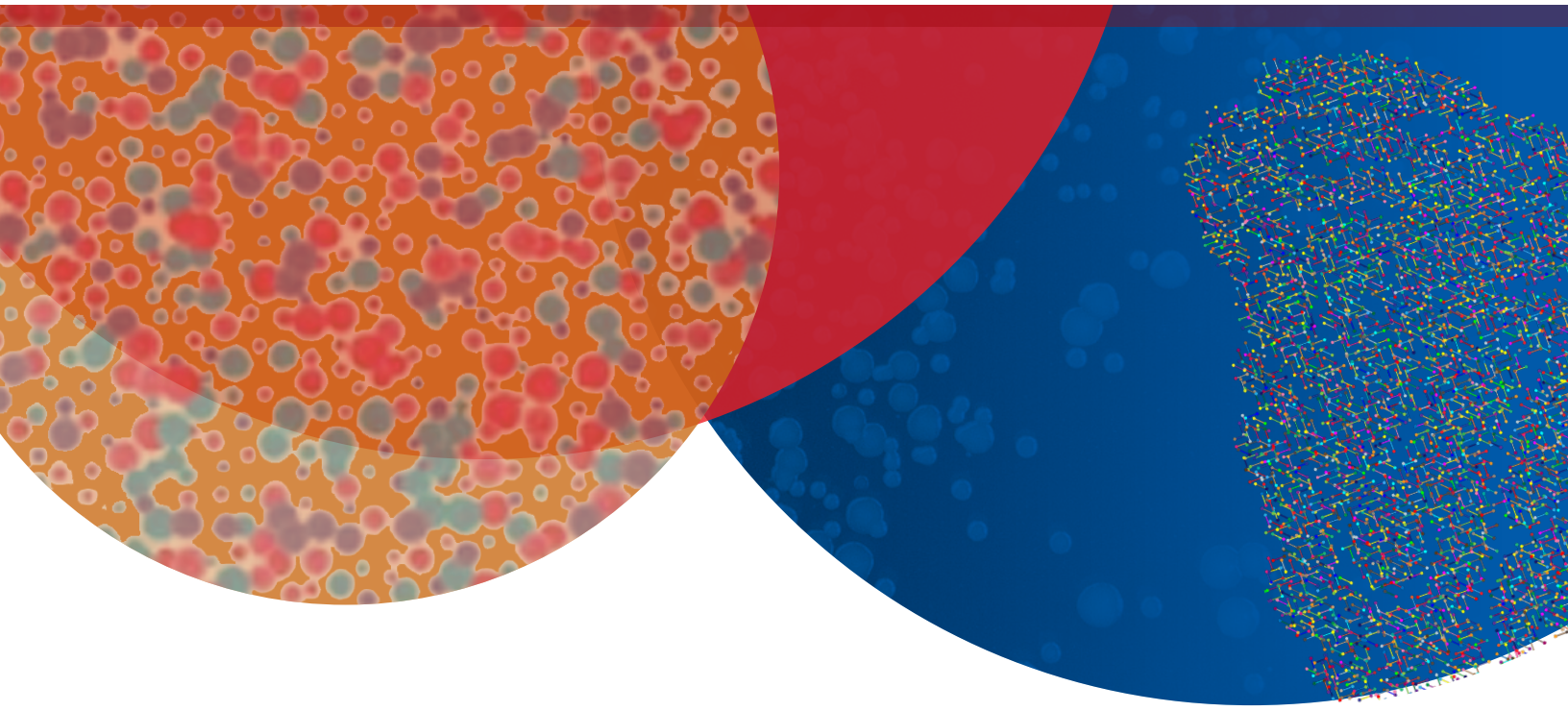
International Journal of

ATHEROGENIC DIABETIC DYSLIPIDEMIA



THIS ISSUE

Editor-in-Chief
Dr. Prof. Subhankar Chowdhury

VOLUME 6
ISSUE 2

Salubris

International Journal of

ATHEROGENIC DIABETIC DYSLIPIDEMIA

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International Journal of ATHEROGENIC DIABETIC DYSLIPIDEMIA

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About the Journal

Atherogenic dyslipidemia, characterized by elevated triglycerides (TGs), raised small dense LDL (low-density lipoprotein) levels and decreased HDL (high-density lipoprotein) cholesterol levels, is the most common pattern of dyslipidemia in type 2 diabetic patients. It is characteristically seen in patients with obesity, metabolic syndrome, insulin resistance, and T2DM and has emerged as an essential marker for the increased CVD risk observed in these populations. In fact, the combined presence of dyslipidemia and diabetes escalates the CV risk by 3–4 times.

Dyslipidemia, diabetes and hypertension are all a part of the cluster that includes nonalcoholic fatty liver disease (NAFLD) too, another major CVD risk factor. As diabetic dyslipidemia is characterized by hypertriglyceridemia, the risk of pancreatitis is also high in these patients.

With the increasing burden of these conditions in the world, clinicians can struggle to keep themselves updated in the advances in research and therapy.

With this journal, we aim to keep doctors updated in the current understanding, trends in therapy and new modalities of care. Our objective is:

- To be the knowledge partner for healthcare professionals by presenting contemporary research and novel treatment options in the field of atherogenic diabetic dyslipidemia.
- To raise awareness about the latest clinical practices, for better management of the condition, thus improving on the standards of overall disease management
- To provide researchers of the field with a medium to elicit like thought processes in their peers working on similar innovations or experiments
- To provide clinicians with a platform to showcase their case studies

International Journal of Atherogenic Diabetic Dyslipidemia will contain literature encompassing all the scientific and clinical aspects that address the cause and management of atherogenic dyslipidemia. The content of the journal shall include, but not limited to subject areas like atherogenic dyslipidemia, obesity, NAFLD, acute pancreatitis, hypertriglyceridemia, pharmacological management/therapeutic options for atherogenic dyslipidemia in type 2 diabetes and new strategies for management.

We hope to provide a platform to publish interesting and informative articles on topics connected with the management of atherogenic diabetic dyslipidemia as well as encourage correspondence and participation from our readers.

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Review

Diabetes and MASLD: An Updated Narrative Review of Emerging Therapeutic Approaches

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Abstract

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed NAFLD, is a leading cause of chronic liver disease and is closely linked with Type 2 Diabetes Mellitus (T2DM). Both conditions share a bidirectional relationship, driven by insulin resistance, lipotoxicity, and systemic inflammation, which accelerates hepatic fibrosis and worsens glycaemic control. Individuals with T2DM are at higher risk of developing MASH, advanced fibrosis, and hepatocellular carcinoma, while MASLD increases the likelihood of incident diabetes. Globally, the prevalence of MASLD and T2DM is rising rapidly, highlighting a growing public health challenge. Lifestyle modification remains central to management, but pharmacologic agents such as GLP-1 receptor agonists, SGLT2 inhibitors, and PPAR agonists are increasingly used to target shared metabolic pathways. These advances underscore the need for integrated, mechanism-based strategies to improve outcomes in patients with coexisting MASLD and T2DM.

Materials and Method: This narrative review synthesizes current evidence on MASLD and T2DM, covering pathophysiology, screening, and management. A targeted literature search of PubMed, Scopus, and Google Scholar up to August 2025 was conducted, including clinical studies, trials, and guidelines, with data qualitatively summarized.

Conclusion: MASLD and T2DM frequently coexist, sharing mechanisms that worsen hepatic and systemic complications. Early detection, risk stratification, and integrated management, including lifestyle interventions and emerging pharmacologic therapies, are key to improving outcomes and preventing disease progression.

