Review Article

Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD): Biochemical Pathways, Clinical Spectrum, and Biomarker Profiling: A Comprehensive Review

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Abstract

Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) is the most common chronic liver disease in the world. The nomenclature was changed lately to stress its strong metabolic basis. It has a high risk of morbidity in the liver and outside of it, and it is significantly linked to being overweight, having type 2 diabetic mellitus (T2DM), and having high cholesterol. This review attempts to provide a thorough rundown of MASLD, emphasizing biochemical pathways, clinical spectrum, and current and emerging biomarkers relevant for diagnosis and prognosis. There was a review of narrative literature undertaken using peer-reviewed articles indexed in Scopus and PubMed (2014–2024). Priority was given to Q1 journals and international consensus guidelines. MASLD pathogenesis is driven by insulin resistance, lipotoxicity, oxidative stress, and immunometabolic dysregulation. Genetic and epigenetic modifiers, alongside gut microbiota alterations, further modulate disease progression. Biochemical pathways involve impaired lipid metabolism, mitochondrial dysfunction, and fibrogenic signaling. Biomarker profiling, including cytokeratin-18, fibrosis panels (FIB-4, ELF), imaging modalities (FibroScan, MRI-PDFF), and emerging molecular biomarkers (microRNAs, metabolomics), has improved noninvasive diagnosis. The mainstay of treatment is still lifestyle change, although there is hope for pharmacological treatments such pioglitazone, GLP-1 receptor agonists, and experimental drugs including FXR agonists and FGF21 analogs. MASLD represents a multisystem disease with substantial health and economic burden. Advances in biomarker discovery and therapeutic strategies highlight the importance of integrating biochemical and molecular insights into clinical practice. Precision medicine strategies to enhance risk assessment and patient outcomes should be the main focus of future studies.

Keyword: Steatosis; Insulin Resistance; Biomarkers; Fibrosis; Noninvasive Diagnosis; MASLD

Introduction

The term non-alcoholic fatty liver disease (NAFLD) has been replaced with metabolic dysfunction–associated steatotic liver disease (MASLD), which more accurately describes the metabolic processes underpinning the disease spectrum, as a result of a worldwide multisociety Delphi consensus [1]. In contrast to the previous nomenclature, which focused on the lack of considerable alcohol consumption, MASLD focuses more attention on the role that metabolic dysregulation such as obesity, insulin resistance, dyslipidemia, and type 2 diabetes mellitus (T2DM) plays in the onset and course of the illness [2,3]. MASLD, which affects 25–30% of people, is rapidly rising to the top of the global chronic liver disease list. The prevalence is much higher in places where obesity and diabetes are more prevalent, such as the Middle East, North America, and portions of Asia [4–6]. Importantly, MASLD is not restricted to obese individuals. “Lean MASLD,” defined as hepatic

steatosis in individuals with normal body mass index but with visceral adiposity and insulin resistance, is increasingly recognized, particularly in Asian populations [6]. The clinical significance of MASLD extends beyond hepatic involvement. Despite the potential progression of the condition from simple steatosis to cirrhosis, advanced fibrosis, metabolic dysfunction-associated steatohepatitis (MASH), and hepatocellular carcinoma (HCC), cardiovascular disease (CVD) remains the predominant cause of mortality among affected individuals, followed by liver-related complications [7]. Moreover, MASLD has been independently associated with chronic kidney disease (CKD), endocrine disorders such as polycystic ovary syndrome (PCOS), and metabolic conditions including hypertension and atherosclerosis. This position MASLD as a systemic disorder with complex clinical trajectories rather than a disease confined to the liver [8]. From a socioeconomic perspective, MASLD imposes a substantial healthcare and financial burden worldwide. The economic costs of MASLD management including hospitalization, liver transplantation, and treatment of complications are comparable to or even exceed those of viral hepatitis [9]. In contrast to hepatitis B and C, where antiviral therapy has curative potential, MASLD currently lacks universally approved pharmacological therapies, underscoring the importance of early detection, lifestyle interventions, and the development of novel therapeutic agents [10].

