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# Metabolic Dysfunction–Associated Steatotic Liver Disease: From Pathophysiology to Clinical Management

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**Abstract** Metabolic dysfunction–associated steatotic liver disease (MASLD) is currently one of the most prevalent chronic liver diseases worldwide, closely linked to the growing epidemics of obesity and type 2 diabetes. The pathogenesis of MASLD involves a complex interplay of metabolic, genetic, and environmental factors leading to excessive hepatic lipid accumulation, endoplasmic reticulum stress, inflammation, and progressive fibrosis. Central pathogenic mechanisms include insulin resistance, visceral obesity, atherogenic dyslipidemia, and activation of proinflammatory signaling pathways. Early diagnosis relies on the combination of metabolic risk assessment, laboratory markers (including TyG, HOMA-IR, liver enzymes, fibrosis indices), and non-invasive imaging methods such as ultrasound, elastography, and MRI. Recent international consensus has introduced a new terminology—MASLD and MASH—to better reflect the metabolic nature of the disease and remove stigmatizing elements associated with the former NAFLD/NASH terminology. Management strategies focus on weight reduction through lifestyle modification, optimal control of metabolic comorbidities, and emerging pharmacotherapies, including GLP-1 receptor agonists, SGLT2 inhibitors, and resmetirom. MASLD represents a major global health challenge, requiring interdisciplinary collaboration and early intervention to prevent advanced fibrosis, cirrhosis, and related cardiovascular complications.

**Keywords** MASLD, Steatohepatitis, Insulin resistance, Fibrosis, Metabolic syndrome, Obesity, GLP-1RA, SGLT2i, Resmetirom

Metabolic dysfunction–associated steatotic liver disease (MASLD) is the new term replacing nonalcoholic fatty liver disease (NAFLD), emphasizing the key role of metabolic disorders such as insulin resistance, obesity, type 2 diabetes, dyslipidemia, and hypertension in its pathogenesis. In 2023, an international consensus supported by major hepatology societies (American Association for the Study of Liver Diseases, European Association for the Study of the Liver, Latin American Association for the Study of the Liver, Asian Pacific Association for the Study of the Liver and others) officially recommended abandoning the terms NAFLD and NASH in favor of MASLD and MASH (metabolic dysfunction–associated steatohepatitis) [1–3]. MASLD is defined as hepatic steatosis in the presence of at least one cardiometabolic risk factor, while MetALD refers to cases with moderate alcohol consumption (up to 140–350 g/week for women and 210–420 g/week for men) combined with metabolic abnormalities. In the absence of metabolic or other etiological factors, the condition is classified as cryptogenic steatosis. The updated nomenclature eliminates the stigmatizing term "nonalcoholic," better reflects disease mechanisms, and highlights the importance of screening and managing individuals with metabolic risk factors to prevent cardiometabolic complications [4–6]. Metabolic dysfunction –associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide. According to estimates, its prevalence among the adult population reaches approximately 30–40% [7]. Over the past two decades, the prevalence of MASLD has increased rapidly, with incidence rising by about 50% [8]. The combination of the obesity and type 2 diabetes epidemics makes MASLD a major medical challenge, as it has become a leading cause of liver fibrosis, cirrhosis, and hepatocellular carcinoma, as well as a significant contributor to cardiovascular and overall mortality [9].

The development of MASLD results from a complex interaction of genetic and environmental factors. The disease phenotype is further determined by disturbances in intracellular lipid homeostasis and stress responses: an imbalance between lipolysis and lipogenesis (involving ATGL/CGI-58 and PNPLA3 at the surface of lipid droplets), impaired export of lipids from the liver due to defective VLDL assembly (TM6SF2 variant, phosphatidylcholine deficiency), and suppressed β-oxidation resulting from PPARα dysfunction and impaired carnitine-dependent transport. Chronic endoplasmic reticulum (ER) overload activates unfolded protein response (UPR) pathways — PERK–eIF2α–ATF4, IRE1–XBP1, and ATF6 — leading to proinflammatory transcription, while mitochondrial dysfunction (electron

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leakage, impaired respiratory chain) combined with reduced mitophagy/autophagy enhances oxidative stress and lipotoxicity [10-11].

