysfunction-associated steatohepatitis (MASH), which can progress to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC)[3]. The increasing prevalence of obesity and type 2 diabetes has accelerated the global burden of MAFLD, making it not only a leading cause of chronic liver disease but also a significant contributor to extrahepatic morbidity and mortality[4].

In 2020, an international consensus proposed replacing the long-used term non-alcoholic fatty liver disease (NAFLD) with MAFLD, and in 2023 further refinements introduced the term metabolic dysfunction-associated steatotic liver disease (MASLD)[5,6]. This nomenclature shift reflects the central role of metabolic dysfunction in the disease process, offers clearer diagnostic criteria, and aligns clinical research with the metabolic nature of the condition. However, it also raises new challenges: How to stratify risk more accurately, identify patients who do not fully meet the new criteria, and integrate emerging therapies into clinical practice[7,8].

Given these rapid developments, a timely synthesis is required. This review aims to summarize the evolving terminology, discuss current insights into pathophysiology, highlight key comorbidities and complications, and evaluate therapeutic strategies. By focusing on both the opportunities and controversies created by the nomenclature shift, we aim to clarify the clinical and research implications of MAFLD in the current era.

HISTORY OF DEFINITIONS

From NAFLD to MAFLD

Current epidemiological data suggest that metabolic dysfunction-related fatty liver disease is present in roughly 25% of the global adult population. It seriously threatens the health and economy of all societies[9-11]. The high prevalence of this disease is due to the rapid increase in sedentary lifestyles, low levels of physical activity, and excess caloric intake compared with expenditure due to an unbalanced and unhealthy diet[12]. At the same time, impaired metabolic health is highly prevalent among adults in high-income countries, including individuals who do not meet criteria for overweight or obesity[13,14]. The lack of a precise nomenclature of liver diseases not associated with alcohol consumption, along with the lack of clear clinical criteria for a “positive” diagnosis of this disease, determine the relevance of this problem.

The first descriptions of lipid accumulation in hepatocytes of street drinkers who consume excessive amounts of alcoholic beverages date back to the 19th century, and the term “fatty liver” was first used in 1836[15]. In 1839, it was suggested that fat accumulation in the liver could be the cause of cirrhosis[16]. Forty years later, a higher incidence of fatty liver degeneration was noted in patients with diabetes and obesity[16,17]. However, the similarity of histopathological changes in the liver in patients who abuse alcohol and in patients with obesity and/or diabetes was described much later, in the 1950s-1970s[16].

The concepts of NAFLD and non-alcoholic steatohepatitis (NASH) were introduced in the early 1980s to characterize a progressive liver condition that closely resembles alcoholic steatohepatitis on histological examination, yet occurs in individuals without significant alcohol consumption[18]. Liver steatosis is defined as an initial stage with subsequent development of NASH, fibrosis, and adverse outcomes: Cardiovascular complications, cirrhosis, or HCC; at the same time, the transition from steatosis to NASH is not always observed.

NAFLD has traditionally been diagnosed when HS is detected by imaging or histology in the absence of other identifiable causes of liver injury, including significant alcohol intake, exposure to hepatotoxic drugs or toxins, viral hepatitis, or inherited liver disorders[19].

However, the use of negative, exclusion-based terminology has important clinical and communicative limitations. Disease names that define a condition by what it is not may be confusing for patients and may fail to convey the underlying mechanisms or clinical relevance to healthcare providers. In particular, the term NAFLD emphasizes the absence of alcohol consumption rather than the central role of metabolic dysfunction, thereby underrepresenting its strong association with cardiometabolic risk and systemic complications.

In the following 40 years, the presence of “non-alcoholic” in the definition emphasized this feature as the leading one. The diagnosis of this nosology was based on excluding other possible causes of steatosis. Along with the presence of excess lipids in the liver, the criteria for diagnosis were the absence of a history of chronic alcohol consumption in toxic doses, as well as the exclusion of other causes of fatty liver infiltration: Hepatotrophic viruses, genetically determined diseases, and drug-induced liver injury (DILI)[15,16,18].

Between 2002 and 2017, a diagnostic approach (diagnosis by exclusion) based on exclusion criteria became widespread. Over time, experts began to justify the use of criteria to confirm this diagnosis. In 2005, Loria *et al*[20] suggested introducing positive criteria to define NAFLD.

The proposed approach was based on the fact that NAFLD is primarily a consequence of systemic metabolic dysfunction, particularly metabolic syndrome[21-23]. Another circumstance that must be taken into account when discussing this nosology is the multifactorial nature of the etiopathogenesis, which includes the characteristics of nutrition and alcohol consumption, disruption of the integrity of the intestinal barrier and features of the intestinal microbiota, dysfunction of subcellular structures [mitochondria, endoplasmic reticulum (ER)], as well as metabolic disorders and/or hormonal disorders[24-26]. In this regard, proposals have been put forward to change the term NAFLD by replacing the definition of “non-alcoholic” with one of the options indicating the main contribution to liver damage of one of the listed pathogenesis factors[27].

During the 2020 international discussion involving experts from 22 countries, a consensus was reached on revising the NAFLD definition. The review resulted in a proposal to change the nomenclature, introduce a new term, MAFLD instead of NAFLD, and change the diagnostic criteria, taking into account the importance of metabolic factors[28]. These changes were intended to facilitate a clear assessment of the contribution of etiologic factors to liver damage (dietary habits, alcohol consumption, microbiota, genetics, epigenetics, and individual metabolic imbalances).

Similar to NAFLD, MAFLD represents the hepatic component of a broader multisystem disorder characterized by substantial heterogeneity in etiological factors, clinical presentation, disease trajectory, and long-term outcomes[29]. Owing to the complexity of its underlying mechanisms, the development of a single, definitive diagnostic test is unlikely. Instead, MAFLD will probably require operational diagnostic frameworks based on combinations of clinical, metabolic, and laboratory criteria, analogous to the evolving definitions used for metabolic syndrome[30-32].

Under the updated nomenclature, MAFLD is diagnosed based on documented HS, confirmed by imaging modalities, serum-based biomarkers, or histological assessment[33] in combination with overweight/obesity or type 2 diabetes. In a patient with normal body weight and without type 2 diabetes, HS must be combined with the presence of two or more signs of metabolic dysfunction.

Metabolic dysregulation is defined by the presence of one or more of the following features: (1) Increased waist circumference (≥ 102 cm in men and ≥ 88 cm in women of European ancestry; ≥ 90 cm in Asian men and ≥ 80 cm in Asian women); (2) Elevated blood pressure ($\geq 130/85$ mmHg) or current use of antihypertensive medication; (3) Hypertriglyceridemia [serum triglycerides (TG) ≥ 1.7 mmol/L (150 mg/dL)] or ongoing lipid-lowering treatment; (4) Reduced high-density lipoprotein cholesterol (HDL-C) concentrations [≤ 1.0 mmol/L (40 mg/dL) in men and ≤ 1.3 mmol/L (50 mg/dL) in women] or treatment for dyslipidemia; (5) Impaired glucose metabolism, including prediabetes, defined by elevated fasting plasma glucose, abnormal glucose tolerance, or increased glycated hemoglobin levels; and (6) Additional markers of metabolic dysfunction include an elevated insulin resistance (IR) index, as assessed by the homeostatic model assessment of IR (HOMA-IR ≥ 2.5), and increased systemic inflammatory activity reflected by high-sensitivity C-reactive protein (hsCRP) concentrations exceeding 2 mg/L[28,33].

An essential feature of MAFLD is the exclusion of the fact of abuse of hepatotoxic doses of alcohol, as well as other etiological variants of chronic liver diseases. According to the new nomenclature, simple steatosis and NASH were not two different forms of the disease. However, they were considered a single pathological process, the severity of which depends on the activity of inflammation and the stage of liver fibrosis[28].

Recent changes in nomenclature

The main limitations of the NAFLD and NASH terms are their dependence on the need to formulate a diagnosis by exclusion and the use of potentially stigmatizing formulations[34]. It should be noted that the new MAFLD term also has several shortcomings. The prerequisites for the next stage of revision of the terms were, in particular, the lack of consideration of the role of alcohol, which accelerates the course of the disease[35], the use of HOMA-IR and hsCRP as diagnostic criteria, which are often not assessed in routine clinical practice, and the lack of inclusion of patients with a normal body mass index (BMI)[33].

The revision aims to increase awareness among healthcare workers, society, and patients of the disease, its course, treatment, and outcomes, as well as combat stigma by focusing on the initial cardiometabolic etiological factor. A more precise assessment of risk factors for disease progression, validation of non-invasive diagnostics, an indirect positive effect on the search for new drugs, and the ability to provide personalized medical care to this group of patients are planned[35].

In June 2023, the European Association for the Study of the Liver (EASL) addressed the practical implications and clinical application of the updated terminology during its annual congress[36] and in September 2023 during a summit devoted to updating the NAFLD/MAFLD nomenclature[35]. A total of 236 experts from 56 countries took part in the discussions[34]. The Working Committee consisted of 34 experts from 7 scientific societies and patient advocacy organizations, selected based on the size of the societies or organizations (EASL: 29%, American Association for the Study of Liver: 27%, Asian Pacific Association for the Study of the Liver: 13%, Latin American Association for the Study of the Liver: 12%, other societies: 7%, patient advocacy organizations: 11%) and divided into six working groups.

During these discussions, a substantial proportion of respondents reported that the descriptors “non-alcoholic” and “fatty” were perceived as stigmatizing, with 61% and 66% expressing concern, respectively[34].

According to the accepted nomenclature, the term steatotic liver disease (SLD) was introduced; steatosis is confirmed by imaging methods or biopsy, which, in turn, includes MASLD and SLD, in which metabolic dysfunction (Met) is combined with alcoholic liver disease (ALD).

When diagnosing Met is combined with ALD (MetALD), the amount of ethyl alcohol consumed is taken into account. For women, the diagnostic alcohol intake range is defined as 140-210 g per week (approximately 20-50 g/day), while for men it is 350-420 g per week (approximately 30-60 g/day). Within this spectrum, lower intake thresholds (≥ 140 g/week in women and ≥ 350 g/week in men) support a diagnosis of MetALD with a predominant metabolic component. Conversely, higher intake levels (≥ 210 g/week in women and ≥ 420 g/week in men) indicate MetALD with a dominant

contribution of alcohol-related liver injury.

In addition to these categories, the spectrum of SLDs includes ALD; SLD of defined etiology, such as DILI or monogenic disorders (including lysosomal acid lipase deficiency, Wilson disease, hypobetalipoproteinemia, and other inborn errors of metabolism); mixed-etiology SLD associated with conditions such as chronic hepatitis C (CHC) infection, malnutrition, or celiac disease; as well as SLD of indeterminate origin.