At the pathophysiological level, MASLD is best explained by a "multiple-hit" hypothesis, whereby insulin resistance, lipotoxicity, oxidative and endoplasmic reticulum stress, and immuneinflammatory responses act synergis-tically to drive disease progression [11]. Genetic and epigenetic modifiers (e.g., PNPLA3, TM6SF2, and MBOAT7 variants, as well as microRNAs such as miR-21 and miR-34a) and gut microbiota alterations further influence individual susceptibility and clinical outcomes [12]. Given its high prevalence, multisystemic impact, and growing recognition as a public health challenge, MASLD is now positioned at the forefront of hepatology and metabolic medicine. This review provides an updated and comprehensive overview of MASLD, with a particular focus on biochemical pathways, clinical spectrum, biomarker profiling, and therapeutic strategies, while also highlighting current gaps and future directions for research [13].

Epidemiology and Clinical Burden

The primary chronic liver disease worldwide is metabolic dysfunction-associated steatotic liver disease, known as MASLD. According to recent meta-analyses, it affects between 25–30% of adults worldwide, with larger rates seen in areas like the Middle East, North America, and parts of Asia where the incidence of diabetes and obesity is on the rise [3,4]. Because MASLD and lifestyle-associated metabolic risk factors are closely connected, the incidence may be as high as 35–40% in several Middle Eastern and Asian nations [3]. Cirrhosis, severe fibrosis, hepatocellular carcinoma (HCC), metabolic dysfunction–associated steatohepatitis (MASH), and simple steatosis are only a few of the many clinical signs that may be present in the condition and may not change for years. It has been repeatedly shown that the fibrosis stage is the most reliable indicator of liver-related morbidity and death among them [14]. Importantly, MASLD has effects beyond the liver. It is becoming recognized as a systemic metabolic disorder with substantial extrahepatic effects. Cardiovascular disease (CVD) is the leading cause of death for those with MASLD, followed by liver-related disorders such cirrhosis

and HCC [7]. Moreover, MASLD raises the risk of colorectal cancer, endocrine conditions such hypothyroidism and polycystic ovary syndrome (PCOS), and chronic kidney disease (CKD) on its own [15]. These correlations emphasize the need of treating diseases using a multidisciplinary approach [16]. The economic burden of MASLD is considerable. In high-income countries, the **annual direct healthcare costs** including hospitalization, long-term management, and liver transplantation—amount to billions of dollars [17]. Notably, the cost of managing MASLD and its complications now rivals or exceeds that of viral hepatitis; yet effective pharmacological therapies remain unavailable [18].

Pathogenesis

The "multiple-hit" theory, which postulates that metabolic, genetic, and environmental insults work in concert to cause hepatic damage and fibrosis, provides the best explanation for the complex etiology of metabolically associated steatotic liver disease (MASLD) [19,20].

Insulin Resistance and Lipid Metabolism

Insulin resistance is a primary contributor of MASLD. Enhanced lipolysis of adipose tissue results in higher levels of circulating free fatty acids (FFAs), which are transported to the liver in surplus. Hepatic uptake surpasses disposal capacity, resulting in **triglyceride accumulation (steatosis)**. Insulin resistance makes lipid excess worse, and at the same time, it enhances hepatic de novo lipogenesis (DNL) via sterol regulatory element–binding protein-1c (SREBP-1c) and carbohydrate-responsive element–binding protein (ChREBP) [21,22].

Lipotoxicity and Cellular Injury

Lipid species may sometimes be non-inert. Ceramides, diacylglycerols, and free cholesterol are examples of hazardous lipid intermediates that build up and cause endoplasmic reticulum (ER) stress, reactive oxygen species (ROS), and mitochondrial malfunction. These assaults also produce damage-associated molecular patterns (DAMPs), which activate Kupffer cells and draw inflammatory cells, in addition to inducing hepatocyte necrosis and death [23,24].

Oxidative Stress and Inflammation

Lipid peroxidation, protein alteration, and DNA damage result from an excess of ROS that overwhelms antioxidant defenses. Additionally, ROS trigger the NLRP3 inflammasome, which increases the release of proinflammatory cytokines including IL-18 and interleukin-1β (IL-1β), intensifying hepatic inflammation [25].

Fibrogenesis

The development of myofibroblast-like cells from hepatic stellate cells (HSCs) is promoted by chronic inflammation and hepatocyte injury. Type I and type III collagen are the main extracellular matrix proteins secreted by these, which results in fibrosis. PDGF, TGF-β, and CTGF are all crucial mediators [26]. Progressive extracellular matrix deposition ultimately distorts hepatic architecture, leading to cirrhosis [27].