Keywords: MASLD, T2DM, insulin resistance, fibrosis assessment, lifestyle and pharmacologic interventions

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), is increasingly recognized as the hepatic manifestation of systemic metabolic dysfunction and has emerged as one of the most prevalent causes of chronic liver disease worldwide. Its strong bidirectional relationship with T2DM underscores the need for integrated management strategies. Individuals with T2DM not only exhibit a higher prevalence of MASLD but are also more likely to develop its aggressive form, metabolic dysfunction-associated steatohepatitis (MASH), advanced fibrosis, and hepatocellular carcinoma (HCC).[1-3]

The pathophysiological interplay between MASLD and T2DM is mediated by insulin resistance, systemic inflammation, and lipotoxicity, creating a self-perpetuating cycle of metabolic dysfunction. T2DM accelerates hepatic fibrogenesis, while MASLD increases the risk of incident diabetes. Meta-analyses estimate that nearly two-thirds of individuals with T2DM have MASLD, with 31.6% progressing to MASH and up to 15% developing advanced fibrosis.[3,4] This coexistence also amplifies extra-hepatic complications, including cardiovascular disease, chronic kidney disease, and certain malignancies.[3]

The global epidemiological burden of both conditions continues to rise. Diabetes affects over 537 million adults worldwide, with projections reaching 783 million by 2045,[4] while MASLD currently affects more than 35% of the population

and is anticipated to increase to 55% by 2040.[4] Contributing factors include urbanization, sedentary lifestyles, dietary changes, and regional genetic predispositions. Prevalence estimates in India vary widely, ranging from 9% to 53%, depending on socioeconomic and geographic factors.[5]

Despite the magnitude of this dual epidemic, therapeutic options remain limited. Diabetes management primarily focuses on glycaemic control, whereas MASLD has few approved pharmacological interventions. Lifestyle modification remains the cornerstone of treatment for both conditions. The overlapping pathophysiology, however, has spurred interest in agents that target shared metabolic pathways. Drugs such as GLP-1 receptor agonists and SGLT2 inhibitors, initially developed for T2DM, are under investigation for their potential benefits in MASLD through improved insulin sensitivity, reduced hepatic steatosis, and mitigation of cardiovascular risk.[4]

Consensus on terminology and diagnostic criteria is also evolving. The adoption of MASLD over NAFLD emphasizes a non-stigmatizing, pathophysiology-based framework that incorporates metabolic risk factors, allowing for more accurate prevalence estimates and improved patient stratification. Evidence-based reviews are critical to refine diagnostic tools, validate non-invasive assessments, and clarify the influence of lifestyle and cardiometabolic factors on disease progression.[4]

Finally, the concept of T2DM remission defined as a sustained return to near-normal glycemia illustrates the potential for altering disease trajectory through intensive interventions such as weight loss and metabolic surgery.[6] In MASLD, similar advances in risk stratification and the development of dual-purpose therapeutic agents may shift management paradigms from mere control toward remission and prevention.

In summary, the intertwined epidemics of MASLD and T2DM represent both a clinical challenge and an opportunity for innovation. Early detection, multidisciplinary care, and emerging therapeutics that address shared pathophysiological mechanisms are essential to reducing liver-related and cardiometabolic complications.[1-6]

Given the rising prevalence of MASLD in patients with T2DM, the evolving understanding of disease mechanisms, and the rapid expansion of pharmacological and lifestyle-based interventions, there is a critical need to consolidate current evidence. This review aims to provide a comprehensive overview of contemporary management strategies, highlight emerging therapeutic approaches, and offer guidance on optimizing care for patients with MASLD and coexisting diabetes.

Materials and Methods

This narrative review summarizes current evidence on MASLD and T2DM, including pathophysiology, screening, and management strategies. A literature search was conducted in PubMed, Scopus, and Google Scholar using terms such as “MASLD,” “NAFLD,” “T2DM,” “insulin resistance,” “fibrosis,” and “GLP-1 receptor agonists.” Studies in adults reporting pathophysiological mechanisms, diagnostic tools, pharmacologic or lifestyle interventions, and clinical outcomes were included. Data from randomized trials, cohort studies, case series, real-world evidence, and clinical guidelines were extracted and synthesized qualitatively to provide an integrated overview of current knowledge and therapeutic approaches.

Discussion

Pathophysiological Link between T2DM and MASLD

Type 2 Diabetes Mellitus (T2DM), driven by insulin resistance and chronic hyperglycaemia, is a growing global health challenge. A frequent and clinically significant comorbidity is metabolic dysfunction-associated steatotic liver disease (MASLD), considered the hepatic manifestation of metabolic syndrome. Both conditions commonly coexist: most individuals with T2DM develop MASLD, while those with MASLD are at increased risk for T2DM onset. This bidirectional relationship is mediated by overlapping mechanisms, including lipotoxicity, systemic inflammation, and disrupted insulin signaling.[4]

Insulin Resistance as the Central Mechanism

Insulin resistance (IR) is the hallmark of both T2DM and MASLD. In the liver, impaired insulin receptor signalling through the IRS/PI3K/Akt pathway leads to reduced glycogen synthesis and increased gluconeogenesis, perpetuating hyperglycemia. In T2DM, poor glycaemic control (e.g., HbA1c >7.0%) has been linked with worsening hepatocyte ballooning and fibrosis severity, with each 1% rise in HbA1c increasing the likelihood of advancing to a higher fibrosis stage by 15%.[4]

Beyond glucose metabolism, IR contributes to hepatic fat accumulation. Excess free fatty acids (FFAs), released from adipose tissue due to impaired adiponectin signalling, are taken up by hepatocytes. When mitochondrial oxidative capacity is exceeded, incomplete β-oxidation produces reactive oxygen species (ROS) and toxic lipid intermediates, driving inflammation, hepatocyte injury, and fibrosis.[4]

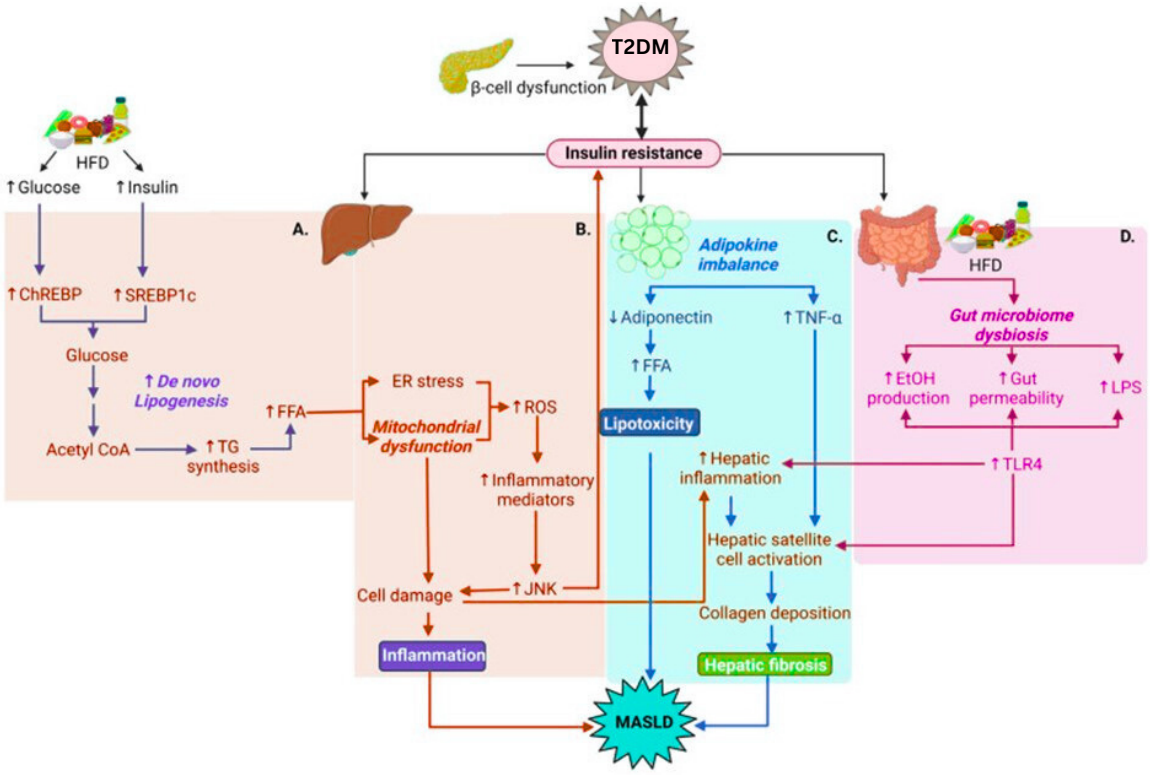

Fig 1. Relationship between T2DM and MASLD.[4]