Following new approaches to diagnostics, the main principle for determining the form of SLD is the presence or absence of the cardiometabolic criterion[34,35].

Cardiometabolic risk in adults is defined by the presence of one or more of the following abnormalities: (1) Excess adiposity, reflected by a BMI ≥ 25 kg/m² (≥ 23 kg/m² in Asian populations) or increased waist circumference (> 94 cm in men and > 80 cm in women, with ethnicity-specific thresholds applied where appropriate); (2) Impaired glucose homeostasis, including elevated fasting or post-load plasma glucose levels, increased glycated hemoglobin, established type 2 diabetes mellitus (T2DM), or ongoing antidiabetic treatment; (3) Elevated blood pressure ($\geq 130/85$ mmHg) or current antihypertensive therapy; (4) Hypertriglyceridemia [plasma TG ≥ 1.7 mmol/L (150 mg/dL)] or lipid-lowering treatment; and (5) Reduced HDL-C concentrations [≤ 1.0 mmol/L (40 mg/dL) in men and ≤ 1.3 mmol/L (50 mg/dL) in women] or therapy for dyslipidemia[34,35].

For children, cardiometabolic criteria include: In pediatric populations, cardiometabolic dysfunction is defined by age- and sex-specific criteria, including: (1) Excess adiposity (BMI at or above the 85th percentile or a BMI z-score $\geq +1$, increased waist circumference above the 95th percentile, or ethnicity-adjusted thresholds); (2) Abnormal glucose metabolism, reflected by elevated fasting or random plasma glucose concentrations, impaired glucose tolerance on oral testing, increased glycated hemoglobin levels, or a prior diagnosis of T2DM and its treatment; (3) Elevated blood pressure (at or above the 95th percentile for children younger than 13 years, or ≥ 130 mmHg in adolescents aged 13 years or older, whichever threshold is lower) or current antihypertensive therapy; (4) Hypertriglyceridemia [plasma TG ≥ 1.15 mmol/L (100 mg/dL) in children younger than 10 years and ≥ 1.7 mmol/L (150 mg/dL) in those aged 10 years or older] or lipid-lowering treatment; and (5) Reduced HDL-C concentrations [≤ 1.0 mmol/L (40 mg/dL)] or ongoing lipid-lowering therapy[34,35].

If the patient has at least one of the cardiometabolic criteria and no other causes of steatosis, the diagnosis of MASLD is made; if there are other causes of steatosis, the diagnosis is MetALD (with high doses of alcohol) or MASLD of other mixed etiology. Suppose there are no cardiometabolic criteria and there are other causes of steatosis. In that case, the diagnosis is SLD of other etiology (for example, ALD, DILI, and monogenic diseases). If there are no other causes of steatosis, the diagnosis is cryptogenic SLD[36]. Instead of the NASH term, the definition of "MASH" is introduced[37]. The chronology of changes in terms is presented in Table 1.

ETIOLOGY

Genetic predisposition

The development of MAFLD and the disease's severity are associated with single nucleotide polymorphisms[38]. Genetic susceptibility plays a key role in interindividual variability of disease severity in MAFLD. Among identified variants, the rs738409 polymorphism in the *PNPLA3* gene represents the strongest genetic determinant of HS and disease progression [39]. Additional single-nucleotide polymorphisms implicated in the development and advancement of steatohepatitis include *TM6SF2* rs58542926, which influences very-low-density lipoprotein (VLDL) assembly and secretion, and *MBOAT7* rs641738, involved in phospholipid acyl-chain remodeling[40,41]. The *PNPLA3* rs738409 variant alters hepatic lipid handling by impairing TG remodeling and disrupting the transfer of polyunsaturated fatty acids required for phosphatidylcholine synthesis[42]. Moreover, homozygosity for this variant enhances the profibrogenic activation of hepatic stellate cells[43]. Reduced activity of enzymes responsible for xenobiotic metabolism and elimination in carriers of *PNPLA3* rs738409 may further increase vulnerability to hepatotoxic injury, potentially contributing to chronic low-grade liver damage[44].

Epigenetics

Epigenetic regulation has emerged as an important contributor to the pathogenesis of steatohepatitis and related metabolic disorders[45]. Key mechanisms include alterations in DNA methylation, post-translational histone modifications, and dysregulation of non-coding microRNAs[46]. In patients with steatohepatitis, hepatic expression of miR-122 is markedly reduced compared with simple steatosis, whereas other microRNAs, such as miR-223, demonstrate increased expression[47]. In addition, elevated methylation of mitochondrial DNA has been observed in liver tissue from patients with steatohepatitis and is thought to promote activation and transdifferentiation of hepatic stellate cells into myofibroblasts, thereby contributing to the development and progression of liver fibrosis[48].

Obesity and body fat distribution

Obesity represents one of the most prevalent and well-established risk factors for MAFLD[49]. More than half of adults diagnosed with MAFLD are affected by obesity, and the rising global burden of the disease closely parallels the worldwide increase in obesity rates[50]. Nevertheless, accumulating evidence suggests that disease risk is driven less by overall adiposity than by fat distribution. In particular, expansion of visceral adipose tissue (VAT) has been consistently linked to a higher likelihood of HS and MAFLD development, underscoring the pathogenic role of central fat accumulation[51,52]. In addition, the size of VAT is directly associated with liver inflammation and the development of fibrosis in patients with MAFLD[53,54]. This association is partly explained by the endocrine activity of VAT, which functions as a

Table 1 Change of terminology

Transcript	Years of use	Features/reasons for introduction
Non-alcoholic fatty liver disease	1980-2020	Emphasized the absence of alcohol as a cause of the disease
Metabolic (dysfunction) associated fatty liver disease	Since 2020	The emphasis is on metabolic disorders
Metabolic dysfunction-associated steatotic liver disease	Since 2023	A more precise definition is adopted in American Association for the Study of Liver Diseases/European Association for the Study of the Liver

metabolically active organ and releases multiple mediators implicated in MAFLD pathogenesis, including adipokines and pro-inflammatory cytokines such as adiponectin, interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). Circulating adiponectin, an adipokine with anti-inflammatory and anti-lipogenic properties, is reduced in patients with steatohepatitis and demonstrates an inverse relationship with visceral fat accumulation[55]. In patients with metabolically unhealthy obesity, IL-6 levels in VAT are more than a hundred times higher than those in the liver, indicating increased proinflammatory activity of VAT[56]. Approximately 30% of normal-weight individuals have metabolic obesity with a high risk of developing metabolic diseases such as MAFLD[51,52]. Lean patients with MAFLD also have the presence of visceral obesity[57] and exhibit altered gut microbiota and higher secondary bile acid levels[58].

PATHOPHYSIOLOGY

The pathogenesis of MAFLD is highly complex and involves multiple, interrelated mechanisms. Earlier concepts described disease development using the “two-hit” model, in which an initial accumulation of hepatic lipids sensitizes hepatocytes to subsequent injurious processes, followed by oxidative stress-driven inflammation and cellular damage. However, this framework has largely been replaced by more integrative models recognizing the simultaneous contribution of metabolic, inflammatory, and oxidative pathways[59,60]. However, at present, the mechanism of MAFLD development appears to be more complex, and the “multiple hit” hypothesis is gaining increasing support[61].

The main mechanisms in the development of MAFLD are considered to be the following: (1) Excessive calorie intake and lipid metabolism disorders-excessive intake of fats and carbohydrates contributes to fat deposition in the liver; (2) IR and hyperinsulinemia-the ability of cells to absorb glucose decreases, which leads to fat accumulation in the liver; (3) Oxidative stress and inflammation-increased lipid peroxidation processes lead to damage to hepatocytes; and (4) Intestinal microflora imbalance.

Lipid metabolism disorders

Hepatic lipid overload in MAFLD results from the convergence of several metabolic pathways, including enhanced lipolysis in adipose tissue, increased de novo lipogenesis (DNL), and excessive dietary intake of fats and simple sugars. Rather than TG accumulation itself, the pathogenic trigger is the excess of lipotoxic free fatty acids (FFA), which promote hepatocellular stress and injury. In steatohepatitis, hepatocytes also exhibit elevated levels of free cholesterol, a factor known to activate inflammatory signaling and fibrogenic pathways[62,63]. This dysregulation is accompanied by alterations in sterol regulatory mechanisms, including upregulation of SREBP-2 activity and HMG-CoA-related pathways, contributing to an atherogenic lipid profile characterized by low HDL-C, hypertriglyceridemia, and increased low density lipoprotein cholesterol (LDL-C)[64,65].

In parallel, liver sinusoidal endothelial cells play a critical role in disease progression. Steatosis-induced endothelial dysfunction disrupts hepatic microcirculation, and as MAFLD advances, progressive impairment of endothelial integrity contributes to inflammation, fibrogenesis, and downstream complications such as increased intrahepatic resistance and portal hypertension[66].

Oxidative stress

Oxidative stress represents a disturbance in redox homeostasis caused by an imbalance between the generation of reactive oxygen species (ROS) and the capacity of antioxidant defense systems[67]. ROS are continuously produced as by-products of cellular metabolism, beginning with the formation of superoxide anions and subsequently giving rise to other highly reactive intermediates. Excessive ROS interact with major cellular macromolecules, including proteins, lipids, and nucleic acids, resulting in oxidative modifications such as protein carbonylation, formation of lipid peroxidation products (including malondialdehyde and 4-hydroxynonenal), and oxidative DNA damage exemplified by 8-hydroxy-2'-deoxyguanosine[68].

Cellular protection against oxidative injury is mediated by a complex antioxidant network comprising enzymatic and non-enzymatic components. Enzymatic defenses include superoxide dismutase, which catalyzes the conversion of superoxide radicals into hydrogen peroxide, and catalase, which further reduces hydrogen peroxide to water. Non-enzymatic antioxidants consist of endogenous molecules such as glutathione (GSH), as well as a broad array of diet-derived compounds, including tocopherols, polyphenols, vitamins, and isoflavones; collectively, these components determine the overall antioxidant capacity of the organism.

In MAFLD, excessive oxidative stress plays a pivotal role in disease progression by promoting lipid peroxidation, impairing mitochondrial fatty acid oxidation, and stimulating the release of pro-inflammatory cytokines. Lipid peroxidation is initiated when ROS abstract hydrogen atoms from unsaturated fatty acids, triggering self-propagating chain reactions that disrupt cellular membranes and generate cytotoxic secondary metabolites[69,70]. These products activate hepatic stellate cells, enhance pro-inflammatory signaling, and may induce hepatocyte necrosis or apoptosis through pathways such as fas ligand activation, thereby contributing to fibrogenesis and progressive liver injury[71,72].