Genetic and Epigenetic Modifiers

Numerous genetic variations affect MASLD vulnerability and the course of the illness. Steatosis, inflammation, and fibrosis are significantly linked to polymorphisms in PNPLA3 (I148M), TM6SF2 (E167K), and MBOAT7 [9]. Further controlling lipid metabolism and fibrogenic pathways are epigenetic processes, which include DNA methylation, histone changes, and microRNAs (e.g., miR-21, miR-34a) [28].

Gut–Liver Axis

Lipopolysaccharide (LPS) and other bacterial products may move into portal circulation due to

changes in the makeup of the gut microbiota and increased intestinal permeability. These worsen fibrosis and inflammation by stimulating hepatic immune cells. In MASLD, the gut-liver axis is becoming more widely acknowledged as a pathogenic component as well as a potential treatment target [29].

Additional Metabolic and Hormonal Factors

Adipokine imbalance (↓adiponectin, ↑leptin), altered bile acid signaling, and disrupted mitochondrial function contribute to disease progression. These systemic factors interlink metabolic dysfunction with hepatic and extrahepatic complications [30]. In patients with MASLD possessing a substantial hepatic hereditary component, hepatic lipid content is heightened, although insulin resistance, obesity, and the risk of type 2 diabetes are not enhanced. The extent of obesity correlates with the risk of cardiovascular disease [31]. Patients with MASLD with a substantial hepatic genetic component have a moderately to considerably increased risk of MASH and fibrosis. Patients with MASLD often exhibit heightened insulin resistance and adiposity, pronounced dyslipidemia, hyperglycemia, and an augmented risk of cardiovascular disease, all of which are closely associated with hepatic de novo lipogenesis driven by factors such as excessive glucose consumption, diabetes-related hyperinsulinemia, and hyperglycemia [32]. In patients with MASLD, insulin resistance, type 2 diabetes, and cardiovascular disease are significantly more common, especially when there is a prominent metabolic component linked to adipose tissue dysfunction (e.g., lipodystrophy, increased visceral fat, decreased gluteofemoral fat, insulin-resistant adipose tissue, increased lipolysis, inflammation, and dysregulated adipokines), despite also demonstrating low adiposity and moderate dyslipidemia. MASH and fibrosis are much more probable in both MASLD phenotypes characterized by a substantial metabolic component. MASH stands for steatohepatitis linked to metabolic dysfunction. MASLD stands for steatotic liver disease linked to metabolic dysfunction. A decline of modest magnitude is denoted by ↓. ↑↑ = significant rise. ↑↑↑=extremely high rise in disease risk or prevalence. -= no change in disease risk or prevalence Figure 1 illustrates how variation in PNPLA3 and TM6SF2 is linked to a lower risk of cardiovascular disease [33].