Lipotoxicity, Adipose Dysfunction, and Systemic Inflammation

Hyperinsulinemia and hyperglycemia stimulate hepatic lipogenesis through transcription factors such as SREBP and ChREBP, promoting lipid droplet accumulation. Once hepatocellular lipid export and oxidation are overwhelmed, toxic metabolites including diacylglycerol and ceramides accumulate, activating ER stress pathways, inflammasomes, and fibrogenic signaling cascades.[3]

Adipose tissue dysfunction further amplifies this pathology. Expanded visceral adipose tissue secretes pro-inflammatory cytokines (TNF-α, IL-1, IL-6, MCP-1) and exhibits a pathogenic adipokine profile with elevated leptin, visfatin, chemerin, and reduced adiponectin. This imbalance contributes to hepatocellular injury, pancreatic β-cell decline, and cardiovascular complications in patients with both MASLD and T2DM.[3]

Role of the Gut–Liver Axis

Gut microbiota dysbiosis is increasingly recognized as a contributor to the MASLD–T2DM relationship. Altered microbial composition increases gut permeability, enabling endotoxin translocation that triggers hepatic toll-like receptor–mediated inflammation. MASLD patients commonly demonstrate reduced Bacteroidetes and increased Prevotella and Porphyromonas species. Ethanol-producing bacteria (e.g., *E. coli*, *Klebsiella*) raise systemic alcohol levels, while metabolites such as trimethylamine-N-oxide (TMAO) exacerbate metabolic dysfunction. In T2DM, reduced populations of *Akkermansia muciniphila* and *Bifidobacterium* are associated with impaired fatty acid oxidation and systemic inflammation, accelerating progression to fibrosis and even hepatocarcinogenesis.[3]

Bile Acid Pathways and Metabolic Crosstalk

Bile acid (BA) signalling, mediated by farnesoid X receptor (FXR) and TGR5, links glucose and lipid homeostasis to MASLD and T2DM progression. FXR activation reduces hepatic lipogenesis, enhances fatty acid oxidation, and suppresses gluconeogenesis, while TGR5 activation stimulates GLP-1 secretion, promoting insulin release and reducing glucagon.7 Altered BA composition in MASLD and T2DM patients disrupts these pathways. Interestingly, bariatric surgery enhances ileal BA exposure, stimulating FXR/TGR5 and contributing to improved insulin sensitivity and hepatic outcomes.[3]

Genetic Susceptibility

Genetic predisposition modifies individual risk for both diseases. Over 400 loci have been associated with T2DM, influencing β-cell function, insulin action, and adiposity. For MASLD, variants in genes such as PNPLA3, TM6SF2, MBOAT7, and HSD17B13 affect hepatocellular lipid handling, VLDL secretion, and fibrogenesis. These variants increase lipotoxicity, hepatic insulin resistance, and progression to advanced liver disease in genetically susceptible individuals.[3]

The pathophysiological relationship between T2DM and MASLD is underpinned by a complex network of insulin resistance, lipotoxicity, adipose tissue dysfunction, gut microbiota alterations, bile acid signalling, and genetic predisposition. Together, these mechanisms explain the frequent coexistence and mutual acceleration of both disorders, highlighting the need for therapeutic approaches targeting shared metabolic pathways.[3,4]

Screening for MASLD in T2DM

The strong association between T2DM and progressive hepatic fibrosis highlights the need for timely screening, given its impact on mortality and liver-related complications. Several non-invasive approaches, including serum-based tests and imaging modalities, are available to assess fibrosis risk in this population. Among these, vibration-controlled transient elastography (VCTE) is regarded as one of the most reliable tools.[7]

A stepwise strategy is often applied to stratify risk, beginning with the Fibrosis-4 (FIB-4) index, followed by VCTE in individuals with FIB-4 scores above 2.67. Nonetheless, the accuracy of individual non-invasive tests (NITs)—such as FIB-4, the NAFLD fibrosis score (NFS), and the aspartate aminotransferase-to-platelet ratio index (APRI)—remains limited in patients with T2DM.[7]

In a prospective study of 96 biopsy-confirmed MASLD patients (50 followed for 12 months), liver stiffness (LS) by elastography, PRO-C3, and multiple NITs (ADAPT, FIB-4, NFS, APRI) were compared. LS demonstrated the best diagnostic performance for advanced fibrosis (AUROC 0.82, threshold 9.4 kPa), with ADAPT showing the highest accuracy among the NITs (AUROC 0.80, cut-off 5.02, sensitivity 62%, specificity 89%). No significant difference was observed between LS and ADAPT (DeLong test, $p = 0.348$). Over the follow-up period, LS showed a slight reduction, whereas PRO-C3 and ADAPT increased significantly, suggesting progression of fibrosis. Other markers (FIB-4, NFS, APRI) remained unchanged.[7]

Similarly, a cross-sectional study of 213 patients reported AUCs of 0.85 (FIB-4), 0.86 (APRI), and 0.64 (NFS) for detecting advanced fibrosis in T2DM, all lower in accuracy compared with N-terminal propeptide of type 3 collagen, a direct marker of fibrogenesis. Another cohort analysis found the AUC of FIB-4 to be markedly lower in patients with T2DM (0.653) compared with those without diabetes (0.826).[7]

To address these limitations, newer diagnostic models have been introduced. The Fibrotic MASH Index, for example, achieved an AUC of 0.89 in T2DM, outperforming FIB-4 (AUC 0.67), with consistent accuracy across different disease durations and HbA1c levels. Other emerging assays, including the Enhanced Liver Fibrosis (ELF) panel, FibroSpect, and the FIB-C3 model, integrate biomarkers of fibrogenesis and may further improve detection. However, their utility still requires validation specifically in diabetic cohorts.[7]

Recent clinical practice guidelines advocate routine screening for liver fibrosis in individuals with T2DM. Yet, uncertainties persist regarding the most effective NIT combinations and the optimal thresholds to apply. For these strategies to be integrated into real-world care, they must be validated within structured pathways in both primary care and diabetes-focused settings. Additionally, many studies fail to clearly distinguish fibrosis due to MASLD/MASH from fibrosis caused by other conditions, which can introduce bias into risk assessment and subsequent management.[7]

Pharmacological Therapies with Evidence in MASLD and Diabetes

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), has emerged as a major global public health concern, particularly in populations with rising rates of obesity and T2DM. It encompasses a spectrum ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH) with varying degrees of fibrosis, increasing the risk of progression to cirrhosis, hepatocellular carcinoma, and cardiovascular complications. While lifestyle modification remains the cornerstone of management, pharmacologic therapies are increasingly essential for patients with progressive disease or higher risk of complications.

Therapeutic strategies for MASLD in patients with T2DM leverage agents initially developed for diabetes and obesity, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose cotransporter 2 inhibitors (SGLT2is), and peroxisome proliferator-activated receptor (PPAR) agonists—as well as liver-specific drugs including thyroid hormone receptor-β agonists (resmetirom), fibroblast growth factor (FGF) analogues, farnesoid X receptor (FXR) agonists, and acetyl-CoA carboxylase (ACC) inhibitors. These agents target key pathogenic mechanisms in MASLD, including hepatic steatosis, insulin resistance, inflammation, and fibrosis. Recent advances have enabled histological improvements in steatohepatitis and fibrosis, particularly with GLP-1 RAs, PPAR agonists, and thyroid hormone receptor-β agonists, while SGLT2 inhibitors and combination therapies provide additional metabolic, cardiovascular, and renal benefits. The evolving pharmacologic landscape underscores a shift toward mechanism-based, disease-modifying strategies for MASLD in patients with diabetes, with combination therapies offering potential to address multiple pathogenic pathways simultaneously.