Oxidative stress has been postulated as a central process contributing to liver injury and driving the transition from simple steatosis to MAFLD[73]. Mitochondrial dysfunction in liver tissue in MAFLD has been reported to alter liver lipid balance, promote ROS production, and affect LPO and cytokine release, ultimately leading to cell death[74]. Due to impaired mitochondrial function, mitochondria in MAFLD become more susceptible to mitochondrial permeability transients, leading to cell death during ischemia and reperfusion injury[75]. Mitochondrial membrane phospholipids are oxidized, reducing fluidity and impeding GSH entry into the mitochondria, causing an imbalance between antioxidants and ROS. This causes oxidative stress, which leads to a decrease in mitochondrial ATP synthesis. Consequently, patients with MAFLD have decreased ATP stores, which makes cells more susceptible to necrosis and triggers an inflammatory response when the liver is damaged by ischemia and hypoxia[75].

In MAFLD, obligate-induced oxidative metabolism due to increased anabolism can lead to oxidative stress, in which leucine aminopeptidases (LAPs) play a significant role[76]. LAPs, cell maintenance enzymes, have multiple functions. LAP3, one of the critical members of M1 LAP, has multifunctional roles in tumor metastasis[77] and progressive malignancy of human esophageal squamous cell carcinoma[78]. Overexpression of LAP3 decreases Hsp27 phosphorylation and increases fascin expression, Akt phosphorylation, and MMP2/9[79], which are involved in the pathogenesis and progression of MAFLD[80]. In addition, LAP3 has been shown to be markedly upregulated in conditions characterized by excessive inflammatory responses and has therefore been proposed as a potential therapeutic target for anti-inflammatory interventions[81]. Recent proteomics-based analyses further demonstrated significantly increased circulating levels of LAP3 in patients with MAFLD, supporting its possible role as a biomarker of disease-associated inflammation [82].

IR and hyperinsulinemia

Today, IR is considered one of the primary pathogenetic mechanisms involved in developing MAFLD and its progression to NASH[23]. The prevalence of IR in patients with MAFLD is higher than in patients with simple steatosis, and in NASH it is even higher[83]. IR is traditionally described as a state in which target tissues exhibit a diminished biological response to insulin signaling at the receptor and post-receptor levels. This impairment leads to reduced glucose utilization and is accompanied by broader metabolic disturbances, particularly affecting insulin-sensitive organs such as adipose tissue and the liver[84]. Numerous biological links between adipose and liver tissues support glycolipid homeostasis, whose dysfunction creates a dysmetabolic context that can trigger the onset of MAFLD and contribute to its progression[85]. In addition, insulin physiologically plays an anabolic role in adipose tissue, suppressing lipolysis and enhancing lipogenesis, especially in the postprandial period. Conversely, in individuals with IR, altered regulatory pathways fuel lipolysis, releasing FFA, which reach the liver and cause fat overload in hepatocytes[86]. Hyperinflux of FFA causes mitochondrial dysfunction by inducing incomplete FFA and worsening hepato-IR; it also enhances gluconeogenesis by suppressing insulin-dependent glycogen synthesis[87]. In the liver, failure of insulin to adequately suppress hepatic glucose production promotes DNL, a key pathogenic mechanism underlying MAFLD[88]. These alterations are, at least in part, attributable to defects in intracellular signaling pathways downstream of the insulin receptor. Under conditions of IR, hepatic lipid accumulation reflects a combined disturbance in FFA uptake, synthesis, export, and oxidation. Consistent with this, the severity of HS in MAFLD correlates with increased circulating FFA concentrations, largely resulting from insufficient insulin-mediated inhibition of adipose tissue lipolysis.

Under physiological conditions, insulin suppresses lipolysis in adipocytes; however, IR within adipose tissue leads to excessive mobilization of FFAs[89,90]. As visceral fat mass expands, lipolysis from visceral depots becomes a dominant source of hepatic FFA influx[91]. Accordingly, patients with MAFLD exhibit markedly elevated circulating FFA levels, which have been identified as an independent predictor of advanced liver fibrosis[92]. Beyond their metabolic effects, increased FFAs also activate pro-inflammatory signaling pathways in the liver, including nuclear factor- κ B (NF- κ B), thereby amplifying hepatic inflammation and disease progression[93]. Thus, the release of fatty acids from dysfunctional and insulin-resistant adipocytes leads to lipotoxicity, accumulating toxic TG-derived metabolites in ectopic tissues, including the liver[94].

These mechanisms have also been demonstrated in MAFLD patients without obesity or overt diabetes, indicating that IR may precede and independently contribute to disease development. In this context, IR disrupts multiple metabolic processes, including hepatic glucose production, glucose utilization (glycogen synthesis and glucose oxidation), lipolysis, and lipid oxidation. Although VAT is not the primary contributor to circulating FFAs, it represents a major source of pro-inflammatory mediators delivered to the liver, as evidenced by the strong association between IL-6 and C-reactive protein concentrations in portal venous blood.

Under insulin-resistant conditions, the liver progressively loses its capacity to suppress glucose output in response to insulin, while DNL is simultaneously enhanced, in part through activation of the Notch signaling pathway. This dual disturbance accounts for the markedly increased contribution of DNL to hepatic lipid accumulation in MAFLD compared with healthy individuals and may also explain the heightened susceptibility to type 2 diabetes observed in this population.

Insulin-like growth factor-1 is a peptide hormone structurally related to insulin, predominantly synthesized by hepatocytes under growth hormone regulation and circulating bound to IGF-binding protein-3[95]. IGF-1 plays an important role in hepatocyte proliferation, differentiation, and survival[96,97]. Meta-analytic data indicate that circulating

IGF-1 levels are reduced in patients with MAFLD compared with healthy controls, supporting a potential link between IGF-1 deficiency and disease progression[98]. Consistently, lower IGF-1 concentrations have been reported in patients with advanced liver fibrosis compared with those with absent or mild fibrosis[99]. Although the precise molecular pathways remain incompletely defined, emerging evidence suggests that IGF-1 may modulate liver fibrosis by regulating stress-induced premature hepatocyte senescence.

The evidence presented above has developed a classic pathogenetic model in which IR unilaterally fuels MAFLD[100]. From a modern perspective and in terms of identifying potential pharmacological targets, MAFLD and IR can be considered as “two faces of Janus”[100]. An increasing body of evidence supports a bidirectional relationship between MAFLD and IR, whereby HS not only results from impaired insulin signaling but may also exacerbate both hepatic and systemic IR[101]. This reciprocal interaction establishes a self-perpetuating cycle that drives disease persistence and progression, although the underlying molecular mechanisms remain incompletely defined. Within this context, IR is tightly interconnected with oxidative stress and chronic low-grade inflammation, forming a pathogenic axis that contributes to metabolic dysregulation and immune dysfunction[102]. Mitochondrial impairment, a hallmark of HS, plays a central role by promoting incomplete fatty acid oxidation, excessive generation of ROS, and accumulation of toxic lipid intermediates. These processes further amplify oxidative stress, trigger inflammatory signaling, and disrupt insulin-responsive pathways, thereby reinforcing disease progression[103].

In advanced stages of MAFLD, particularly in the presence of cirrhosis, IR represents a central driving force of chronic liver disease progression. At the same time, cirrhosis itself predisposes patients to IR irrespective of etiology, as structural and functional hepatic impairment profoundly alters glucose metabolism[104]. Nevertheless, the severity of IR, commonly assessed using the HOMA-IR, varies according to the underlying cause of cirrhosis and appears to be more pronounced in MAFLD- and hepatitis C virus (HCV)-related liver disease than in alcohol-associated liver disease or chronic hepatitis B (CHB)[105].

Hepatic-derived mediators may further aggravate IR in this setting. Certain hepatokines, such as selenoprotein P, have been shown to directly impair insulin signaling in peripheral tissues, particularly skeletal muscle, in patients with MAFLD[106]. In parallel, sustained necroinflammatory activity within the liver leads to increased production of pro-inflammatory cytokines, including TNF- α and IL-6, which contribute to systemic IR and metabolic dysregulation.

Microbiota

In the last decade, the role of gut-liver interactions in developing MAFLD has attracted increasing attention.

The human microbiota encompasses the diverse community of microorganisms residing in the body; however, because the vast majority are located within the gastrointestinal tract, the term “gut microbiota” is commonly used[107,108]. The intestinal ecosystem represents a highly complex microbial network composed of bacteria, viruses, fungi, and other microorganisms that coexist in a dynamic and tightly regulated equilibrium. Interactions within this microbial community and the bioactive metabolites they produce are increasingly recognized as key modulators of host metabolism and have been implicated in the development and progression of multiple metabolic disorders[109].

Under physiological conditions, the gut microbiota and the host exist in a state of mutual equilibrium. Disruption of this balance by genetic, dietary, or environmental factors leads to gut dysbiosis, which has been increasingly implicated in the pathogenesis of MAFLD through the gut-liver axis. The gut-liver axis refers to the bidirectional communication between the intestinal microbiota and the liver, mediated by epithelial, vascular, and immune pathways that link intestinal barrier function with hepatic circulation[110].

The intestinal barrier is a multilayered defense system composed of a mucus layer-characterized by an outer loose layer and an inner dense layer-followed by a monolayer of epithelial cells that constitutes the second major protective barrier. These epithelial cells are interconnected by tight junctions, multiprotein complexes primarily formed by claudins, occludin, and zonula occludens proteins, as well as junctional adhesion molecules[111]. Tight junctions are essential for preserving epithelial integrity, selectively permitting nutrient absorption while restricting the translocation of microbial products and pathogens across the intestinal epithelium[112].

In addition to the mucin layer produced by goblet cells and TJs between IECs, the immune system's involvement is equally important. Mucosal immune defense within the intestine is further supported by locally produced immunoglobulin A, which binds and neutralizes invading microorganisms at the luminal surface. In parallel, activation of interleukin-23-dependent signaling pathways stimulates group 3 innate lymphoid cells, leading to the secretion of interleukin-22. IL-22 plays a key role in enhancing epithelial defense by inducing the production of antimicrobial peptides from paneth cells and intestinal epithelial cells. Beyond the epithelial layer, the gut-vascular barrier provides an additional level of protection by limiting the translocation of bacteria, microbial antigens, and other luminal components into the systemic circulation[113].

The gut-liver axis constitutes an essential defense system that restricts the translocation of pathogens and toxic microbial products, thereby limiting systemic inflammation. This protective function, however, depends on the maintenance of microbial and barrier homeostasis. In the setting of gut dysbiosis, this integrated defense network becomes compromised. In MAFLD/MASLD, dysbiosis is characterized by pronounced alterations in gut microbial composition and reduced microbial diversity, which contribute to disruption of intestinal barrier function and enhanced hepatic exposure to microbial-derived signals[114].