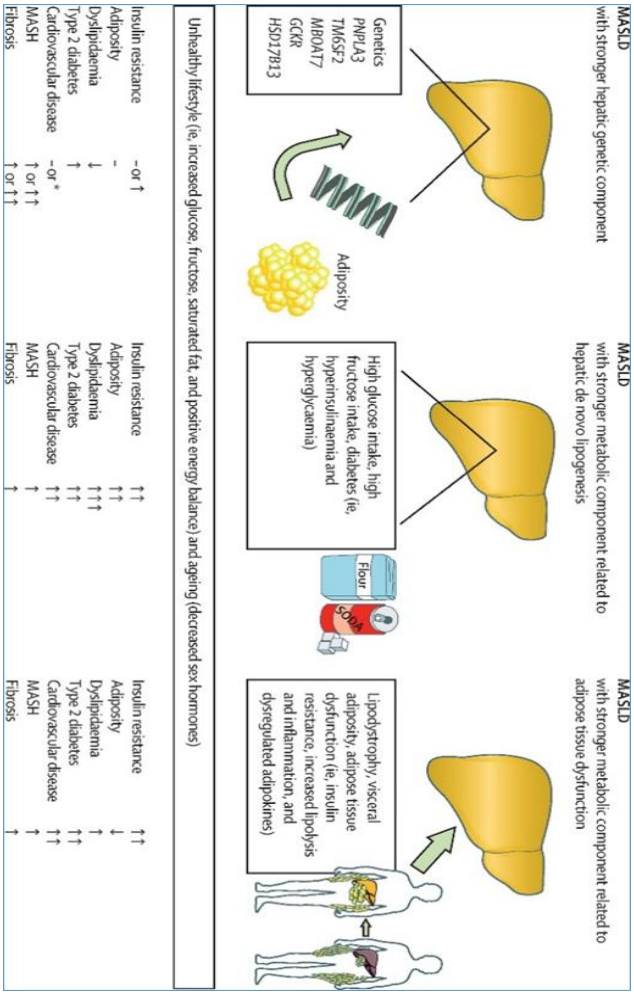

Figure 1: Key mechanisms that cause MASLD and how they relate to fibrosis, insulin resistance, obesity, dyslipidemia, type 2 diabetes, cardiovascular disease, and MASH.

Biochemical Pathways

The main reason for MASLD is an imbalance between how the body takes in and gets rid of lipids which is essentially a failure of hepatic lipid homeostasis. The onset and course of illness are driven by a number of interrelated metabolic processes [22].

Hepatic Lipid Uptake and De Novo Lipogenesis

Hepatocytes absorb additional circulating free fatty acids (FFAs), which are mostly generated by adipose tissue lipolysis, with the aid of transport proteins including CD36 and fatty acid transport proteins (FATPs). The liver's production of triglycerides is significantly impacted by the process of de novo lipogenesis (DNL), which is the conversion of carbohydrates into fatty acids. Transcription factors that control de novo lipogenesis (DNL), such as sterol regulatory element-binding protein-1c (SREBP-1c) and carbohydrate response element-binding protein (ChREBP), are elevated in hyperinsulinemia and excessive carbohydrate consumption [22].

Fatty Acid Oxidation and Mitochondrial Dysfunction

To produce energy, FFAs typically proceed via β-oxidation in mitochondria and peroxisomes. Lipid buildup is encouraged by mitochondrial failure in MASLD, which lowers β-oxidation capability. Oxidative stress is exacerbated by impaired mitochondrial activity, which also increases the generation of reactive oxygen species (ROS) [34].

Triglyceride Assembly and Export

FFAs are converted by hepatocytes into triglycerides, which are then exported as VLDL (very-low-density lipoproteins). Intracellular lipid retention results from VLDL production being disrupted in MASLD by ER stress, genetic variations (such as TM6SF2), and decreased microsomal triglyceride transfer protein (MTTP) function [34].

Lipotoxicity and Cellular Stress Pathways

Protein kinase C (PKC) isoforms are activated by the buildup of lipotoxic intermediates (ceramides, diacylglycerols, and free cholesterol), which disrupts insulin signaling and triggers inflammatory cascades. By activating the PERK, IRE1, and ATF6 pathways, lipid excess also causes endoplasmic reticulum (ER) stress and an unfolded protein response (UPR), which, if left unchecked, results in hepatocyte death [35].

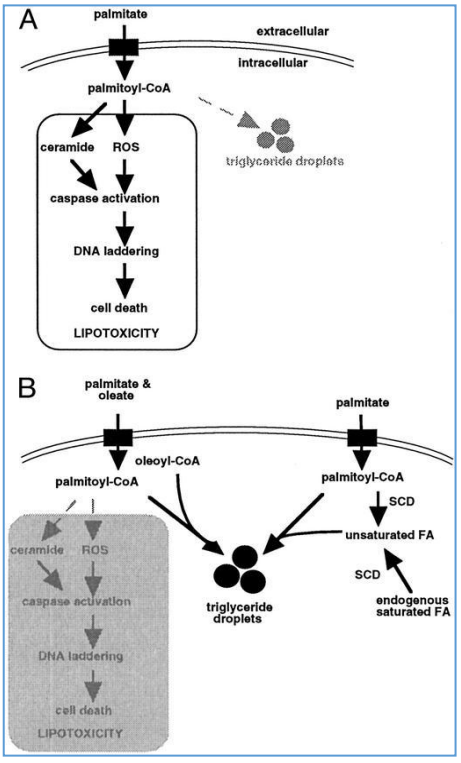

Figure 2: Lipotoxicity prevention mechanism via triglyceride storage.