PPAR Agonists in MASLD/MASH

Pioglitazone, a peroxisome proliferator–activated receptor gamma (PPARγ) agonist, enhances insulin sensitivity, modulates glucose and lipid metabolism, reduces hepatic and intestinal inflammation, and redistributes adipose tissue by lowering the visceral-to-subcutaneous fat ratio while increasing circulating adiponectin levels. Multiple randomized controlled trials (RCTs) and meta-analyses have demonstrated that pioglitazone can induce resolution of NASH and improve fibrosis, even in patients without diabetes, although weight gain and fluid retention remain notable adverse effects. A deuterium-stabilized R-enantiomer (PXL065) has been developed to retain non-genomic benefits while limiting weight gain and edema, showing encouraging results in phase 2 trials.[8]

Real-world evidence also supports these findings; for example, a retrospective study of 65 Brazilian patients treated with pioglitazone for 1–10 years reported significant improvements in aminotransferases, GGT, and steatosis assessed by CAP, representing the first Brazilian cohort evaluating pioglitazone in MASLD.[9] Similarly, Cusi et al. reported 47% NASH resolution with pioglitazone in patients with and without diabetes, accompanied by reductions in liver enzymes, which, while not definitive markers of disease severity, have been associated with histological improvement.[9–11]

Meta-analyses indicate an odds ratio (OR) of 3.65 (95% CI 2.32–5.74) for NASH resolution and an OR of 10.17 (95% CI 2.8–36.5) for regression of advanced fibrosis (F3–F4) compared with controls. Despite these outcomes, pioglitazone is not formally approved for MASLD; U.S. guidance permits its use in biopsy-confirmed MASH regardless of diabetes status, whereas European guidelines consider it safe in non-cirrhotic MASH but do not recommend it as a specific therapy.[11]

Other PPAR agonists, including rosiglitazone, lanifibranor, and saroglitazar, have shown potential in MASLD/MASH management. Lanifibranor, a pan-PPAR agonist, significantly reduced SAF-A scores in a phase 2b trial and improved insulin resistance across hepatic, muscle, and adipose tissues, while saroglitazar, a PPAR-α/γ agonist, improved both histological and metabolic markers.[7]

Overall, thiazolidinediones and other PPAR-targeting agents effectively modulate metabolic and inflammatory pathways in MASLD, with pioglitazone consistently demonstrating MASH resolution and improvements in liver inflammation and steatosis.[7]

Saroglitazar, a dual PPAR-α/γ agonist, is currently the only MASLD-approved therapy in India, demonstrating improvements in NAFLD Activity Score without worsening fibrosis.[9] It exerts its effects through multiple metabolic pathways, enhancing insulin sensitivity, modulating adiponectin and leptin levels, promoting fatty acid β-oxidation, and reducing lipotoxicity-mediated oxidative stress. Clinical and preclinical studies have shown that saroglitazar improves lipid profiles, achieves optimal glycaemic control, and reduces liver enzymes in patients with diabetic dyslipidaemia, MASLD,

and T2DM. Notably, its benefits extend to non-diabetic MASLD patients and those with compensated cirrhosis, highlighting its broad therapeutic potential.[12]

Real-world longitudinal evidence further supports its efficacy. In a 2-year case series of four adult T2DM patients with imaging-confirmed MASLD, saroglitazar 4 mg once daily, in combination with semaglutide (7–14 mg as tolerated), led to marked reductions in HbA1c, triglycerides, ALT, and AST. Three patients showed improvements in hepatic steatosis (S2–S3 to S0–S1) and fibrosis (F2–F3 to F0–F1), with one patient demonstrating complete regression from advanced fibrosis (F3) to no fibrosis (F0).[13] Another prospective case series of eight T2DM patients with MASLD treated with saroglitazar 4 mg daily for 32 weeks reported significant reductions in HbA1c, triglycerides, ALT, CAP, and LSM scores, confirming its beneficial effects on glycemic-lipid control and liver health.[13]

These studies collectively indicate that saroglitazar can address both metabolic and hepatic derangements in MASLD, offering potential disease-modifying benefits in patients with T2DM. Its favorable safety profile, broad applicability across diabetic and non-diabetic MASLD populations, and ability to improve fibrosis and steatosis support its role as a promising therapeutic option, pending further confirmatory trials.[12–14]

Efficacy of GLP-1 and Multi-Agonists in MASLD/MASH

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), synthetic analogs of endogenous GLP-1, enhance insulin secretion, inhibit glucagon release, suppress appetite, and delay gastric emptying. Their benefits in hepatic steatosis are largely attributed to weight loss and systemic metabolic improvements rather than direct hepatic actions. Among the first agents evaluated in MASLD/MASH were liraglutide and semaglutide, both approved for T2DM and obesity, which demonstrated significant histologic resolution of steatohepatitis in phase 2 and 3 trials, though consistent fibrosis improvement remains limited. In the LEAN trial, liraglutide achieved MASH resolution in 39% of patients versus 9% with placebo, with reduced fibrosis progression but no significant fibrosis reversal. Semaglutide showed superior efficacy in glycemic control, weight reduction, and MASH resolution. A phase 2 trial in patients with F1–F3 fibrosis reported resolution rates up to 59% compared with 17% for placebo, while an interim phase 3 analysis revealed 63% resolution and 37% fibrosis improvement versus 34% and 23% with placebo, respectively. However, studies in cirrhotic patients did not show significant histologic benefit. Genetic variants in *GLP1R* and *ARRB1*, which influence glycemic responses, have not yet been linked to variable outcomes in MASLD. Beyond GLP-1 monotherapy, incretin-based combination agents are under active investigation. Tirzepatide, a dual GLP-1/GIP agonist, achieved greater weight loss and HbA1c reduction than GLP-1 RAs, and in a phase 2 trial, produced MASH resolution in up to 62% of patients, with fibrosis improvement in approximately 51–55%, although these fibrosis data require further validation. Survodutide, a GLP-1/glucagon co-agonist, showed notable improvements in MASH resolution (up to 62% vs. 14% for placebo) and modest fibrosis benefit, while pemvidutide, another GLP-1/glucagon co-agonist, remains under evaluation. Retatrutide, a triple GLP-1/GIP/glucagon agonist, achieved dramatic reductions in liver fat (up to 82%) and body weight (24.2% at 48 weeks) in early trials; phase 3 biopsy-based outcomes are awaited, though preliminary data suggest potential to overcome genetic and metabolic barriers in MASLD management. Collectively, incretin-based therapies demonstrate consistent benefits in weight reduction, glycemic control, and hepatic fat reduction, with encouraging but variable effects on fibrosis—positioning them as promising therapeutic candidates for MASLD/MASH.[7,11,15]

The U.S. Food and Drug Administration (FDA) has granted accelerated approval to semaglutide (Wegovy) 2.4 mg once weekly for adults with metabolic dysfunction-associated steatohepatitis (MASH) and moderate-to-advanced liver fibrosis, making it the first GLP-1 receptor agonist approved for this indication.[16,17]

Wegovy, initially approved in 2017 for obesity and overweight, also reduces cardiovascular (CV) events such as myocardial infarction in at-risk individuals. MASH affects approximately 6% of U.S. adults (≈14.9 million people) and continues to rise in prevalence.[16] Semaglutide is not indicated for cirrhotic patients and should be used alongside a reduced-calorie diet and increased physical activity. Semaglutide now joins resmetirom (Rezdiffra), a thyroid hormone receptor-β selective agonist, as the only approved therapies for MASH with fibrosis.[17]

Approval was based on part 1 of the phase 3 ESSENCE trial (NCT04822181), which evaluated semaglutide in adults with MASH and stage F2–F3 fibrosis.[17] After 72 weeks, 63% of participants receiving semaglutide achieved resolution of steatohepatitis without worsening fibrosis, compared with 34% in the placebo group (difference = 29 percentage points; 95% CI, 21–36). Improvement in fibrosis without worsening steatohepatitis occurred in 37% of the semaglutide arm versus 22% of the placebo arm (difference = 14 percentage points; 95% CI, 8–21). Furthermore, 33% of Semaglutide-treated participants

achieved both MASH resolution and fibrosis improvement, compared with 16% receiving placebo (difference = 17 percentage points; 95% CI, 10–23). About 88% of patients maintained the target 2.4 mg dose through week 72.22 This conditional approval marks a pivotal milestone for the MASH community, expanding therapeutic options for a population with limited pharmacologic interventions.[17]