Patients with MAFLD and MASH have altered gut microbiota composition and a higher prevalence of small intestinal bacterial overgrowth[115]. Disruption of the gut microbial ecosystem adversely affects the integrity of the gut-vascular barrier, resulting in increased intestinal vascular permeability, particularly in the context of a high-fat diet[116]. In patients with MAFLD, accumulating evidence demonstrates profound alterations in gut microbial composition, accompanied by a significant reduction in α -diversity, further supporting the role of dysbiosis in disease pathogenesis[117]. MAFLD patients often exhibit a predominantly *Firmicutes*-dominant gut microbiota, resulting in an increased

Firmicutes to *Bacteroidetes* ratio compared to healthy controls[118-121].

In MAFLD, enrichment of specific bacterial taxa, including *Bacteroides vulgatus*, *Escherichia coli*, and *Klebsiella pneumoniae* (*K. pneumoniae*), has been linked to adverse metabolic phenotypes such as obesity and IR. These microorganisms contribute to hepatic lipid accumulation and metabolic dysfunction through the production of lipopolysaccharides, which activate Toll-like receptor 4-dependent signaling in the liver and downstream NF- κ B-mediated inflammatory pathways. Under inflammatory conditions, hepatic lipid handling is further disrupted, as reflected by reduced expression of hepatic lipase and concomitant upregulation of HMG-CoA reductase, the key regulatory enzyme of cholesterol biosynthesis[122]. This imbalance favors impaired lipid hydrolysis alongside enhanced hepatic cholesterol production, thereby exacerbating steatosis and metabolic injury[123,124]. *K. pneumoniae* increases oxidative stress and proinflammatory cytokine release, directly damaging hepatocytes[125]. Beneficial gut bacteria also exert protective effects against MAFLD through the production of short-chain fatty acids (SCFAs). *Akkermansia muciniphila* generates SCFAs that activate G protein-coupled receptors, thereby regulating host energy metabolism and conferring metabolic protection[126]. Similarly, *Faecalibacterium prausnitzii* produces anti-inflammatory SCFAs, particularly butyrate, which suppresses NF- κ B signaling and limits the production of pro-inflammatory cytokines. Members of the genus *Bifidobacterium* further contribute to intestinal homeostasis by strengthening epithelial barrier function, thereby reducing endotoxin translocation into the systemic circulation. In addition, *Bifidobacterium* species promote immune tolerance by enhancing regulatory T cell activity and increasing the secretion of anti-inflammatory cytokines such as IL-10 and transforming growth factor- β (TGF- β), collectively attenuating hepatic and systemic inflammation[127]. The pathophysiology of the development of metabolically associated fatty liver disease can be graphically represented as follows (Figure 1).

COMORBID DISEASES

Diabetes mellitus

The clinical and pathogenetic relationship between NAFLD and T2DM is beyond doubt; however, estimates of the extent of this comorbidity vary widely across studies, likely due to differences in diagnostic criteria and patient selection methods[128-130]. While the prevalence of each disease in the general population is estimated at 25% and approximately 10%, respectively[131,132], the figures are significantly higher when they coincide. According to data[133], almost half (54%) of patients with MAFLD have concomitant T2DM. However, data from individual studies are not so homogeneous: For example, in one cohort, liver steatosis in patients with T2DM was detected in 85.3% of cases[134], while in another, it was 42.6%, with NAFLD itself accounting for approximately 70% of these cases[135]. Thus, a large meta-analysis indicates that 55.48% of patients with T2DM suffer from NAFLD[136]. This wide range only highlights the complexity of epidemiological assessments and the need for standardized diagnostic protocols for this patient group. Nevertheless, the mutually aggravating influence of NAFLD and T2DM is a clinically significant fact that requires the attention of physicians.

The bidirectional nature of the MAFLD-T2DM association extends beyond mere coexistence to a mutual aggravation of clinical outcomes. While MAFLD elevates the risk of incident T2DM and its vascular complications[137], diabetes, in turn, acts as a potent accelerator of hepatic disease progression. In patients with MAFLD, the presence of T2DM is linked to a more severe histological phenotype, including NASH, advanced fibrosis, cirrhosis, and HCC[138]. This is robustly evidenced by biopsy-based studies, where T2DM conferred a 70% increased relative risk of fibrosis progression, independent of other confounders[139]. Consequently, the prevalence of advanced fibrosis (stages F3-F4) in unselected T2DM cohorts is notably high, ranging from 15% to 38%[140]. Given that fibrosis stage is the paramount predictor of liver-related morbidity and mortality[141], this accelerated fibrogenesis underpins a critical clinical consequence: Patients with T2DM face an approximately three-fold higher risk of liver-related death compared to their non-diabetic counterparts[142].

Hepatitis C

Although the prevalence of the HCV is declining, CHC remains a significant cause of liver cirrhosis and HCC worldwide [143]. An estimated 58 million people worldwide suffer from CHC[144].

Chronic HCV infection represents a complex clinical entity that extends beyond purely viral liver damage, intersecting significantly with metabolic dysfunction. While the natural history of HCV infection is well-characterized-with a high rate of chronicity (60%-80%) leading to fibrosis, cirrhosis, and HCC[145-147]- its metabolic implications are of growing relevance. A striking and genotype-dependent association exists between HCV and HS[148-150]. This metabolic-viral interplay has critical clinical consequences: HCV is a leading etiology for end-stage liver disease and HCC in the West [151,152], and its numerous extrahepatic manifestations[153] further complicate management. Notably, genotype 3 infection exhibits a direct steatogenic viral effect, contributing to the remarkably high prevalence of fatty liver (40%-80%) in the HCV population[154]. Even after accounting for common metabolic confounders (*e.g.*, obesity, diabetes), the prevalence remains elevated at approximately 40%, underscoring a multifactorial pathogenesis involving both viral and host metabolic factors[154]. Therefore, in the modern management of CHC, assessment of metabolic comorbidities is not optional but essential, particularly for risk stratification and comprehensive care in patients presenting with HS.

The revised MAFLD nomenclature introduces a critical paradigm shift in categorizing patients with HCV infection and HS. While HCV genotype 3 remains recognized as a direct viral cause of fat accumulation and is thus excluded from the standalone MAFLD diagnosis, the new criteria explicitly account for metabolic cofactors. Consequently, patients with HCV who also exhibit metabolic dysregulation now fall under the dual diagnosis of "HCV infection with concomitant MAFLD". This creates a clear dichotomization within the HCV population: "HCV with MAFLD" *vs* "HCV without

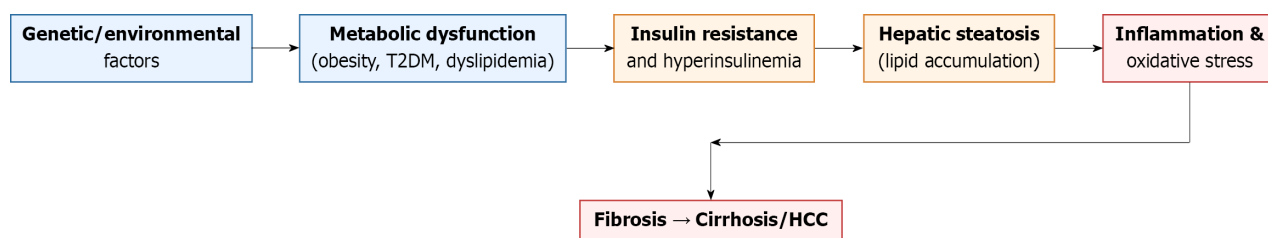


Figure 1 Pathophysiology of metabolically associated fatty liver disease development. T2DM: Type 2 diabetes mellitus; HCC: Hepatocellular carcinoma.

MAFLD” (where steatosis is presumed to be purely virally induced, typically by genotype 3).

This refined classification has direct clinical utility. By distinguishing the primary driver of steatosis-metabolic, viral, or both-it paves the way for more targeted management. The differential diagnosis should hinge on a composite assessment of metabolic risk factors, HCV genotype and viral load, and the response to antiviral therapy[155]. For instance, persistent steatosis after sustained virologic response would strongly point toward underlying metabolic disease. Thus, the new framework moves beyond mere labeling, aiming to stratify patients for combined therapeutic strategies that address both the viral infection and the metabolic syndrome where present.

Relationship between HCV infection and metabolism

The interplay between HCV and host metabolic pathways is bidirectional and central to disease pathogenesis, creating a vicious cycle that worsens outcomes. HCV actively remodels lipid metabolism to facilitate its own life cycle, impairing VLDL secretion and promoting hepatic lipogenesis, which directly contributes to HS-a common histological feature in CHC[156]. This virus-induced dysregulation manifests clinically as a distinct hypolipidemic profile (low total cholesterol, hypobetalipoproteinemia)[157].

The impact of this metabolic hijacking, however, extends beyond viral fitness to influence disease progression. Interestingly, the relationship between lipids and viral replication is complex and not merely facilitative. While lipids are essential for HCV replication, certain fatty acids and products of lipid peroxidation (a feature of NASH) can conversely inhibit it, suggesting the existence of a delicate regulatory network within a fatty liver[158,159]. Liver steatosis in CHC is a well-established accelerator of fibrosis[160] and HCC[161]. This metabolic-viral synergy culminates in significant clinical cross-talk[162,163]. HCV infection independently increases the risk of IR and type 2 diabetes[164,165], effectively creating and exacerbating the metabolic drivers of MAFLD. Furthermore, the associated metabolic milieu-particularly IR and elevated BMI is linked to a poorer response to interferon-alpha-based therapies[166]. Consequently, although a direct link to metabolic syndrome remains debated, patients with the dual burden of HCV and MAFLD face a disproportionately worse prognosis. Compared to those with HCV alone, they experience accelerated fibrogenesis, a heightened risk of HCC and atherosclerosis, and potentially suboptimal responses to certain therapies, underscoring the critical need for a combined metabolic and antiviral management approach[167].

Relationship between HCV infection and IR

IR emerges as a critical pathogenic nexus and a potent amplifier of liver injury in both MAFLD and CHC, with its prevalence and impact being particularly severe in the context of co-existing disease. While IR is a hallmark of MAFLD, affecting approximately 70% of patients[168], its frequency escalates dramatically to over 80% in patients with CHC and concomitant MAFLD, underscoring the synergistic role of HCV infection in disrupting carbohydrate metabolism[169]. Crucially, the severity of IR, as measured by insulin levels and the HOMA index, correlates directly with the degree of histological liver damage[170,171], positioning it not merely as a comorbidity but as a key driver of disease progression.