Triglyceride storage is a mechanism that prevents lipotoxicity... (A) CHO cells undergo apoptosis when exposed to long-chain saturated

FA palmitate via a process that involves the production of ceramide and reactive intermediates (ROS). When no other signals are present, palmitate is not well integrated into the cellular triglyceride pools. (B) palmitate is channeled toward triglyceride storage when unsaturated FAs are present, which keeps palmitate out of the pathways that cause cell death. This is the outcome of unsaturated FAs produced by cellular desaturase enzymes (e.g., SCD) or supplied as media supplements (e.g., cosupplementation with oleate) [36].

Inflammatory and Fibrogenic Signaling

Damage to cells activates Kupffer cells, which attract circulating immune cells. Tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are among the cytokines that these cells subsequently generate. The NLRP3 inflammasome boosts inflammation by promoting the maturation of IL-1β and IL-18. Transforming growth factor-β (TGF-β) and other profibrotic mediators induce chronic injury to activate hepatic stellate cells (HSCs), which produce extracellular matrix proteins and lead to progressive fibrosis [25,26].

Hormonal and Metabolic Crosstalk

MASLD development is modulated by adipokines and hepatokines. Adiponectin has anti-inflammatory and fatty acid oxidation-enhancing properties, however its levels are decreased in MASLD. Leptin, on the other hand, promotes fibrogenesis and inflammation. Because fibroblast growth factors (FGF19, FGF21) control lipid homeostasis and bile acid metabolism, their dysregulation leads to steatosis and the development of steatohepatitis [37]. In summary, MASLD reflects the convergence of impaired lipid metabolism, mitochondrial dysfunction, ER stress, inflammation, and fibrogenesis. Understanding these biochemical pathways provides a framework for biomarker discovery and therapeutic interventions [38].

Clinical Presentation

In its first phases, MASLD often presents asymptomatically and is incidentally identified during regular imaging or laboratory evaluations for unrelated ailments, particularly in individuals with dyslipidemia, obesity, or type 2 diabetic mellitus (T2DM). Subtle clinical symptoms may appear as the illness advances toward fibrosis or metabolic dysfunction–associated steatohepatitis (MASH) [39].

Common Symptoms

- **Fatigue**: The most frequently reported symptom, often chronic and disproportionate to physical activity.
- **Malaise and decreased energy**: Non-specific complaints that may precede biochemical abnormalities.
- **Right upper quadrant discomfort**: Usually a dull ache related to hepatomegaly or capsular stretching.
- **Bloating or early satiety**: Occasionally reported due to hepatomegaly compressing adjacent structures [40].

Physical Examination Findings

Clinical signs are typically absent in early MASLD but may appear with disease progression:

- **Hepatomegaly**: Smooth, non-tender enlargement in up to 25–50% of patients.
- **Central obesity**: Frequently associated with metabolic syndrome.
- **Acanthosis nigricans**: Common in insulin-resistant individuals, especially children and adolescents.

- **Stigmata of chronic liver disease**: Spider nevi, palmar erythema, and gynecomastia may develop in advanced fibrosis or cirrhosis.
- **Signs of portal hypertension**: Splenomegaly, ascites, and caput medusae indicate progression to cirrhosis [3].

Laboratory Findings

Biochemical abnormalities are usually mild and non-specific:

- **Alanine aminotransferase (ALT) and aspartate aminotransferase (AST):** Mild to moderate elevations (< 4× upper limit of normal), with ALT > AST in early disease. In advanced fibrosis, the ratio reverses (AST > ALT).
- **Elevated γ-glutamyl transferase (GGT):** Reflects hepatocellular stress.
- **Hyperferritinemia:** May reflect hepatic inflammation and insulin resistance, but iron overload must be excluded.
- **Thrombocytopenia and hypoalbuminemia:** Suggest advanced fibrosis or cirrhosis [41].

Spectrum of Disease in Clinical Practice

- **Simple steatosis (non-progressive):** Hepatic fat accumulation without inflammation or fibrosis.
- **MASH:** Lobular inflammation, hepatocyte ballooning, and variable fibrosis.
- **Advanced fibrosis or cirrhosis:** Can present with decompensated features such as ascites, variceal bleeding, or hepatic encephalopathy.
- **Hepatocellular carcinoma (HCC):** May occur even in non-cirrhotic MASLD, especially in patients with long-standing disease [42].