At the level of programmed cell death in MASH, apoptosis, pyroptosis (via caspase-1/NLRP3 inflammasome), and ferroptosis (iron-catalyzed peroxidation of polyunsaturated lipids) intensify, accompanied by the release of DAMP molecules, TLR signaling activation, and recruitment of innate immune cells [12]. The gut–liver axis is modulated not only by lipopolysaccharides but also by bacterial metabolites—short-chain fatty acids, endogenous ethanol, and secondary bile acids—and by altered FXR–FGF19 /TGR5 signaling, which affects lipid–glucose metabolism and bile flow [13]. Endocrine crosstalk between adipose tissue, liver, and skeletal muscle (fetuin-A, ANGPTL8, FGF21; myokines irisin/myostatin) sustains systemic insulin resistance and low-grade inflammation [14].

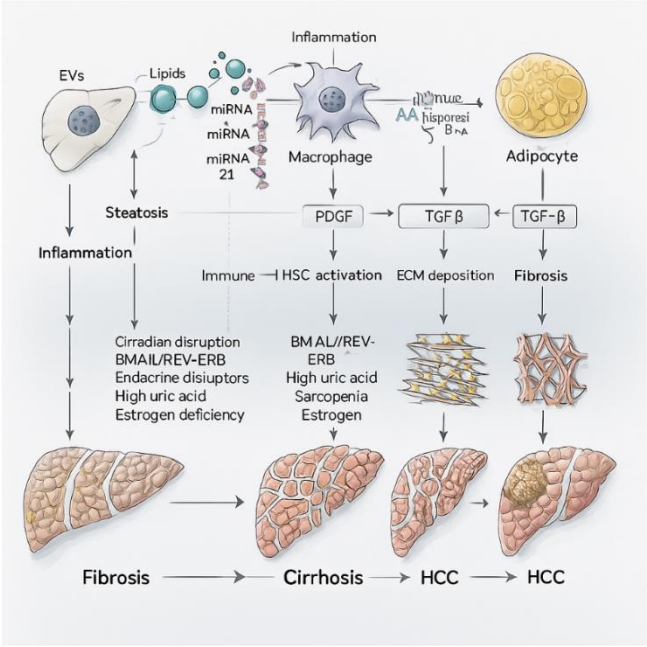


**Figure 1**

Fibrogenesis involves not only TGF-β, PDGF, Hedgehog pathways, and MMP/TIMP imbalance but also intercellular signaling through extracellular vesicles (adipocyte-, macrophage-, and hepatocyte-derived exosomes) carrying miRNA and lipids that activate hepatic stellate cells [15]. Epigenetic modifications, including DNA methylation, histone acetylation, and miRNA regulation (e.g., miR-122, miR-34a, miR-21), further consolidate the inflammatory–fibrotic phenotype [16]. Key progression modifiers include estrogen deficiency in peri- and postmenopausal women, circadian disruption (shift work, late-night eating; BMAL1 /REV-ERBα dysregulation), hyperuricemia, iron overload, sarcopenia or myosteatosis, obstructive sleep apnea, and exposure to endocrine disruptors such as bisphenol A and phthalates, all of which amplify insulin resistance, lipotoxicity, and proinflammatory cascades [17]. Ultimately, this leads to a transition from simple steatosis to immune-mediated hepatocyte injury, persistent hepatic stellate cell activation, and extracellular matrix remodeling with collagen I/III deposition, resulting in bridging fibrosis and, in some patients, cirrhosis and hepatocellular carcinoma [18]. The systemic nature of this process simultaneously increases cardio-renal risk and overall mortality, highlighting the need for multilevel pathogenetic targeting (DNL/ACC–FASN, FXR/TGR5, GLP-1R/FGF21 axis, NLRP3, TGF-β/PDGF) and comprehensive lifestyle modification [19].