The mechanisms by which IR exacerbates hepatocyte damage and accelerates fibrosis are multifaceted. Hyperinsulinemia, a direct consequence of IR, promotes hepatic fibrogenesis through several pathways[172]. Furthermore, IR and the associated lipid dysregulation lead to fatty degeneration of hepatocytes and alter the lipid composition of their membranes. This cellular steatosis disrupts fundamental biochemical processes, including gluconeogenesis, rendering hepatocytes more vulnerable to injury. Against this backdrop of metabolic stress, persistent viral-driven (in CHC) and/or diet-driven inflammation creates a profibrogenic milieu, where progressive mesenchymal activation rapidly translates into collagen deposition and fibrosis[165]. Thus, IR acts as a common metabolic driver that synergizes with viral factors to fuel a self-perpetuating cycle of inflammation, hepatocyte dysfunction, and accelerated fibrogenesis.

Hepatitis B: The convergence of two major global liver epidemics-CHB and MAFLD-presents a growing clinical and public health challenge. Chronic HBV infection, affecting an estimated 248 million people worldwide, remains a leading cause of cirrhosis and HCC, accounting for nearly 680000 annual deaths[173,174].

With the parallel rise in MAFLD prevalence, co-existing disease is increasingly common. Reported prevalence rates of MAFLD in CHB cohorts vary widely, from 14% to 70%, a discrepancy largely attributable to differences in diagnostic methodologies [ultrasound (US), transient elastography, biopsy] and study population characteristics[175]. Regardless of the exact figure, this overlap is clinically significant. Both conditions independently drive chronic liver injury, progressive fibrosis, and carcinogenesis, suggesting a potential for synergistic harm. Consequently, understanding the interaction between viral and metabolic liver damage has become a priority, as their coexistence may accelerate disease progression,

complicate management, and significantly threaten long-term hepatic health[176].

Effect of HBV on systemic metabolism: The relationship between HBV infection and MAFLD is complex and appears paradoxical, characterized by seemingly protective metabolic effects that contrast with synergistic harm when both diseases coexist. Epidemiological studies consistently report an inverse association between chronic HBV infection and the development of MAFLD, as evidenced by lower prevalence rates of HS, hypertriglyceridemia, and metabolic syndrome in HBsAg-positive individuals across different populations[177-179]. This protective phenotype is mechanistically linked to HBV-induced alterations in lipid metabolism, specifically a reduction in hepatic lipoprotein biosynthesis, leading to favorable serum lipid profiles (lower TG, LDL-C) and a decreased prevalence of hyperlipidemia[179-181]. Consequently, HBV-infected patients often exhibit lower intrahepatic lipid content compared to those with MAFLD alone [182]. Thus, while HBV may modestly modulate systemic lipid metabolism, likely influenced by the natural history of infection[183], it does not confer protection against the detrimental hepatic consequences of metabolic dysfunction. This inverse relationship between HBV infection and serum lipid profile may also contribute to the decreased prevalence of metabolic syndrome[184-186].

However, this apparent metabolic “benefit” does not translate into improved outcomes when MAFLD is established. On the contrary, the coexistence of MAFLD and HBV creates a high-risk phenotype. IR is more prevalent in patients with dual pathology than in those with either condition alone[187]. Critically, the presence of metabolic syndrome—a core diagnostic component of MAFLD—acts as a potent independent driver of disease progression in CHB, accelerating the risks of liver fibrosis[188], cirrhosis[189], and hepatitis B-related mortality/HCC[190], irrespective of viral load or ALT levels. The superimposition of MAFLD on CHB creates a synergistic injurious milieu where metabolic and viral insults converge, outweighing any modestly favorable lipid effects and leading to worse clinical outcomes.

Mechanism of MAFLD inhibiting HBV replication

Emerging evidence points to a complex immunomodulatory role of HS in the natural history of CHB, which may paradoxically suppress viral activity while potentially altering immune clearance. Clinical observations consistently reveal a negative association between HS and markers of HBV activity. This is evidenced by an increased likelihood of HBsAg seroclearance and a higher rate of transition out of the immunotolerant phase in patients with concomitant fatty liver[182,188,191,192]. Furthermore, a significant inverse correlation is noted between steatosis and HBV replication levels in humans, though the precise mechanisms remain undefined[193].

Preclinical models provide direct causal support for these clinical findings. In mouse models of co-existing MAFLD and HBV infection, HS consistently leads to a reduction in HBV DNA load and antigen levels[194,195]. Importantly, these studies suggest that the suppressive effect is unidirectional: While steatosis inhibits viral replication, HBV infection does not appear to significantly alter the underlying metabolic phenotype of MAFLD in these models[195].

The mechanisms underlying this viral suppression are likely multifactorial and may involve both direct metabolic interference and enhanced immune surveillance. Proposed pathways include: (1) Direct metabolic inhibition, where lipid accumulation within hepatocytes creates an intracellular environment unfavorable for HBV replication; (2) Activation of innate immunity by MAFLD-related lipotoxicity or inflammation, which enhances antiviral responses; and (3) MAFLD-mediated hepatocyte apoptosis, which could selectively reduce the pool of HBV-infected cells[196]. Thus, the steatotic liver microenvironment appears to exert a net restrictive pressure on HBV, adding a novel metabolic dimension to the host-virus interplay in CHB.

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is increasingly recognized not merely as a sleep disorder but as a systemic metabolic stressor that contributes to the pathogenesis and progression of MAFLD through intermittent hypoxia (IH)-mediated pathways. Diagnosis, based on the apnea-hypopnea index (AHI) *via* polysomnography, stratifies severity from mild to severe[197-200].

Clinical evidence consistently links OSA severity with MAFLD phenotypes. Epidemiological and meta-analytic data robustly associate OSA, particularly in its moderate to severe forms, with an increased prevalence and severity of MAFLD, NASH, and liver fibrosis[201,202]. Crucially, the AHI serves as an independent predictor of significant liver fibrosis in this population, correlating with validated non-invasive markers such as fibrosis-4 index and liver stiffness measurements[203-205]. Meta-regression analyses showed that OSA was associated with steatosis, lobular inflammation, ballooning, and fibrosis independent of age, gender, BMI, and abdominal obesity[206-208].

The central mechanistic link is IH, which drives MAFLD progression *via* two interconnected axes: Oxidative stress and dysregulated hypoxia signaling.

Oxidative stress and mitochondrial dysfunction: The cyclical hypoxia-reoxygenation cycles of IH generate ROS, overwhelming hepatic antioxidant defenses and causing systemic oxidative stress[209]. This remodels liver mitochondria, exacerbating DNA damage and creating a pro-inflammatory, profibrogenic milieu[210,211].

Hypoxia-inducible factor activation: IH potently upregulates the master transcriptional regulator hypoxia-inducible factor (HIF-1 α). Elevated HIF-1 α , in turn, activates a cascade of genes involved in lipogenesis, inflammation, and fibrogenesis[212,213]. This pathway integrates the hypoxic stimulus into sustained metabolic dysregulation and hepatic injury, directly promoting IR, hepatocyte damage, and the progression toward NASH and fibrosis[211,214].

In summary, OSA, through the recurrent hypoxic insult of IH, acts as a direct promoter of MAFLD by inducing a state of chronic oxidative stress and activating the HIF-1 α -mediated hypoxic response, thereby accelerating steatosis, inflammation, and fibrogenesis.

IH and dyslipidemia

Furthermore, IH and OSA critically exacerbate dyslipidemia—a hallmark of MAFLD—creating a vicious metabolic cycle. The condition is a well-established risk factor for lipid metabolism disorders, with which it shares a bidirectional relationship[215]. Mechanistically, IH enhances adipose tissue lipolysis, flooding the liver with FFA while simultaneously impairing hepatic mitochondrial β -oxidation and postprandial lipid clearance. This results in a net increase in hepatic lipid synthesis and accumulation[216]. A key mediator of this metabolic shift is HIF-2 α , which is upregulated by IH and directly promotes disordered hepatic lipid metabolism. Evidence of this pathway in humans includes the significant elevation of the lipid transport molecule CD36 in the livers of OSA patients, a finding strongly correlated with AHI severity and oxygen desaturation indices[217]. Thus, the HIF-mediated hypoxic response, through both HIF-1 α (inflammation, fibrosis) and HIF-2 α (lipid metabolism), acts as a central conductor orchestrating multiple metabolic hits that drive MAFLD progression in the context of sleep apnea.

IH and insulin and/or leptin resistance

Ultimately, IH converges on inducing insulin and leptin resistance, a fundamental pillar in the pathogenesis of MAFLD and a critical metabolic bridge linking OSA to liver disease. Clinical data robustly position IH/OSA as an independent risk factor for the development and severity of MAFLD specifically through the induction of IR[218,219]. This is evidenced by studies where the AHI and the HOMA-IR are independently associated with MAFLD prevalence and elevated liver enzymes, even after adjustment for confounders like obesity[219,220].

Thus, the pathophysiological cascade from OSA to MAFLD can be summarized as a self-reinforcing cycle: OSA-driven IH activates hypoxic signaling (HIF-1 α /2 α), which simultaneously: (1) Promotes systemic and hepatic oxidative stress; (2) Dysregulates lipid metabolism promoting steatosis; and (3) Induces insulin/Leptin resistance.

The resulting hyperinsulinemia and metabolic dysfunction further accelerate hepatic lipogenesis, inflammation, and fibrogenesis, thereby fueling MAFLD progression. While the precise molecular intermediaries require further elucidation, the central role of IH-induced metabolic resistance in this pathway is unequivocal, establishing OSA not merely as a comorbidity but as an active driver of metabolic liver disease.

IH and gut microbiota

Emerging research points to two additional, interlinked pathways through which OSA may exacerbate MAFLD: Gut microbiota dysbiosis and the promotion of hepatocyte death.

Gut-liver axis disruption: OSA and its characteristic IH are implicated in inducing gut dysbiosis, though human data remain limited compared to animal evidence[221–224]. The proposed alterations—reduced microbial diversity, a decrease in beneficial SCFAs producers, and an increase in pro-inflammatory pathobionts like *Prevotella*—mirror changes observed in MAFLD[225–229]. This dysbiosis is hypothesized to increase intestinal permeability, facilitating the translocation of microbial products into the portal circulation. This, in turn, fuels hepatic inflammation and IR, creating a vicious gut-liver axis that accelerates MAFLD progression[227].

Hepatocyte death pathways: OSA-induced IH directly promotes hepatocyte injury *via* multiple programmed cell death mechanisms. Experimental models demonstrate that IH exacerbates apoptosis through ER and oxidative stress, effects that can be mitigated by antioxidants[230–233]. Furthermore, IH is shown to promote necroptosis, a pro-inflammatory form of cell death mediated by RIPK3/MLKL, thereby amplifying liver injury[231]. Given the crosstalk between these pathways, a holistic concept like “panoptosis”—the simultaneous activation of multiple death pathways—may best describe the hepatocyte demise in OSA-related MAFLD[234].