Extrahepatic Manifestations

MASLD is increasingly recognized as a **multisystem disorder**, with several extrahepatic associations:

- **Cardiovascular disease (CVD):** The leading cause of mortality in MASLD patients [7].
- **Chronic kidney disease (CKD):** Risk increases with MASLD severity.
- **Endocrine disorders:** Polycystic ovary syndrome (PCOS), hypothyroidism, and obstructive sleep apnea (OSA).
- **Musculoskeletal complications:** Sarcopenia and osteoporosis, largely due to chronic inflammation and hormonal dysregulation [43].

Pediatric Considerations

In children and adolescents, MASLD presentation differs from adults:

- Often discovered via **asymptomatic elevation of liver enzymes** during routine screening.
- Strongly associated with **obesity and insulin resistance**.
- Histologically, children more often show **portal inflammation**, in contrast to lobular inflammation in adults [44].

Biomarker Profiling

Liver biopsy is now regarded as the definitive standard for diagnosing and staging MASLD, which is invasive, expensive, and subject to sample variability. As a result, noninvasive biomarkers have become more important in clinical practice and research, providing useful instruments for risk assessment, diagnosis, and therapy response monitoring [45].

Routine Biochemical Markers

- **Alanine aminotransferase (ALT)** and **aspartate aminotransferase (AST):** often raised yet insensitive and unspecific.
- **Gamma-glutamyl transferase (GGT):** May indicate hepatocellular stress but is not MASLD-specific [39].

Cell Death Markers

- **Cytokeratin-18 (CK-18) fragments (M30, M65):** Reflect hepatocyte apoptosis and necrosis. Elevated levels help differentiate **simple steatosis from MASH** [46].

Fibrosis Assessment Panels

- **FIB-4 Index:** Incorporates age, AST, ALT, and platelet count; widely validated for fibrosis staging.
- **NAFLD Fibrosis Score (NFS):** Combines age, BMI, glucose status, liver enzymes, platelet count, and albumin.
- **Enhanced Liver Fibrosis (ELF) test:** Assesses procollagen type III N-terminal peptide (PIIINP), hyaluronic acid, and tissue inhibitor of metalloproteinase-1 (TIMP-1); helpful in identifying advanced fibrosis [47].

Imaging Biomarkers

- Transient Elastography (FibroScan): Offers controlled attenuation parameter (CAP) for steatosis and liver stiffness evaluation (fibrosis).
- Hepatic fat content is accurately measured by the Magnesium Resonance Imaging–Proton Density Fat Fraction (MRI-PDFF).
- Magnetic Resonance Elastography (MRE): Provides better precision for advanced fibrosis, although its affordability and accessibility are limited [48].

Emerging Molecular Biomarkers

- **MicroRNAs (miRNAs):** miR-21, miR-34a, and miR-122 are strongly associated with steatohepatitis and fibrosis progression.
- **Metabolomics and lipidomics:** Provide insights into altered metabolic pathways.
- **Circulating cell-free DNA (cfDNA) methylation patterns:** Promising tools for noninvasive molecular diagnosis [11].

Table 1: Key Biochemical and Imaging Biomarkers in MASLD

Biomarker Type	Examples	Clinical Utility	Ref
Routine enzymes	ALT, AST, GGT	Initial screening; limited specificity	[2]
Cell death markers	CK-18 fragments	Differentiate steatosis vs. MASH	[3]
Fibrosis panels	FIB-4, NFS	Noninvasive fibrosis staging	[4]
Serum fibrosis markers	ELF test (HA, TIMP-1, PIIINP)	Advanced fibrosis detection	[4]
Imaging	FibroScan, MRI-PDFF, MRE	Liver stiffness & fat quantification	[5]
Molecular biomarkers	miR-21, miR-34a, cfDNA methylation	Predict disease progression	[6]

Table 2: Diagnostic Performance of Selected Biomarkers

Biomarker / Panel	Target	Sensitivity (%)	Specificity (%)	Notes	Ref
CK-18 (M30)	NASH	78	87	Reflects apoptosis	[3]
FIB-4	Fibrosis ≥F3	70	75	Age-adjusted cut-offs recommended	[4]
NFS	Fibrosis ≥F3	72	74	Uses clinical & lab parameters	[4]
ELF test	Fibrosis ≥F3	80	90	Combines ECM turnover markers	[4]
MRI-PDFF	Steatosis ≥5%	92	95	Highly accurate for fat quantification	[5]
FibroScan	Fibrosis ≥F3	85	88	Limited in obesity, operator-dependent	[5]

Management

The majority of therapy for MASLD is still lifestyle change since there are presently no well recognized medicinal therapies for the condition. The goals of the treatment plan are to lower body weight, improve insulin sensitivity, lessen hepatic inflammation, and halt the progression of fibrosis [39].