Unhealthy dietary habits—particularly excessive intake of calories, saturated fats, and fructose—and abdominal obesity deliver the "first hit" to the liver, leading to chronic, often subclinical inflammation (elevated TNF-α, IL-6, oxidative stress) and impaired adipokine regulation (e.g., reduced adiponectin) [20]. Dysfunctional adipose tissue secretes proinflammatory cytokines, aggravating insulin resistance and hepatic steatosis. Additionally, intestinal dysbiosis and increased gut permeability in MASLD result in translocation of bacterial metabolites and endotoxins (e.g., lipopolysaccharides) into the portal circulation, activating hepatic macrophages and promoting fibrogenesis [21-22]. This creates a vicious cycle in which hepatic lipid overload and inflammation drive fibrosis progression and hepatocellular injury. According to the new classification, MASLD is defined by the presence of hepatic steatosis (confirmed by ultrasound, CT, MRI, or biopsy) together with metabolic risk factors [5]. For the diagnosis of MASLD, it is sufficient to meet at least one of the five cardiometabolic criteria: obesity (by BMI or waist circumference), type 2 diabetes or prediabetes, hypertriglyceridemia/low HDL, elevated blood pressure, or age over 50 years [3]. The "exclusion of alcohol" is operationalized through the introduction of the MetALD category: if a patient meets MASLD criteria and consumes moderate amounts of alcohol, they are classified as having metabolic plus alcohol-associated liver disease. If the alcohol component is absent or minimal, a MASLD diagnosis is sufficient; in cases of significant alcohol consumption, alcoholic liver disease is considered [3].

**Table 1**

| Category | Diagnostic criteria |
|---|---|
| MASLD | Hepatic steatosis + ≥1 cardiometabolic factor (obesity, T2DM, dyslipidemia, hypertension, insulin resistance); alcohol <140 g/week (women) / <210 g/week (men) |
| MetALD (MASLD + alcohol) | MASLD criteria + moderate alcohol consumption (140–350 g/week for women, 210–420 g/week for men) |
| Cryptogenic SLD | Steatosis without metabolic factors and without other known causes |
| Inflammation grade | Steatosis without inflammation (MASLD) and with inflammation (MASH, replacing NASH) |
| Fibrosis/cirrhosis | Fibrosis stage F0–F4; cirrhosis (sometimes without prior NASH) |

When evaluating patients with suspected MASLD, a combination of imaging and biochemical tests is essential. Ultrasound is a widely available and cost-effective method

for primary detection of steatosis; however, its sensitivity is limited, particularly for mild fatty infiltration [23]. Non-contrast CT can detect moderate to severe steatosis but is less effective in identifying mild disease and involves exposure to ionizing radiation [24]. MRI, especially using proton density fat fraction (PDFF) measurement, remains the most accurate noninvasive method for quantifying liver fat content and assessing disease severity [25]. Liver biopsy is still considered the "gold standard" for diagnosis because it enables direct evaluation of inflammation, hepatocyte ballooning, and fibrosis, which cannot be reliably detected by noninvasive methods [26]. However, due to its invasive nature, biopsy is reserved for cases with diagnostic uncertainty or when accurate staging (≥F2–F4) is required to guide treatment decisions [1].

Laboratory tests play a key role not only in screening but also in pathogenetic risk stratification for MASLD. Elevated transaminases (ALT, AST) and GGT are often the first signals of hepatocellular injury, although many patients may have normal levels, especially in early steatosis. This reflects the pathophysiological sequence in which lipid accumulation and metabolic dysfunction precede cytolytic changes [4]. Baseline laboratory evaluation includes ALT, AST, GGT, alkaline phosphatase, bilirubin, albumin, INR, and parameters of lipid and glucose metabolism (fasting glucose, HbA1c, insulin, triglycerides, LDL, HDL, total cholesterol). These indicators reflect early metabolic disturbances that trigger a cascade of metabolic, inflammatory, and fibrotic remodeling of the liver [27].

Role of SIRT1 in MASLD, an $NAD^+$-dependent deacetylase, is a central regulator of metabolic homeostasis and a key mediator in the multifactorial pathogenesis of MASLD. It influences lipid remodeling, mitochondrial function, autophagy/ER-stress balance, and inflammatory signaling in hepatocytes[33]. Clinically, circulating SIRT1 levels are significantly reduced in MASLD patients and inversely correlate with insulin resistance and dyslipidemia. In a recent case-control study, serum SIRT1 below ~23.75 ng/mL predicted MASLD (AUC≈0.76) with 78.9% sensitivity and 61.1% specificity[33]. Thus, low serum SIRT1 is a promising noninvasive biomarker for early MASLD detection and reflects its pathogenic role in promoting hepatic steatosis and fibrogenesis.