In summary, OSA contributes to MAFLD through a multifactorial network of interconnected insults. Systemic IH acts as the primary driver, concurrently: (1) Inducing oxidative stress and HIF activation; (2) Dysregulating lipid and glucose metabolism; (3) Altering the gut microbiota and gut-liver axis; and (4) Triggering inflammatory hepatocyte death pathways. These processes collectively create a profibrogenic and pro-steatotic hepatic microenvironment, positioning OSA as a significant modifiable risk factor in the pathogenesis and progression of metabolic liver disease.

Hypertension

Hypertension and MAFLD are intricately linked components of the metabolic syndrome, sharing a bidirectional relationship that significantly amplifies the risk of adverse hepatic and cardiovascular outcomes. Epidemiological data robustly support this mutual aggravation. Prospective studies demonstrate that normotensive individuals with MAFLD have a markedly higher incidence of hypertension, with risk escalating in proportion to the severity of HS[235,236]. Conversely, hypertension is an independent risk factor for the development and progression of MAFLD, including advanced fibrosis and NASH[237,238]. This synergy is evident in long-term cohorts, where MAFLD is associated with a three-fold higher incidence of hypertension, and the presence of hypertension, in turn, predicts a greater risk of liver fibrosis progression[239–242].

The pathophysiological crosstalk between MAFLD and hypertension is mediated by several interconnected mechanisms, creating a self-perpetuating cycle.

The renin-angiotensin system: A central pathway: Dysregulation of the hepatic and systemic renin-angiotensin system (RAS) serves as a key nexus. In hypertension, angiotensin II promotes systemic inflammation and hepatic stellate cell activation, driving fibrogenesis and altering lipid metabolism to favor intrahepatic TG (IHTG) accumulation[243–245]. Reciprocally, MAFLD itself induces intrahepatic RAS overactivity, further exacerbating liver inflammation, fibrosis, and contributing to systemic vascular tension[246,247]. Pharmacological RAS inhibition in experimental models attenuates

steatosis and fibrosis, highlighting its pathogenic role[247].

IR and chronic inflammation: A common soil: Shared metabolic disturbances form a critical link. IR, a hallmark of MAFLD, impairs the PI3K/Akt vasodilatory pathway in endothelium while potentiating vasoconstrictive MAPK signaling, promoting hypertension[248,249]. Concurrently, chronic low-grade inflammation in MAFLD, driven by pro-inflammatory cytokines (*e.g.*, from activated NF- κ B), not only perpetuates hepatic injury but also contributes to endothelial dysfunction and increased arterial stiffness[122,242].

Sympathetic nervous system hyperactivation and adipokine imbalance: Autonomic dysfunction bridges both conditions. Hyperactivation of the sympathetic nervous system (SNS) is implicated in the pathogenesis of hypertension and, through its metabolic effects on the liver and adipose tissue, exacerbates MAFLD[250,251]. This neural overdrive may directly stimulate hepatic stellate cells, accelerating fibrogenesis[252,253]. Furthermore, MAFLD alters adipokine secretion, characterized by elevated leptin and reduced adiponectin. This imbalance promotes vascular damage, inflammation, and contributes to obesity-related hypertension, creating another reinforcing loop[248].

In conclusion, the MAFLD-hypertension association is not merely coincidental but causal and bidirectional, rooted in shared pathophysiological pathways-RAS activation, IR with inflammation, and SNS dysregulation. This interplay necessitates an integrated clinical approach where the diagnosis of one condition should prompt screening and targeted management of the other to mitigate the compounded risk of hepatic and cardiovascular morbidity. The most common comorbidities associated with MAFLD are presented in Table 2.

COMPLICATIONS

Cardiovascular diseases

MAFLD is now unequivocally recognized not merely as a liver-specific disorder but as a pivotal independent risk factor for cardiovascular disease (CVD), contributing significantly to both morbidity and mortality. This association extends beyond shared risk factors, positioning MAFLD as an active player in atherogenesis and cardiac dysfunction. Prospective cohort studies and meta-analyses consistently demonstrate a 1.5- to 2.5-fold increased risk of cardiovascular events in individuals with MAFLD, with risk escalating with disease severity[254-259].

Major adverse cardiovascular events: Increased incidence of coronary heart disease, myocardial infarction, and stroke [256,259].

Subclinical atherosclerosis: Strong associations with carotid plaque, increased intima-media thickness, arterial stiffness, endothelial dysfunction, and coronary artery calcification[260-272].

Mortality: CVD is a leading cause of death in the MAFLD population, with a significantly elevated all-cause and cardiovascular mortality risk[257,265,266]. Consequently, current guidelines advocate for routine cardiovascular risk assessment in all MAFLD patients[268].

The MAFLD-CVD nexus is rooted in a common soil of metabolic and inflammatory disturbances: A hallmark of MAFLD, characterized by elevated pro-inflammatory cytokines (*e.g.*, IL-6, TNF- α), which directly promote vascular inflammation, endothelial activation, and plaque instability[273-276].

Dyslipidemia MAFLD fundamentally disrupts hepatic lipid homeostasis, generating a highly atherogenic lipid profile (the lipid triad).

Increased very-low-density lipoprotein secretion: Enhanced hepatic DNL and TG synthesis stimulate the production and secretion of VLDL[277-279].

Lipoprotein remodeling: Elevated plasma TGs promote the cholesterol ester transfer protein-mediated exchange of TGs from VLDL for cholesteryl esters from low density lipoprotein (LDL) and high-density lipoprotein (HDL). This leads to the formation of: Small, dense LDL particles: More prone to oxidation and endothelial penetration.

Dysfunctional, cholesterol-depleted HDL: With impaired atheroprotective capacity[280].

IR

Drives hepatic DNL and systemic dyslipidemia while promoting endothelial dysfunction *via* impaired PI3K/Akt signaling and enhanced MAPK vasoconstrictive pathways[281-285]. Reduced adiponectin (vasoprotective) and elevated leptin levels exacerbate IR, inflammation, and vascular damage[286].

Coagulation dysfunction

The liver's role in synthesizing coagulation factors is dysregulated in MAFLD. Increased production of fibrinogen, factor VIII, and von Willebrand factor, alongside impaired fibrinolysis (*e.g.*, elevated PAI-1), creates a pro-thrombotic milieu [287-290]. Fibrinogen deposition in the vessel wall facilitates LDL retention and plaque development[291-293]. In advanced disease, a fragile rebalancing occurs, often with reduced synthesis of both pro- and anti-coagulant factors, but the net effect remains an elevated risk of thrombosis[290].

Table 2 Comorbidities associated with metabolically associated fatty liver disease

Condition	Mechanisms/links with MAFLD	Clinical outcomes	Ref.
Type 2 diabetes mellitus	Insulin resistance, chronic hyperglycemia, lipotoxicity	Faster progression to NASH and fibrosis; higher risk of CVD	Byrne <i>et al</i> [263]
Chronic hepatitis B/C	Additive hepatocellular injury, inflammation, altered lipid metabolism	Increased fibrosis progression, higher risk of HCC	Choi <i>et al</i> [175]
Arterial hypertension	Systemic inflammation, endothelial dysfunction, insulin resistance	Greater cardiovascular morbidity, worse liver outcomes	Lonardo <i>et al</i> [235]
Obstructive sleep apnea	Intermittent hypoxia, oxidative stress, systemic inflammation	Worsening fibrosis; increased CVD and metabolic complications	Zhang <i>et al</i> [220]

NASH: Non-alcoholic steatohepatitis; CVD: Cardiovascular disease; HCC: Hepatocellular carcinoma; MAFLD: Metabolically associated fatty liver disease.

The increased cardiovascular risk in MAFLD is not incidental but causal, mediated by a constellation of interrelated metabolic, inflammatory, thrombotic, and vascular insults originating from or exacerbated by the dysfunctional liver. This understanding mandates a paradigm shift in clinical management: Patients diagnosed with MAFLD must undergo comprehensive cardiovascular risk stratification and receive integrated treatment targeting both HS and cardiometabolic risk factors.

KIDNEY DISEASES

Emerging evidence positions MAFLD as a significant independent risk factor for the development and progression of chronic kidney disease (CKD), establishing a formidable liver-kidney axis within the spectrum of metabolic syndrome. This association extends beyond mere coexistence, implicating shared pathophysiology and bidirectional organ crosstalk.

Meta-analyses of large longitudinal cohorts confirm that individuals with MAFLD face a approximately 45%-80% increased risk of developing incident CKD, with the risk magnitude escalating in parallel with the severity of liver disease, particularly the stage of hepatic fibrosis[294-299]. The prevalence of CKD is substantially higher in MAFLD populations (20%-55%) compared to controls (5%-30%), and this association persists after adjustment for traditional renal and metabolic risk factors[300-308]. Notably, MAFLD appears to be more strongly associated with early-stage CKD, suggesting a role in disease initiation[308-319].

The MAFLD-CKD link is rooted in a common pathogenic milieu characterized by: (1) IR and hyperinsulinemia: A central driver that promotes glomerular hyperfiltration, endothelial dysfunction, and mesangial cell proliferation[311, 316]; (2) Chronic low-grade inflammation: A hallmark of both conditions, fueled by adipokine imbalance (*e.g.*, elevated leptin), pro-inflammatory cytokines, and oxidative stress, which directly contributes to renal tubular injury and interstitial fibrosis[315,317,319]; and (3) Dysregulated lipid metabolism: Atherogenic dyslipidemia and ectopic lipid deposition (lipotoxicity) can induce renal cellular injury *via* ER stress and apoptosis[311,318].

MAFLD likely contributes to CKD through multiple, intertwined systemic pathways.

Endocrine and metabolic mediators

Hepatokine dysregulation: The steatotic liver alters the secretion of hepatokines (*e.g.*, fibroblast growth factor-21, fetuin-A) that can directly influence renal insulin sensitivity, inflammation, and lipid metabolism[312].

Adipokine imbalance: Adipose tissue dysfunction leads to elevated leptin (pro-fibrotic, pro-inflammatory) and reduced adiponectin, exacerbating IR and renal injury[319,320].

Dyslipidemia and HDL dysfunction: MAFLD-induced atherogenic dyslipidemia and the generation of dysfunctional, pro-inflammatory HDL particles contribute to endothelial damage and glomerulosclerosis[321,322].

Activation of profibrotic and vasoactive systems

RAS: Systemic and intrahepatic RAS activation, prevalent in MAFLD, promotes renal vasoconstriction, sodium retention, and fibrotic signaling, creating a direct link to hypertension and CKD progression[311,314].

Integrated stress responses: Converging pathways of ER stress, oxidative stress (mediated by Nrf2 dysregulation), and activation of transcription factors like SREBP and TGF- β create a pro-fibrotic, pro-apoptotic microenvironment in both liver and kidney cells[316-318].