Semaglutide, a long-acting GLP-1 RA with proven glycemic and weight-reducing efficacy, has drawn attention for its pleiotropic anti-inflammatory and antifibrotic properties, which may confer additional hepatic benefits. Clinical evidence demonstrates improvements in liver histology, reductions in hepatic fat content, and favorable changes in inflammatory markers. The landmark phase 2 trial of semaglutide in NASH established significant resolution of steatohepatitis without fibrosis worsening compared with placebo, while the STEP program confirmed substantial weight loss benefits—an indirect but crucial factor in MASLD management. More recently, ESSENCE data confirmed that semaglutide 2.4 mg leads to both fibrosis improvement and MASH resolution in patients with stage F2–F3 fibrosis, underscoring its therapeutic promise.[18]

A large real-world retrospective cohort of MASLD patients followed for up to 8 years demonstrated that semaglutide therapy is associated with improved overall survival and reduced liver-related complications. Propensity score matching across 34 baseline parameters minimized confounding by demographics, comorbidities, and liver disease severity. The absolute mortality reduction of 1.11% at 1 year and 2.39% at 5 years reflects substantial clinical benefit, especially in non-cirrhotic, ambulatory patients. These outcomes are consistent with or exceed those seen in other metabolic intervention trials, reinforcing semaglutide's potential to improve long-term MASLD outcomes. Metabolic and cardiovascular findings from this cohort align with prior GLP-1 RA studies, including SUSTAIN-6 and PIONEER 6, which established cardiovascular benefits in diabetic populations, as well as trials of liraglutide showing similar effects. Semaglutide treatment in MASLD was associated with a 44% relative risk reduction in cardiovascular events during follow-up.[18]

SGLT2 Inhibitors in MASLD: Metabolic and Hepatic Outcomes

SGLT2 inhibitors, including empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin, improve glycemic control, reduce visceral adiposity, elevate adiponectin, lower uric acid, decrease systemic inflammation, and confer consistent cardiovascular and renal benefits. Although histological evidence in MASLD is limited, multiple randomized controlled trials (RCTs) and imaging-based studies have demonstrated reductions in hepatic fat, aminotransferase levels, body weight, and HbA1c.[15,19] In patients with biopsy-proven MASLD and type 2 diabetes, tofogliflozin showed trends toward greater improvements in steatosis, hepatocellular ballooning, lobular inflammation, and fibrosis compared with glimepiride over 48 weeks, along with superior reductions in AST, γ-glutamyl transferase, fibrosis-4 index, and body weight. Combination therapy with low-dose pioglitazone and an SGLT2 inhibitor, such as empagliflozin, has demonstrated synergistic reductions in liver fat, stiffness, and fibrosis indices, mediated in part by increased adiponectin and reduced hepatic free fatty acid influx.[20] Empagliflozin and dapagliflozin have shown improvements in liver steatosis and ALT/GGT levels, although fibrosis improvement is modest, and dapagliflozin has been associated with serious renal adverse effects. Large population studies and systematic reviews support the role of SGLT2 inhibitors in reducing liver-related adverse outcomes, likely through both weight- and glucose-lowering effects, as well as potential direct actions including decreased hepatic inflammation, ketogenesis induction, glucagon elevation, and enhanced adiponectin levels.[7]

DEAN Trial (Dapagliflozin Efficacy and Action in NASH)

In the DEAN trial, 48 weeks of treatment with dapagliflozin resulted in a significant improvement in MASH without worsening of fibrosis compared with placebo. The findings also demonstrated that dapagliflozin treatment provided benefits in terms of MASH resolution without worsening fibrosis and fibrosis improvement without worsening MASH among participants with biopsy-confirmed disease, including those with stage 2 or 3 fibrosis. These outcomes suggest that dapagliflozin may influence key pathological aspects of MASH by improving both steatohepatitis and fibrosis.[21]

In this study, 53% of participants receiving dapagliflozin achieved MASH improvement without fibrosis worsening, compared with 30% in the placebo group. Notably, dapagliflozin treatment produced a placebo-subtracted effect of 15% for MASH resolution without worsening of fibrosis and 25% for fibrosis improvement without worsening of MASH. These confirmatory secondary endpoints align with the criteria proposed by the U.S. Food and Drug Administration (FDA) as being reasonably predictive of long-term clinical benefit in MASH. Furthermore, the results indicated that dapagliflozin conferred

similar benefits on MASH improvement and resolution irrespective of participants' obesity or diabetes status, or the severity of their MASH.[21]

Consistent with earlier studies, the DEAN trial also showed that the SGLT2 inhibitor dapagliflozin improved several metabolic parameters, such as body weight, waist circumference, visceral fat, glucose, insulin resistance, lipid profile, and blood pressure, all of which are closely linked to MASH. Moreover, the findings suggested that the beneficial effects of dapagliflozin on MASH improvement and resolution without fibrosis worsening were largely mediated through weight loss.[21]

THR-β Agonists in MASLD/MASH: Targeted Hepatic Therapy

In March 2024, the U.S. Food and Drug Administration (FDA) granted accelerated approval to resmetirom, a selective thyroid hormone receptor-β (THR-β) agonist, as the first pharmacologic therapy for non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced fibrosis.[18]

Resmetirom exerts its action through liver-selective activation of THR-β, thereby enhancing mitochondrial fatty acid oxidation, reducing de novo lipogenesis, promoting cholesterol efflux, and suppressing pro-inflammatory and pro-fibrotic mediators such as transforming growth factor-β (TGF-β). This targeted mechanism improves hepatic steatosis, necroinflammatory activity, and fibrosis while minimizing systemic thyromimetic effects, distinguishing resmetirom from earlier, non-selective thyroid analogues.[17]

In early-phase clinical studies, resmetirom demonstrated favorable pharmacodynamic and safety profiles. Phase 1 trials showed dose-dependent reductions in low-density lipoprotein (LDL) cholesterol (up to 30%), non-high-density lipoprotein (non-HDL) cholesterol, apolipoprotein B, and triglycerides (up to 60%), with predominantly mild gastrointestinal adverse events and no significant alterations in thyroid function or cardiac markers. Phase 2 studies in biopsy-confirmed MASH demonstrated a 32.9% reduction in hepatic fat, accompanied by improvements in aminotransferases, non-invasive fibrosis biomarkers, NAFLD activity score (NAS), and atherogenic lipid parameters, collectively supporting both hepatic and cardiometabolic benefits.[7]

Resmetirom's pharmacologic selectivity for THR-β avoids thyrotoxic effects mediated through THR-α, thereby conferring a liver-specific metabolic advantage. Other THR-β agonists, including sobetirome, eprotirome, and VK2809, have also demonstrated reductions in hepatic triglycerides and steatosis in clinical and preclinical studies, although effects on insulin sensitivity and glycaemic control have been variable.[7] Resmetirom is generally well tolerated, with mild gastrointestinal adverse effects and no evidence of weight gain or fluid retention. It is currently approved for adults with non-cirrhotic MASH and moderate to advanced fibrosis, in combination with lifestyle modification.[8]

The pivotal Phase 3 MAESTRO program (MAESTRO-NAFLD-1, MAESTRO-NAFLD-OLE, and MAESTRO-NASH) evaluated once-daily resmetirom at 80 mg and 100 mg in a diverse MASH population. At week 52, MASH resolution without worsening of fibrosis was achieved in 25.9% (80 mg) and 29.9% (100 mg) of participants, compared with 9.7% for placebo ($p < 0.0001$ for both). Improvement in fibrosis by ≥1 stage occurred in 24.2% and 25.9% of participants receiving 80 mg and 100 mg, respectively, versus 14.2% with placebo ($p < 0.0001$ for both). The treatment effect (active minus placebo) was 16.4% and 20.7% for MASH resolution and 10.2% and 11.8% for fibrosis regression with 80 mg and 100 mg, respectively—corresponding to approximately two in ten patients achieving MASH resolution and one in ten demonstrating fibrosis improvement.[19]