A key pathogenic mechanism of MASLD is insulin resistance, which leads to increased hepatic lipogenesis, reduced β-oxidation of fatty acids, and accumulation of toxic lipid intermediates. Quantitative assessment can be performed using the HOMA-IR index and the triglyceride–glucose (TyG) index, which are sensitive markers of subclinical disturbances in glucose–lipid metabolism [28]. Abnormal lipid profiles (ApoB, ApoA1, lipoprotein(a)) are associated with atherogenic states and fibrosis progression [29]. Elevated ferritin and iron saturation index reflect metabolic inflammation and oxidative stress, further damaging hepatocytes. At later stages, inflammatory and oxidative stress is accompanied by activation of proinflammatory cytokines (IL-6, TNF-α, hs-CRP). These mediators promote activation of Kupffer cells and hepatic stellate cells, initiating fibrogenesis [12].

At this stage, markers of hepatocyte injury and fibrosis formation become diagnostically significant: cytokeratin-18 (CK-18) indicates hepatocyte apoptosis, while hyaluronic acid, Pro-C3, and TIMP-1 reflect extracellular matrix remodeling activity [30]. The ELF test (Enhanced Liver Fibrosis), based on these components, enables accurate fibrosis staging without the need for biopsy [31]. Clinical risk stratification of MASLD progression relies on noninvasive indices such as the NAFLD Fibrosis Score, FIB-4, and APRI, which integrate laboratory and clinical data to identify patients at high risk of significant fibrosis (F≥2). Imaging methods such as liver elastography (FibroScan), CAP (Controlled Attenuation Parameter), MR elastography, and MR spectroscopy provide quantitative assessment of liver stiffness and steatosis, complementing laboratory markers [32].

An important component of pathogenesis evaluation involves assessing systemic risk factors, including anthropometric parameters (BMI, waist circumference), genetic variants (PNPLA3, TM6SF2, MBOAT7), and oxidative stress markers (MDA, SOD, GSH, catalase). These reflect individual mechanisms of disease progression and may be used for personalized risk assessment. Comprehensive stratification based on biochemical markers, noninvasive indices, and elastography enables early identification of patients at high risk of disease progression and supports the development of individualized therapeutic strategies [4].

Key risk factors for MASLD include components of metabolic syndrome, genetic predisposition, age and sex characteristics, and lifestyle factors. Central to this is abdominal obesity, reflected by increased BMI and waist circumference. Visceral adipose tissue acts as an active endocrine organ with enhanced lipolytic activity, increasing the flux of free fatty acids to the liver. This promotes hepatic insulin resistance, activates lipogenesis, reduces β-oxidation of fatty acids, and leads to the accumulation of toxic lipid metabolites in hepatocytes. Simultaneously, adipokine imbalance develops (decreased adiponectin and increased leptin and resistin), further amplifying inflammation and fibrogenesis [29,14].

The second major risk factor is type 2 diabetes mellitus and prediabetic states. Chronic hyperglycemia and hyperinsulinemia enhance de novo lipogenesis in the liver, leading to mitochondrial dysfunction, activation of proinflammatory signaling pathways (JNK, NF-κB), and progression of steatosis to steatohepatitis and fibrosis. Patients with diabetes have a significantly higher risk of advanced disease stages. Atherogenic dyslipidemia exerts a similar effect: elevated levels of triglycerides, LDL, and ApoB, together with reduced HDL, create a favorable background for steatosis and accelerated fibrosis [17,31].

Arterial hypertension and the presence of multiple components of metabolic syndrome increase MASLD risk through endothelial dysfunction, activation of the renin–angiotensin–aldosterone system, and systemic inflammation [17]. Genetic predisposition, especially the PNPLA3 I148M

variant, is associated both with hepatic fat accumulation and with a higher risk of fibrosis progression. Other variants —TM6SF2, MBOAT7, and GCKR—also contribute to pathogenesis through mechanisms of lipid metabolism disruption and inflammation [2].

Ethnic characteristics influence disease risk as well. The highest MASLD prevalence is observed among Latin American and Middle Eastern populations, due to both genetic factors and dietary patterns and body fat distribution. In contrast, African Americans show lower prevalence, partly explained by a lower frequency of risk alleles [2,6].