In the context of advanced MAFLD progressing to cirrhosis, a distinct hepatorenal reflex becomes clinically paramount, culminating in hepatorenal syndrome (HRS). This functional renal failure is driven by: (1) Severe splanchnic vasodilation leading to reduced effective arterial blood volume; (2) Compensatory activation of vasoconstrictor systems (RAS, SNS); and (3) Systemic inflammation and cirrhotic cardiomyopathy[323-325]. While HRS represents an extreme on the spectrum, it underscores the profound physiological interconnection between hepatic hemodynamics, systemic circulation, and renal function, principles that may be at play, albeit in an attenuated form, in earlier stages of MAFLD and

CKD[326].

The relationship between MAFLD and CKD is causal and incremental, mediated by a constellation of metabolic, inflammatory, and endocrine disturbances originating from the dysfunctional liver. The strength of association correlates with liver disease severity, particularly fibrosis stage. This evidence mandates a proactive clinical approach: Patients diagnosed with MAFLD, especially those with signs of advanced fibrosis, should be considered at high risk for CKD and warrant regular monitoring of renal function (*e.g.*, estimated glomerular filtration rate, albuminuria). Conversely, unexplained CKD should prompt evaluation for MAFLD.

Hepatocarcinoma

HCC represents a formidable and growing complication of MAFLD, emerging as a leading etiology of liver cancer worldwide, particularly in the absence of advanced cirrhosis[327-335]. This paradigm shift underscores MAFLD as a direct and potent oncogenic driver.

MAFLD is now recognized as the fastest-growing risk factor for HCC globally, with its attributable fraction rising dramatically, especially in Asian countries[336-338]. Projections indicate an increase in MAFLD-related HCC incidence by 47%-86% across Asia by 2030[339]. Despite the high population prevalence of MAFLD, the absolute risk of HCC in an individual patient remains low (2.4%-12.8%), highlighting the critical need to identify high-risk subgroups[340-343].

A defining and challenging feature of MAFLD-associated HCC is its frequent development in the absence of established cirrhosis, accounting for up to 50%-54% of cases[344-349]. This non-cirrhotic carcinogenesis distinguishes MAFLD from other chronic liver diseases and complicates surveillance paradigms. Key risk factors within the MAFLD spectrum include advanced liver fibrosis, T2DM (the strongest metabolic risk factor)[341,348], male gender, older age, and the presence of metabolic syndrome[346,347]. Historically, many MAFLD-driven HCC cases were misclassified as “cryptogenic”, obscuring the true burden. It is now clear that metabolic dysfunction underlies a substantial proportion of these cases[340].

Hepatocarcinogenesis in MAFLD is driven by a complex interplay of local and systemic factors.

Metabolic dysregulation and IR: Chronic hyperinsulinemia and altered hepatocyte metabolism create a pro-proliferative, anti-apoptotic microenvironment. Diabetes and metabolic syndrome are potent co-factors[347,348].

Chronic inflammation and oxidative stress: Persistent low-grade inflammation, cytokine release, and lipid peroxidation generate DNA damage and promote a tumor-promoting niche.

Gut-liver axis disruption: MAFLD-associated gut dysbiosis (*e.g.*, reduction in *Akkermansia*, *Bifidobacterium*) increases intestinal permeability, facilitating the translocation of microbial products that fuel hepatic inflammation and carcinogenesis[350-354].

Fibrosis as a key driver: While cirrhosis is not a prerequisite, advanced fibrosis (F3-F4) is the most significant histological risk marker, acting as a surrogate for the duration and severity of liver injury and creating a pro-fibrogenic, pro-oncogenic stroma[355].

The high prevalence of non-cirrhotic HCC and patient factors like obesity create unique surveillance hurdles in MAFLD.

Limitations of standard US: While US remains the first-line surveillance tool, its sensitivity for early HCC, especially in obese patients, is suboptimal (approximately 47% in cirrhosis) and operator-dependent[356-360].

The evolving role of biomarkers and advanced imaging

Abbreviated magnetic resonance imaging: Emerging as a highly sensitive alternative or adjunct for high-risk patients (*e.g.*, those with advanced fibrosis, inadequate US views, or diabetes). Prospective data shows superior sensitivity of magnetic resonance imaging (MRI) over US (85.7% *vs* 26.7%) for early HCC detection[361-363].

Alpha-fetoprotein: Adds modest sensitivity (increasing detection by approximately 18% when combined with US) but lacks sufficient specificity or sensitivity for standalone use[360,364].

Computed tomography: Not recommended for routine surveillance due to radiation exposure and inferior contrast resolution compared to MRI for early lesions. Clinical manifestations of the most common complications of MAFLD are presented in Table 3.

TREATMENT

Non-pharmacological interventions

Standard treatment for MAFLD focuses on lifestyle changes leading to weight loss, which includes calorie reduction, exercise, and healthy eating[365].

Weight loss

Intentional weight loss through lifestyle modification remains the foundational and most effective strategy for treating MAFLD, with histological benefits directly proportional to the degree of weight reduction[366-368]. This approach targets

Table 3 Complications of metabolically associated fatty liver disease

Complication	Mechanisms/links with MAFLD	Clinical outcomes	Ref.
Cardiovascular disease	Atherosclerosis, dyslipidemia, systemic inflammation	Myocardial infarction, stroke, heart failure	Mantovani <i>et al</i> [254]
CKD	Shared risk factors (diabetes, hypertension), systemic inflammation	Higher CKD incidence, faster progression	Agustanti <i>et al</i> [296]
HCC	Fibrosis/cirrhosis, lipotoxicity, chronic inflammation	Increased HCC risk even without cirrhosis	Tan <i>et al</i> [356]
Advanced liver disease (fibrosis, cirrhosis)	Persistent steatosis, oxidative stress, inflammation	End-stage liver disease, need for transplantation	Spahis <i>et al</i> [73]

MAFLD: Metabolically associated fatty liver disease; CKD: Chronic kidney disease; HCC: Hepatocellular carcinoma.

the root cause of the disease-metabolic dysfunction.

A dose-response relationship exists between weight loss and histological improvement. Clinical evidence establishes clear therapeutic thresholds: (1) $\geq 5\%$ body weight loss: Leads to significant improvement in HS; (2) 7%-10% body weight loss: Results in amelioration of necroinflammation (ballooning, lobular inflammation) and improvement in the NAFLD Activity Score (NAS); and (3) $> 10\%$ body weight loss: Is typically required to demonstrate regression of liver fibrosis, the most critical predictor of long-term outcomes[369,370].

The efficacy of combined dietary and exercise interventions is robust. Structured programs combining caloric restriction with moderate-intensity physical activity (*e.g.*, ≥ 150 -200 minutes per week) can achieve a mean reduction in hepatic fat content of up to 40%, with higher-intensity interventions yielding greater benefits[371-373]. The key mechanism is the reversal of positive energy balance, which reduces adipose tissue lipolysis and DNL while improving hepatic and peripheral insulin sensitivity.

Successful implementation requires a structured, behavioral framework. Effective weight loss is a chronic process best supported by intensive, behavior-based interventions that include: (1) Professional counseling (from physicians, dietitians, psychologists); (2) Self-monitoring strategies (*e.g.*, food/activity diaries); and (3) Peer support groups and structured relapse prevention plans[374,375].

Lifestyle intervention is the first-line therapy for all patients with MAFLD. For patients with a BMI ≥ 30 kg/m² (or ≥ 27 kg/m² with weight-related comorbidities such as type 2 diabetes or hypertension) who fail to achieve or maintain clinically meaningful weight loss (5%-10%) through lifestyle measures alone, the addition of anti-obesity pharmacotherapy should be considered as an adjunct to enhance and sustain weight loss efforts[376].

Diet

While caloric deficit is the primary driver for reducing IHTG content, the composition of the diet plays a critical modulating role in achieving sustained metabolic and hepatic benefits. The therapeutic goal extends beyond mere weight loss to improving dietary quality and reducing systemic inflammation.

A consistent energy deficit of 500-1000 kcal/day reliably reduces IHTG and improves hepatic IR within days, with long-term adherence (*e.g.*, 11 weeks) further enhancing peripheral glucose uptake in muscle[377-379]. This underscores that quantitative calorie control is the non-negotiable foundation of dietary therapy.

For qualitative dietary composition, the Mediterranean diet emerges as the best-supported pattern for MAFLD management. Its benefits are multifactorial.

Direct hepatic impact: Randomized trials confirm its superiority in reducing HS and improving insulin sensitivity compared to standard low-fat diets[380,381].

Anti-inflammatory and antioxidant properties: Rich in polyphenols, monounsaturated fats (olive oil), and fiber, it actively lowers systemic inflammation-a key driver of MAFLD progression. This is reflected in its favorable Dietary Inflammatory Index (DII) score[379,382].

Cardiometabolic synergy: It concurrently improves glycemic control and reduces cardiovascular risk, addressing the two leading causes of morbidity and mortality in the MAFLD population[383].

Ketogenic diet shows promise for rapid improvement in IR and steatosis due to profound carbohydrate restriction [384]. However, its long-term sustainability, safety, and effects on fibrosis and cardiovascular risk markers require further evaluation before it can be recommended as a first-line strategy.

Macrobiotic and other anti-inflammatory diets characterized by low DII scores, they share the principle of high food quality and low processed food intake, suggesting that reducing dietary inflammation is a beneficial universal principle [379].

For clinical practice, a stepwise dietary approach is recommended: (1) Establish a caloric deficit (500-1000 kcal/day deficit) tailored to the patient; (2) Implement the mediterranean diet framework as the preferred nutritional pattern to achieve this deficit, emphasizing vegetables, fruits, whole grains, nuts, and olive oil while limiting saturated fats and refined carbohydrates; and (3) Consider patient preference and adherence; while the Mediterranean diet is ideal, any sustainable diet that creates a caloric deficit and improves dietary quality (low DII) is beneficial. More restrictive

regimens like ketogenic diets may be considered on a case-by-case basis with monitoring.

Physical exercise

Regular physical activity constitutes an independent and essential therapeutic component for MAFLD, conferring metabolic and hepatic benefits that extend beyond and often occur in the absence of significant weight loss[385,386]. Current evidence does not establish the clear superiority of any single exercise modality (aerobic, resistance, or high-intensity interval training) for reducing HS[387]. The most significant benefit is derived from regular performance of any exercise the patient can adhere to. However, a combined approach is rational.

Aerobic exercise (e.g., brisk walking, cycling, swimming): Effectively improves cardiorespiratory fitness and whole-body insulin sensitivity.