MAESTRO-NASH was the first Phase 3 trial in MASH to meet both histologic endpoints required for conditional regulatory approval, establishing the feasibility of large-scale, biopsy-driven efficacy assessment in this population. The ongoing MAESTRO-NASH OUTCOMES study is designed to evaluate long-term efficacy over 54 months, including progression to cirrhosis, all-cause mortality, and liver-related events (LREs), while post-approval (Phase 4) investigations will assess cardiovascular and oncologic outcomes.[19]

As of late 2025, Rezdiffra (resmetirom) and Wegovy (semaglutide) remain the only FDA-approved pharmacotherapies for MASH, while no treatment options are available for early-stage MASLD.[19]

Future research is focused on evaluating combination regimens (e.g., with incretin-based agents) and expanding therapeutic use in patients with compensated cirrhosis, who represent the highest unmet need and greatest disease burden. Results from the MAESTRO-NASH OUTCOMES program are anticipated to further delineate resmetirom's long-term hepatic and cardiometabolic benefits in MASLD/MASH populations.[7]

FGF-21 Analogues and ACC Inhibitors: Modulating Hepatic Lipid Metabolism and Fibrosis

Fibroblast growth factor 21 (FGF-21) analogues, including pegozafermin, efruxifermin, and pegbelfermin, have emerged as promising therapies for MASLD and MASH by targeting FGF receptors (FGFR1–3) and the β-klotho co-receptor to enhance energy expenditure, improve insulin sensitivity, modulate dyslipidaemia, and increase adiponectin levels. In phase 2b trials, pegozafermin led to MASH resolution in 23–37% of patients and fibrosis improvement in 25–44%, without significant changes in body weight or HbA1c. Efruxifermin demonstrated similar improvements in MASH activity and fibrosis. Meta-analyses of five phase 2 trials confirmed that FGF-21 analogues consistently produced higher rates of MASH resolution and fibrosis improvement compared with placebo.[11]

Acetyl-CoA carboxylase (ACC) inhibitors, such as PF-05221304, act by suppressing hepatic lipogenesis, thereby reducing steatosis, inflammation, and fibrosis. Phase 2a studies demonstrated 50–65% reductions in liver fat, with additive benefits when combined with complementary agents like PF-06865571.[7]

Fibroblast growth factor 19 (FGF19) analogues, including aldafermin and NGM282, provide an alternative pathway by promoting hepatocyte proliferation and repair, reducing liver fat, and showing trends toward fibrosis improvement in early-phase trials.[7]

FXR Agonists: Targeting Metabolic and Inflammatory Pathways in MASLD/MASH

Farnesoid X receptor (FXR) agonists represent another therapeutic class targeting metabolic and inflammatory pathways in MASLD/MASH. Obeticholic acid (OCA) improves insulin sensitivity and reduces inflammatory markers, while newer FXR modulators such as EDP-305, MET409, tropifexor, and nidufexor have demonstrated reductions in ALT, liver fat, steatosis, and inflammation in phase 2 studies. However, adverse effects such as pruritus have been noted with some agents. In addition, combination therapy with cilofexor and firsocostat in patients with advanced fibrosis or compensated cirrhosis improved NAS, liver biochemistry, and fibrosis markers compared with placebo.[7]

Gut Microbiome Modulators: Emerging Adjunctive Therapies

Emerging therapies targeting the gut–liver axis aim to modulate microbiome dysbiosis, which contributes to increased gut permeability and hepatic inflammation. Preliminary interventions include IMM-124E, a bovine colostrum-derived product, which reduced AST and ALT levels over 24 weeks, and faecal microbiota transplantation (FMT), though clinical evidence remains limited.[7]

Pharmacologic management of MASLD in patients with T2DM has evolved to encompass therapies that target both metabolic and hepatic derangements. Agents such as PPAR agonists, GLP-1 receptor agonists, SGLT2 inhibitors, and thyroid hormone receptor-β agonists have demonstrated efficacy in improving liver steatosis, inflammation, and, in some cases, fibrosis, while also providing glycemic, cardiovascular, and renal benefits. Emerging therapies—including FGF analogues, ACC inhibitors, FXR agonists, and gut microbiome modulators—offer additional mechanisms to address key pathogenic pathways, including insulin resistance, lipotoxicity, and hepatic inflammation. Real-world evidence and clinical trials highlight the potential of combination strategies to achieve superior outcomes by targeting multiple pathways simultaneously.

Individualized therapy should consider disease severity, fibrosis stage, comorbidities, and patient-specific metabolic risk. While lifestyle modification remains foundational, multi-targeted pharmacologic approaches provide a mechanism-based, disease-modifying strategy in MASLD, particularly for patients with T2DM and advanced fibrosis. Ongoing studies and novel agents promise further expansion of effective treatment options, with the goal of improving both hepatic and systemic outcomes in this high-risk population.

Lifestyle and Weight-Loss Interventions for MASLD Management

Weight Loss as the Cornerstone

Weight loss remains the primary intervention for managing MASLD. According to the 2024 European Association for the Study of the Liver (EASL) guidelines, a reduction of ≥5% of body weight decreases liver fat, 7–10% improves liver inflammation, and ≥10% is required for fibrosis regression. Even in adults without overweight or obesity, modest weight

loss of 3–5% is recommended to reduce hepatic lipid content and metabolic risk. Achieving and maintaining these targets, however, is challenging, as long-term adherence to behavioural interventions often declines, with most weight loss occurring within the first six months and an average net loss of ~5% by 12–24 months, often accompanied by partial return of liver fat and stiffness.[2]

Dietary Interventions

Caloric restriction and high-quality diets are effective non-pharmacologic strategies to improve MASLD biomarkers, including liver enzymes, steatosis, MASH, and fibrosis. A deficit of ~500 kcal/day or a total intake of 1200–1500 kcal/day is recommended for weight reduction. Diets rich in whole grains, vegetables, fruits, legumes, nuts, olive oil, and fish, such as the Mediterranean diet have demonstrated benefits in reducing hepatic fat and providing cardiovascular protection.[22,23]

Saturated fats, particularly from red and processed meats, and added sugars, especially fructose, should be limited, as they promote intrahepatic triglyceride accumulation and progression to MASH. Coffee consumption, with or without caffeine, may offer protective effects against MASLD.[23]

For patients with sarcopenia or advanced fibrosis, protein intake of 1.2–1.5 g/kg and shorter overnight fasting periods are advised.[19] In India, dietary patterns high in refined carbohydrates and low in protein and fiber highlight the need for culturally tailored interventions emphasizing plant-based proteins and healthy fats.[22]

Physical Activity

Sedentary behaviour independently predicts MASLD progression. Regular physical activity improves hepatic and peripheral insulin sensitivity, reduces free fatty acid flux to the liver, and decreases de novo lipogenesis. Patients are advised to engage in ≥150 minutes/week of moderate-intensity or 75 minutes/week of vigorous-intensity activity. Aerobic, resistance, high-intensity interval training, or combined approaches have all been shown to reduce liver fat, even without significant weight loss. Exercise also enhances gut microbiota composition, bile acid metabolism, and cardiometabolic outcomes, reinforcing its systemic benefits.[2,23]

Behavioural and Support-Based Interventions

Long-term adherence to lifestyle interventions is enhanced by structured behavioural strategies, including self-monitoring, goal setting, stimulus control, and cognitive-behavioural approaches addressing emotional and environmental triggers. Individualized medical visits facilitate early detection, monitoring, and management of comorbidities, while group-based programs and peer support foster accountability, improve adherence, and can be delivered virtually. Studies have shown that both group-based and internet-based interventions can achieve significant weight loss, reduce liver fat, and lower diabetes risk, with comparable effectiveness.[19]

Digital and Mobile Interventions

Web-based programs and mobile applications provide scalable, personalized approaches for MASLD management. Interventions using smartphone apps or social media platforms have demonstrated improved weight loss, reductions in liver enzymes, and favourable changes in liver stiffness, highlighting their potential as adjuncts to conventional care.[19]

Surgical Interventions

Bariatric surgery, including Roux-en-Y gastric bypass (RYGB), is effective in achieving substantial and sustained weight loss and improving obesity-related comorbidities such as T2DM, hypertension, dyslipidaemia, and obstructive sleep apnoea. It also reduces hepatic steatosis, inflammation, and fibrosis, with studies reporting resolution of steatosis in 91.6%, steatohepatitis in 81.3%, and fibrosis in 65.5% of patients at one-year post-surgery. Improvements in liver inflammation markers such as MCP-1, IL-8, TGF-β1, TIMP-1, α-SMA, and collagen-a1 (I) have been documented, emphasizing the metabolic and hepatic benefits of surgical weight reduction.[23]

Gaps and Future Directions

Key gaps in managing MASLD in patients with T2DM include limited awareness among clinicians and patients, delayed diagnosis, fragmented multidisciplinary care, inconsistent adherence to guidelines, and inadequate training of primary care providers. The lack of structured screening pathways and systematic risk stratification often results in missed opportunities for early intervention. Addressing these challenges requires enhanced education and awareness, routine implementation of non-invasive fibrosis and steatosis assessments, development of coordinated interprofessional care models, and optimized use of lifestyle interventions and emerging pharmacologic therapies. Emphasis on early detection and integrated management is critical to reduce progression to advanced liver disease and associated cardiometabolic complications.