Among demographic factors, age plays an important role: as age increases, the likelihood of MASLD rises, associated with sarcopenia, reduced mitochondrial activity, and low-grade chronic inflammation. There is also a marked gender difference: men are more commonly affected before menopause, whereas after menopause, prevalence among women rises. This is linked to the loss of the protective effect of estrogens, which normally inhibit lipogenesis and fibrogenesis [7,9]. Modifiable risk factors, especially lifestyle, are critical. Physical inactivity and a diet high in saturated fats, refined carbohydrates, and fructose increase insulin resistance, lipogenesis, and gut dysbiosis, accelerating disease progression. Regular aerobic and resistance physical activity, in contrast, is associated with reduced liver fat even in the absence of significant weight loss [14,16].

Additionally, comorbid conditions such as obstructive sleep apnea syndrome, hypothyroidism, hypogonadism, polycystic ovary syndrome, chronic kidney disease, and cardiovascular disease contribute to MASLD risk. Environmental factors —including exposure to endocrine disruptors (phthalates, BPA), air pollution, and social determinants of health—also play a role [14,21].

The main goal of MASLD therapy is the correction of metabolic disturbances and weight reduction. A weight loss of 7–10% through calorie- and fat-restricted diet and increased physical activity is the most effective non-pharmacological intervention. Such weight loss significantly reduces steatosis, inflammation, and may even lead to fibrosis regression [4,21]. A Mediterranean or hypocaloric diet with reduced refined carbohydrate intake, along with regular aerobic exercise (≥150 minutes per week), is recommended. In patients with obesity, bariatric surgery is indicated and often results in significant and sustained improvement in MASLD [4]. For many years, no approved pharmacological therapies existed for MASLD, but effective approaches have recently emerged. GLP-1 receptor agonists (e.g., liraglutide, semaglutide) and SGLT2 inhibitors (e.g., empagliflozin) have demonstrated significant reduction in hepatic steatosis and histological improvement in patients with MASLD and T2DM. Pioglitazone improves hepatic inflammation but may be associated with weight gain. In March 2024, the U.S. FDA approved Resmetirom, a selective thyroid hormone receptor-β agonist, as the first drug for the treatment of non-cirrhotic MASH with fibrosis [29]. Other promising agents in clinical development include FXR agonists, ACC inhibitors, FGF19 mimetics, and hepatoprotective agents such as celecoxan and essential phospholipids [4,20,32].

## Conclusions

MASLD represents a rapidly growing public health problem, closely linked to the epidemics of obesity and diabetes. Modern clinical practice requires a multidisciplinary approach: gastroenterologists, endocrinologists, cardiologists, and dietitians must collaborate on early detection, prevention, and treatment. In the coming years, new breakthroughs are expected in noninvasive diagnostics (advanced elastography, biomarkers) and therapeutic options (personalized pharmacotherapy). Emphasizing public health interventions and lifestyle promotion is critical to curbing the MASLD epidemic and its complications.

**Table 2**

| Risk factor | Mechanism of action | Clinical significance |
|---|---|---|
| Abdominal obesity | Increased lipolysis → ↑FFAs to liver, insulin resistance, lipotoxicity | The most significant modifiable risk factor |
| Type 2 diabetes and prediabetes | Hyperglycemia, hyperinsulinemia, lipogenesis, mitochondrial dysfunction | Increased risk of fibrosis and steatohepatitis |
| Dyslipidemia | ↑TG, ↑ApoB, ↓HDL, atherogenic state | Worsening of steatosis and cardiometabolic risk |
| Hypertension and metabolic syndrome | Endothelial dysfunction, inflammation | Higher likelihood of progression |
| Genetic factors | PNPLA3, TM6SF2, MBOAT7, GCKR — impaired lipid metabolism and inflammation | Higher fibrosis risk, especially with PNPLA3 I148M |
| Ethnic and demographic | Ethnic predisposition, age, hormonal status | Influence on prevalence and disease severity |
| Lifestyle | Physical inactivity, high-calorie diet | Worsening of metabolic disturbances |
| Comorbidities and environmental factors | OSA, endocrine disorders, CKD, pollution, stress | Additional acceleration of disease progression |

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