Resistance training (weight lifting, bodyweight exercises): is crucial for preserving or increasing lean muscle mass, countering the sarcopenia often exacerbated by calorie-restricted diets in obese patients, and independently improving insulin signaling[385,386].

Minimum effective dose: Engaging in ≥ 150 minutes of moderate-intensity activity per week is associated with significant improvements in liver enzymes and metabolic health[388].

Systemic protection: Regular exercise mitigates key MAFLD risk factors, including visceral adiposity and IR, thereby lowering the risk of progression to type 2 diabetes and CVD[389,390].

Hepatic impact: Even without weight loss, sustained exercise programs (e.g., 30-60 minutes, 2-3 times per week for 6-12 weeks) reliably reduce intrahepatic lipid content by 20%-30%, as measured by MR spectroscopy[391-393]. Proposed mechanisms include reduced hepatic lipogenesis and enhanced fatty acid oxidation[392].

Probiotics

Modulation of the gut-liver axis *via* probiotics represents an emerging, though not yet firmly established, adjunctive strategy for MAFLD management, targeting underlying dysbiosis and systemic inflammation. Results from human studies using probiotic mixtures primarily *Lactobacillus* and *Bifidobacterium* strains) are promising but inconsistent.

Positive outcomes: Several randomized controlled trials report improvements in surrogate markers, including reductions in liver enzymes alanine aminotransferase, γ -glutamyltransferase, hepatic steatosis index, systemic inflammation (hs-CRP), and IR (HOMA-IR)[394-398].

Negative or neutral findings: Other well-designed studies show no significant benefit on primary liver endpoints, highlighting heterogeneity in strains, dosage, treatment duration, and patient populations[399].

Probiotics are hypothesized to benefit MAFLD by: (1) Reducing intestinal permeability and bacterial translocation; (2) Modulating immune responses and lowering systemic inflammation; and (3) Influencing host metabolism (e.g., bile acid metabolism, SCFAs production). Specific multi-strain formulations like VSL#3 have been extensively studied, showing modest improvements in metabolic and inflammatory parameters[395,397].

Research is shifting toward more targeted approaches: (1) Next-generation probiotics: Defined bacterial strains with specific metabolic functions (e.g., *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*) show potent preclinical promise for improving metabolic health and reducing steatosis[400]; and (2) Precision Microbiota Therapy: Future strategies may involve personalized probiotic cocktails or fecal microbiota transplantation based on individual microbial signatures[401].

Given the current evidence, probiotics cannot be recommended as a standalone or first-line therapy for MAFLD. Their role is best viewed as a potential adjunct within a comprehensive lifestyle modification program, particularly for patients with significant dysbiosis-related symptoms (e.g., bloating, irregular bowels). Further large-scale, long-term trials with histological endpoints are required to define their precise place in the therapeutic algorithm.

Pharmacological intervention

Pharmacotherapy for MAFLD is adjunctive to lifestyle modification and should be tailored to the disease stage, predominant phenotype (metabolic, fibrotic), and individual patient profile, particularly the presence of T2DM and cardiovascular risk[402-424]. The goals are to reduce steatosis, resolve necroinflammation, halt fibrosis, and mitigate associated cardiometabolic risks[425-430].

For patients with MAFLD and concomitant T2DM, antidiabetic drugs offer dual benefits

GLP-1 receptor agonists: This class has emerged as a leading option due to multi-organ benefits. Beyond robust glycemic control and weight reduction (the primary driver of hepatic fat loss[424]), GLP-1 receptor agonists (GLP-1 RAs) (e.g., semaglutide, dulaglutide) demonstrate direct histological efficacy, improving steatosis, inflammation, and fibrosis in randomized trials[421-423]. Their cardiorenal protective effects solidify their position as a first-choice therapy in T2DM with MAFLD, especially with obesity or high cardiovascular risk[418,425-427].

SGLT2 inhibitors: These agents promote glucosuria, leading to weight loss, improved glycemic control, and significant reductions in IHTG and liver enzymes[428]. Their proven benefits in reducing heart failure hospitalizations and slowing CKD progression are critical, given the comorbidity profile in MAFLD[427]. While hepatic benefits are likely secondary to metabolic improvement[429], their cardiorenal protection makes them a cornerstone in T2DM management, often used in

combination with GLP-1 RAs for synergistic effect[430].

Agents with specific histological efficacy in NASH (with or without T2DM)

Pioglitazone (PPAR- γ agonist): This insulin sensitizer has the strongest evidence for improving all key histological features of NASH, including fibrosis, in patients with and without T2DM[412,416]. It increases adiponectin and promotes fat redistribution. However, its use is limited by side effects: Weight gain, edema, and elevated fracture risk, mandating careful patient selection and monitoring[417].

Resmetirom (THR- β agonist): Representing the first FDA-approved drug specifically for NASH with moderate fibrosis, resmetirom targets hepatic metabolism. Phase 3 trials confirm its efficacy in reducing liver fat and improving NASH resolution and fibrosis[431-434]. This marks a shift towards targeted, liver-directed pharmacotherapy.

Vitamin E (α -tocopherol): As an antioxidant, high-dose vitamin E (800 IU/day) is effective in improving steatosis, inflammation, and ballooning, leading to NASH resolution in non-diabetic adults[435-438]. It does not reverse fibrosis. Safety concerns about a potential increase in all-cause mortality at high doses remain controversial but warrant caution and avoidance of long-term, indiscriminate use[439,440].

Established medications with modest or uncertain hepatic effects

Metformin: Despite improving insulin sensitivity and offering weight loss and potential chemopreventive benefits against HCC[404,405], metformin does not lead to significant histological improvement in NASH[411]. Its role in MAFLD is primarily as a first-line glycemic control agent in T2DM, with hepatic benefits being an ancillary, not primary, outcome.

Statins: Safe and recommended in MAFLD patients for primary and secondary cardiovascular prevention, given that CVD is the leading cause of death. Some studies suggest modest improvements in liver enzymes, but this is not a treatment goal[432-434]. Concerns about hepatotoxicity are unfounded in this population.

Clinical takeaway: The pharmacological strategy should be personalized. For a diabetic patient with obesity and high CVD risk, a GLP-1 RA is optimal. For a non-diabetic with active NASH, pioglitazone or vitamin E are first-line options, with resmetirom now as a targeted alternative. All therapy rests on the foundation of lifestyle intervention. The main therapeutic approaches for MAFLD are presented in Table 4.

Surgical treatment

For a subset of patients with severe obesity and MAFLD refractory to lifestyle and pharmacological therapy, metabolic (bariatric) surgery represents the most effective intervention, offering profound and sustained metabolic, histological, and potentially oncological benefits.

Surgery is indicated after failure of intensive conservative management. Current guidelines (*e.g.*, ADA 2022) recommend consideration for patients with: (1) Class III obesity (BMI ≥ 40 kg/m²); or (2) Class II obesity (BMI 35.0-39.9 kg/m²) with comorbid T2DM that is not adequately controlled despite optimal medical therapy[441].

This aligns with the MAFLD population, where a significant proportion struggles to achieve and maintain the > 7%-10% weight loss required for histological improvement through non-surgical means[369]. Bariatric surgery induces transformative changes in liver histology, superior to any pharmacotherapy.

Studies demonstrate durable resolution of steatohepatitis in a majority of patients within 1 year post-surgery[442,443].

Critically, benefits extend to fibrosis, with progressive regression observed over 5 years of follow-up, addressing the key driver of long-term liver-related outcomes[443,444].

Emerging meta-analytic data suggest bariatric surgery may be associated with a reduced risk of HCC, adding a significant long-term protective dimension[445].

The safety profile in patients with compensated MAFLD-related cirrhosis appears acceptable in specialized centers, though risks are higher and require meticulous multidisciplinary assessment[446].

Roux-en-Y gastric bypass appears to offer superior metabolic and histological outcomes compared to restrictive procedures like adjustable gastric banding, likely due to more pronounced hormonal changes[447]. Less invasive endoscopic procedures offer a middle ground between pharmacotherapy and surgery: Endoscopic sleeve gastropasty and aspiration therapy achieve significant weight loss (approximately 15%-17% total body weight loss at 12 months) and improvement in metabolic parameters[448]. Intra-gastric balloons have shown efficacy in improving NAS[449].

While long-term histological data are less robust than for surgery, EBMTs present a valuable option for patients with lower BMI or those seeking a less invasive approach. Metabolic surgery is not a “last resort” but a powerful, disease-modifying therapy for eligible patients. The decision should be made within a multidisciplinary team (hepatologist, endocrinologist, bariatric surgeon, dietitian) and involves weighing the proven benefits of NASH resolution and fibrosis regression against procedural risks. For those ineligible or hesitant about surgery, endoscopic bariatric therapies provide a potent intermediate step.

CONCLUSION

MAFLD is a systemic metabolic disorder with profound hepatic and extrahepatic implications. Its strong bidirectional links with type 2 diabetes, CVD, and CKD necessitate a shift from a hepatocentric to a multidisciplinary care model.

Table 4 Current therapeutic approaches in Metabolically associated fatty liver disease

Therapy	Mechanisms	Clinical outcomes/limitations	Ref.
Lifestyle modification	Weight loss, improved insulin sensitivity, reduced inflammation	Most effective, especially with $\geq 10\%$ weight loss; limited adherence	Vilar-Gomez <i>et al</i> [369]
Metformin	Insulin sensitizer, improves metabolic profile	Improves liver enzymes and insulin resistance, but no histological benefit	Rena <i>et al</i> [403]
Vitamin E	Antioxidant, reduces oxidative stress	Improves steatosis and inflammation, but not fibrosis; conflicting evidence	Yakaryilmaz <i>et al</i> [436]
GLP-1 receptor agonists	Weight loss, improved insulin sensitivity, reduced inflammation	Histological improvement, promising data; long-term outcomes unknown	Hartman <i>et al</i> [425]
SGLT2 inhibitors	Improve glycemic control, promote weight loss, reduce steatosis and fibrosis	Improve metabolic and hepatic parameters; long-term outcomes lacking	Pradhan <i>et al</i> [429]

SGLT2: Sodium-glucose transporter 2; GLP-1: Glucagon-like peptide-1.

Effective management is staged, with lifestyle intervention as the uncontested cornerstone. Pharmacotherapy, including novel agents like resmetirom and GLP-1 receptor agonists, should be tailored to the individual's metabolic phenotype and fibrosis risk. For eligible patients with severe obesity, metabolic surgery offers potent disease modification. A critical clinical imperative is the bidirectional screening between MAFLD and its cardiometabolic comorbidities. Future efforts must prioritize non-invasive biomarkers for risk stratification and the development of integrated care pathways. Ultimately, addressing the MAFLD epidemic requires recognizing it as a multisystem condition, demanding collaborative management to improve long-term patient outcomes.

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FOOTNOTES

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