Conclusion

MASLD and T2DM frequently coexist, sharing complex pathophysiological mechanisms that amplify hepatic and systemic complications. Early detection, risk stratification, and integrated management—encompassing lifestyle modification, weight loss, and pharmacologic therapies targeting shared metabolic pathways—are essential to improve outcomes. Emerging agents, including PPAR agonists, GLP-1 receptor agonists, SGLT2 inhibitors, THR-β agonists, and FGF analogues, offer promising disease-modifying potential, particularly when combined with individualized lifestyle interventions. Continued research, real-world evidence, and mechanism-based strategies are crucial to optimize care, prevent progression, and reduce cardiometabolic and liver-related morbidity in this high-risk population.

Box: Approved Pharmacotherapies for MASH/MASLD (as of late 2025)

USFDA has approved **resmetirom (Rezdiffra)** and **semaglutide (Wegovy)** for the treatment of MASH with moderate-to-advanced fibrosis.[19,16]

The **CDSCO** has approved **saroglitazar** for the treatment of MASH (formerly NASH). No therapies are approved for early-stage MASLD.[24]

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Review

Reframing MASLD Through a Sex-Specific Lens

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Abstract

Background: The transition from non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction–associated steatotic liver disease (MASLD) marks a major update in the classification of hepatic steatosis. This redefinition emphasizes metabolic dysfunction as the core diagnostic criterion, improving disease characterization and risk assessment. MASLD demonstrates marked variability across sex and age groups, influencing disease onset, progression, and outcomes. Understanding these biological and hormonal differences is essential for optimizing clinical management.

Materials and Methods: A comprehensive literature review was performed using PubMed, ScienceDirect, SpringerLink, and Web of Science to identify studies published between January 2020 and October 2025. Search terms included "MASLD," "MAFLD," "sex differences," "estrogen," "androgen," and "metabolic dysfunction." Clinical, epidemiological, and mechanistic studies were reviewed to summarize evidence related to sex- and age-specific differences in MASLD pathogenesis and outcomes.

Discussion: MASLD occurs more frequently in men during reproductive years but becomes increasingly common in women after menopause due to estrogen decline, visceral fat redistribution, and increased insulin resistance. Estrogen exerts protective hepatic effects by regulating lipid metabolism and inflammatory pathways, whereas androgen deficiency in men contributes to steatohepatitis and fibrosis. Genetic polymorphisms, including PNPLA3, TM6SF2, and MBOAT7, further influence susceptibility and disease severity. With advancing age, both sexes experience accelerated fibrosis and a higher risk of hepatocellular carcinoma (HCC); however, men show greater rates of advanced liver disease, liver transplantation, and mortality.

Conclusion: Metabolic dysfunction–associated steatotic liver disease (MASLD) shows distinct sex-based differences driven by hormonal, metabolic, and genetic factors. Recognizing these variations is essential for personalized diagnosis, prevention, and treatment.

Keywords: MASLD; sexual dimorphism; biological; genetic and lean population

Introduction

The transition from non-alcoholic fatty liver disease (NAFLD) to metabolic dysfunction–associated steatotic liver disease (MASLD) marks a pivotal advancement in the nomenclature of steatotic liver disorders. This updated terminology highlights metabolic dysfunction as the defining criterion, ensuring greater diagnostic precision and improved risk stratification. MASLD expands the clinical spectrum to include individuals with varying metabolic phenotypes, such as lean patients with hepatic steatosis, thereby reflecting the multifactorial nature of this condition. The global acceptance of the MASLD framework fosters consistency in clinical practice and research, facilitating multicentre collaborations and promoting the development of targeted diagnostic and therapeutic strategies.[1]

The conceptual shift toward metabolic dysfunction–based classification originated in 2020 when experts across the Asia-Pacific region proposed the term metabolic dysfunction–associated fatty liver disease (MAFLD) as a replacement for NAFLD. Subsequently, in 2023, an international expert consensus led by major liver societies from Europe and the Americas introduced

the refined terminology metabolic dysfunction–associated steatotic liver disease (MASLD). These rapid nomenclature transitions have attracted global attention, given their implications for clinical management and research in both adult and paediatric populations. Although MAFLD and MASLD differ in some definitional aspects, they share core features that link hepatic steatosis with cardiometabolic risk factors and associated increases in all-cause and liver-related mortality. The MASLD framework integrates several innovative concepts from MAFLD, and while conceptual harmonization continues, global efforts must now focus on advancing understanding of disease pathogenesis, outcomes, prevention, and treatment.[2]

MASLD represents the most prevalent chronic liver disease worldwide and exhibits distinct sex-based biological differences in its onset, progression, and outcomes. The influence of sex chromosomes and sex hormones contributes significantly to this sexual dimorphism: estrogens confer protective effects against MASLD, whereas androgens tend to promote its development. Consequently, sex-specific therapeutic strategies, including estrogen replacement, androgen blockade, and hormone-modulating therapies, have gained attention as personalized approaches. However, the interplay between hormonal regulation and genetic predisposition adds complexity to disease susceptibility, emphasizing the need for more tailored interventions.[3]

Biological sex profoundly influences MASLD progression and outcomes. Males are more likely to develop downstream complications such as hepatocellular carcinoma (HCC), whereas females more commonly progress to metabolic dysfunction–associated steatohepatitis (MASH) and cirrhosis. Beyond biological factors, gender-related sociocultural influences—including dietary habits, physical activity, and alcohol use—further modify disease trajectories. The increasing recognition of gender diversity and fluidity introduces additional dimensions to MASLD pathophysiology and management, underscoring the need for inclusive and personalized care frameworks.[4]

Understanding the sex disparities in MASLD pathogenesis and outcomes is essential for developing effective, personalized management strategies. Addressing these sex-specific pathways through dedicated clinical research and tailored interventions will be central to optimizing MASLD management and improving long-term outcomes.[3]

Material and Methods

This narrative review was conducted to synthesize current evidence on metabolic dysfunction–associated steatotic liver disease (MASLD) with emphasis on sex-based biological, hormonal, and genetic factors. Relevant literature published between January 2020 and October 2025 was identified through PubMed, ScienceDirect, SpringerLink, and Web of Science using the keywords: “MASLD”, “MAFLD”, “sex differences”, “sexual dimorphism”, “estrogen”, “androgen”, and “menopause”. Articles were included if they discussed biological or hormonal influences on MASLD.