Lifestyle Modification

- **Weight loss:** A reduction of ≥7–10% of body weight significantly improves steatosis, necroinflammation, and even fibrosis [49].
- **Dietary interventions:** Hypocaloric diets, particularly those reducing refined carbohydrates and saturated fats, are effective. The Mediterranean diet has shown benefits in reducing hepatic fat [49].
- **Physical activity:** Both aerobic and resistance training improve hepatic steatosis and insulin sensitivity, independent of weight loss [50].

Pharmacological Therapies

Although no drugs are yet approved specifically for MASLD, several agents are used off-label or under investigation:

- **Pioglitazone (PPAR-γ agonist):** Improves histological features of NASH, particularly in patients with T2DM [51].
- **GLP-1 receptor agonists (e.g., liraglutide, semaglutide):** Promote weight loss, improve insulin sensitivity, and reduce hepatic fat. Clinical trials suggest potential benefits in biopsy-proven NASH [52].
- **Vitamin E (α-tocopherol):** Demonstrates histological improvement in non-diabetic patients with NASH by reducing oxidative stress [53].
- **Other insulin sensitizers:** Metformin has not shown consistent histological benefit, and is not recommended solely for MASLD [54].

Emerging Investigational Therapies

Multiple novel agents are in advanced clinical trials:

- **FXR agonists (e.g., obeticholic acid):** Improve fibrosis and bile acid signaling but may cause pruritus and dyslipidemia [55].
- **FGF21 analogs and FGF19 mimetics:** Regulate lipid and glucose metabolism, showing promise in reducing steatosis.
- **Thyroid hormone receptor-β agonists (e.g., resmetirom):** Enhance hepatic fat oxidation and reduce steatosis [56].
- **Anti-inflammatory and anti-fibrotic agents:** Target specific pathways including CCR2/CCR5 antagonists and caspase inhibitors [57].

Bariatric and Endoscopic Interventions

- **Bariatric surgery:** shows a significant reduction in fibrosis, inflammation, and steatosis in obese individuals, with long-lasting advantages [58].
- **Endoscopic bariatric therapies (EBTs):** Minimally invasive interventions such as intragastric balloons are under evaluation for MASLD management.

Table 3: Lifestyle and Pharmacological Therapies in MASLD

Therapy	Mechanism of Action	Target Population	Evidence Level	Ref
Weight loss (≥7–10%)	Caloric restriction, fat reduction	All MASLD patients	Strong	[2]

Mediterranean diet	Improves insulin sensitivity, reduces hepatic fat	MASLD with obesity/T2DM	Strong	[3]
Pioglitazone	PPAR-γ agonist; ↑ insulin sensitivity	NASH with T2DM	Moderate	[4]
GLP-1 agonists (liraglutide, semaglutide)	↓ weight, ↓ liver fat, ↑ insulin sensitivity	Obese/T2DM with NASH	Moderate-High	[5]
Vitamin E	Antioxidant, ↓ oxidative Stress	Non-diabetic NASH	Moderate	[6]

Table 4: Emerging Therapies under Investigation

Drug Class	Examples	Mechanism	Clinical Status	Ref
FXR agonists	Obeticholic acid	Modulates bile acid and fibrosis pathways	Phase 3 trials	[8]
FGF analogs	Pegbelfermin (FGF21)	Improves lipid /glucose Metabolism	Phase 2–3	[9]
THR-β agonists	Resmetirom	↑ hepatic fat oxidation	Phase 3	[9]
CCR2/CCR5 antagonists	Cenicriviroc	Anti-inflammatory, anti-fibrotic	Phase 2	[10]

Prognosis and Outcomes

Stable non-progressive steatosis, cirrhosis, severe fibrosis, and HCC are among the diseases that may result from MASLD. The best predictor of liver-related morbidity and death has been repeatedly shown to be the stage of fibrosis [14].

Natural History

- **Simple steatosis** is often regarded as benign in many individuals, although some develop fibrosis-associated metabolic dysfunction-associated steatohepatitis (MASH). [59].
- **Fibrosis progression** occurs at an average rate of one stage every 7 years in simple steatosis and every 2–3 years in MASH [60].
- **Cirrhosis and HCC**: MASLD is now one of the leading causes of cryptogenic cirrhosis and is an increasingly important etiology of HCC, even in patients without cirrhosis [61].

Predictors of Adverse Outcomes

- **Histological severity:** Fibrosis stage is the most robust predictor of mortality, independent of other histological features [14].
- **Metabolic comorbidities:** Coexisting T2DM, obesity, hypertension, and dyslipidemia accelerate disease progression and increase both hepatic and extrahepatic mortality [16].
- **Genetic variants:** Carriers of *PNPLA3* I148M and *TM6SF2* variants have a higher risk of progressive fibrosis and HCC [62].

Extrahepatic Outcomes

MASLD is not confined to the liver. The **leading cause of mortality** in MASLD patients is **cardiovascular disease (CVD)**, followed by liver-related complications [7]. Other systemic associations include:

- **Chronic kidney disease (CKD):** MASLD is an independent risk factor for CKD incidence and progression [63].
- **Malignancy:** Increased risk of colorectal cancer and other gastrointestinal malignancies has been reported [64].
- **Endocrine and metabolic complications:** Higher prevalence of PCOS, hypothyroidism, and obstructive sleep apnea [65].

Long-Term Outcomes

Individuals who have cirrhosis or severe fibrosis are more likely to:

- **Liver-related decompensation:** Ascites, variceal bleeding, hepatic encephalopathy.
- **Hepatocellular carcinoma (HCC):** MASLD-related HCC is increasingly recognized as a major global burden, often presenting at later stages due to lack of surveillance [61].
- **Liver transplantation:** MASLD is now among the leading indications for liver transplantation in Western countries [66].

Future Directions

MASLD is becoming more and more common, which highlights the urgent need for innovative preventative, treatment, and diagnostic approaches. The creation of disease-modifying medications, the integration of multi-omics technology, and precision medicine methodologies are the main areas of future study.

Noninvasive Diagnostics and Biomarker Discovery

Although current biomarkers and imaging tools improve risk stratification, their diagnostic accuracy is still suboptimal.

- **Multi-omics approaches** (genomics, transcriptomics, metabolomics, lipidomics) are expected to provide a deeper understanding of disease heterogeneity and progression [67].
- **Circulating microRNAs, extracellular vesicles, and cfDNA methylation** represent promising next-generation biomarkers with potential for early detection and personalized monitoring [68].
- Integration of **artificial intelligence (AI) and machine learning (ML)** with imaging and biomarker data may enhance predictive accuracy for fibrosis and clinical outcomes [69].

Novel Therapeutic Strategies

- **Targeted antifibrotic therapies:** new molecules modulating TGF-β, galectin-3, and LOXL2 pathways are under development.
- **Combination therapies:** Given the multifactorial pathogenesis of MASLD, combining agents (e.g., GLP-1 receptor agonists + FXR agonists) may provide synergistic benefits [70].
- **Gut microbiome modulation:** Probiotics, prebiotics, and fecal microbiota transplantation (FMT) are being explored for their role in altering gut-liver axis signaling [71].
- **Gene-based therapies:** CRISPR and RNA-based therapeutics targeting genetic risk factors (e.g., *PNPLA3* I148M variant) are in early investigation [72].

Preventive Strategies

- **Public health interventions** addressing obesity, sedentary behavior, and unhealthy diets remain fundamental to reducing MASLD incidence.
- **Screening in high-risk populations** (e.g., T2DM, metabolic syndrome) should be optimized to allow early intervention [73].
- **Precision nutrition** based on genetic and metabolic profiles is expected to tailor dietary strategies for individualized prevention [74].

Clinical Trials and Global Collaboration

- Ongoing **Phase 3 clinical trials** of agents such as obeticholic acid, resmetirom, and GLP-1 receptor agonists will likely define the first wave of approved treatments.
- Establishment of **international registries and consortia** will facilitate data sharing, accelerate biomarker validation, and harmonize clinical trial endpoints [75].

Conclusion

MASLD is a rapidly evolving global health challenge with complex pathogenesis and significant hepatic and extrahepatic implications. Early detection using novel biomarkers, lifestyle interventions, and the advent of emerging therapies are critical to improving patient outcomes. The integration of omics-based diagnostics, artificial intelligence, and precision medicine will likely shape the future of MASLD management.

Conflict of interest

None

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