Discussion

Sex-Based and Age-Related Differences in MASLD Prevalence

Metabolic dysfunction–associated steatotic liver disease (MASLD) demonstrates pronounced sexual dimorphism, with a consistently higher prevalence in men than in women. Women of reproductive age generally exhibit a lower risk of MASLD than age-matched men; however, this protection diminishes after menopause, when prevalence becomes comparable or even higher among women. This variation reflects a complex interplay of sex hormones, adipose tissue distribution, and metabolic regulation.[3]

Epidemiological data shows variability in MASLD prevalence across populations and methodologies. A recent meta-analysis confirmed a lower overall prevalence in women, though no significant sex difference was observed in metabolic dysfunction–associated steatohepatitis (MASH). Advanced liver fibrosis is more frequent in women, particularly post-menopause, whereas hormone replacement therapy has been linked to reduced MASLD incidence. In a multinational cohort with histologically confirmed MASLD and advanced fibrosis, older age and male sex correlated with poorer survival and higher hepatocellular carcinoma (HCC) incidence, underscoring estrogen’s protective role in disease progression.[5] Consistent epidemiological findings indicate that premenopausal women have lower MASLD rates than men, but this difference narrows or reverses following menopause.[6]

MASLD is one of the most common causes of chronic liver disease in India, with a reported prevalence ranging from 9% to 32% in the general population and a higher occurrence among obese and diabetic individuals. A large multicentric study involving 924 non-alcoholic type 2 diabetes mellitus (T2DM) patients (355 females and 569 males), aged 25–84 years, enrolled from 189 centres across 101 cities, reported that 522 (56.5%) participants had MASLD based on elevated

aminotransferase levels as per NHANES III criteria. Notably, the disease was more prevalent among females (60%) than males (54.3%), with regional variation ranging from 44.1% in western India to 72.4% in northern India.[8]

A systematic review by Shalimar et al. analysed 16 datasets (n = 10,282) providing gender-specific estimates. The pooled prevalence of MASLD was 39.4% among males and 35.4% among females, showing no significant difference between sexes. The overall pooled prevalence of MASLD in India was 38.6% among adults and 35.4% among children. Despite these findings, the available data remains limited. Most studies lack comprehensive demographic and clinical details, such as stratification by age, BMI category (lean versus obese), comorbidities (diabetes, hypertension, metabolic syndrome, or polycystic ovary disease), and regional or lifestyle variations.[9]

Aging and Metabolic Dysfunction in MASLD Pathogenesis

Age is a key determinant of hepatic health and MASLD progression. With increasing global life expectancy, steatotic liver disease poses a growing public health concern. Approximately one-ninth of the global population is aged ≥60 years, a proportion projected to rise to one-fifth by 2050, reflecting the expanding clinical burden of age-related hepatic dysfunction.[7]

MASLD diagnosis requires evidence of hepatic steatosis accompanied by at least one cardiometabolic risk factor. While early hepatic steatosis may be reversible, persistent metabolic stress contributes to lipid accumulation, mitochondrial dysfunction, oxidative stress, and inflammation, collectively driving progression to MASH.[7]

At the cellular level, aging promotes senescence-associated lipid accumulation and fibrosis. The classical "two-hit" hypothesis proposed that metabolic dysregulation triggers hepatic fat accumulation ("first hit"), followed by oxidative stress and inflammation ("second hit") that accelerate fibrosis and hepatocarcinogenesis. The updated "multiple-hit" model integrates the influence of gut microbiota, insulin resistance, and adipokine signalling through the gut–liver axis as synergistic contributors to disease progression.[7]

The prevalence of MASLD increases progressively with age, beginning from childhood and extending through adulthood. Findings from the Study of Child and Adolescent Liver Epidemiology (SCALE), which assessed liver histology in children aged 2–19 years who underwent autopsy in San Diego County (1993–2003), revealed an overall prevalence of 9.6%, with a distinct age-related rise: 0.7% in children aged 2–4 years, 3.3% in those aged 5–9 years, 11.3% in children aged 10–14 years, and 17.3% among adolescents aged 15–19 years. Complementing these data, a systematic review and meta-analysis of global studies estimated a MASLD prevalence of 7.6% in the general pediatric population.[10]

Although MASLD is most commonly diagnosed during the peripubertal period, increasing evidence indicates that hepatic steatosis can develop even in early childhood. The Viva La Familia study, using elevated ALT as a surrogate marker, identified suspected MASLD in 15% of children aged 4–5 years, 21% in those aged 6–11 years, and 30% among adolescents aged 12–19 years. Similarly, a Canadian review of CT scans and an Israeli study of children with obesity demonstrated the early onset of MASLD, with cases increasingly detected in children under 6 years of age presenting with elevated ALT and increased adiposity.[10]

In the general pediatric population, MASLD affects approximately 11% of males and 7% of females, with this gap widening during adolescence. This sex difference is largely due to variations in fat distribution — males tend to accumulate more visceral fat, a major contributor to hepatic steatosis, while females generally have higher levels of subcutaneous fat, which poses a lower risk. Hormonal changes during puberty further amplify these disparities. MRI-based proton density fat fraction analyses in children with obesity show MASLD prevalence rates of 29% in males compared with 22% in females.[10]

Sex hormones, particularly estrogens, exert protective effects against MASLD by enhancing fatty acid oxidation, reducing hepatic lipogenesis, and limiting inflammation. Consequently, premenopausal women exhibit lower MASLD prevalence, whereas its incidence rises sharply after menopause, peaking around 70 years of age. In contrast, younger and middle-aged men display higher rates of MASLD due to increased visceral adiposity and altered fatty acid metabolism.[11] The loss of estrogen's protective role post-menopause contributes to higher MASLD prevalence in older women. Studies consistently show that MASLD is more common in men during reproductive years but becomes more prevalent in women after menopause. Estradiol regulates fatty acid synthase expression in hepatic and adipose tissues, while saturated fatty acids induce endoplasmic reticulum stress and mitochondrial free radical generation, leading to hepatocellular injury and steatosis.[12]

Sex- and age-specific variations in MASLD prevalence have also been documented across populations. A 12-year Japanese study reported a fatty liver prevalence of 26% in men, about twice that observed in women (13%). Although men

showed relatively stable prevalence across age groups, women exhibited a progressive increase with age, surpassing men in the 70–79-year category. Similarly, a South China study reported higher MASLD prevalence in men than women below 50 years (22.4% vs. 7.1%), but this trend reversed beyond 50 years (20.6% vs. 27.6%).[20] Overall, MASLD incidence rises with advancing age in both sexes, reaching its peak between 70 and 79 years.[12] Liu et al. further observed that MASLD was most prevalent in individuals aged 50–59 years, with the highest rates in men aged 40–49 years and in women aged 50–59 years, likely reflecting hormonal changes associated with menopause. Younger men, conversely, tend to exhibit earlier disease onset, potentially due to the coexistence of metabolic and cardiovascular comorbidities.[12]

At the global level, the burden of MASLD continues to rise in parallel with aging and metabolic disorders. In a large-scale meta-analysis encompassing 8,515,431 samples from 22 countries, Younossi et al. reported a global MASLD prevalence of 25.24%, with the highest rates in the Middle East and South America and the lowest in Africa. The disease prevalence strongly correlated with obesity, diabetes, and dyslipidaemia. In the United States, the median age of MASLD patients increased from 50 years in 2015 to a projected 55 years by 2030, underscoring the impact of an aging population on disease burden.[7]

Menopause and Ethnic Variations in MASLD Outcomes

Ethnicity, genetic susceptibility, and cardiometabolic factors substantially influence MASLD prevalence and fibrosis progression. Multiple studies report higher MASLD incidence in men and postmenopausal women than in premenopausal women. Estrogen confers metabolic protection by reducing hepatic fat deposition and cardiometabolic risk, whereas menopause—marked by estrogen decline—induces insulin resistance, dyslipidaemia, weight gain, and hepatic fibrosis.[13] Consequently, MASLD prevalence rises sharply in women after menopause, often matching or exceeding that in men around age 50, particularly among those with obesity.[14]

Ethnic disparities are well established. Nguyen et al. found that Black patients with MASLD had the highest all-cause and non-liver-related mortality, followed by Hispanic patients, while Asian patients had the lowest risk compared with White counterparts. Despite lower overall prevalence, Black individuals exhibit worse outcomes, reflecting higher rates of obesity, diabetes, dyslipidaemia, and limited healthcare access. Conversely, Hispanic populations show the highest MASLD prevalence, largely attributed to obesity, diabetes, and diets rich in carbohydrates and fats. Culturally tailored dietary interventions may therefore mitigate MASLD burden in these groups.[15]

Sex Hormone Influence on Hepatic Metabolism and MASLD Risk Across Genders

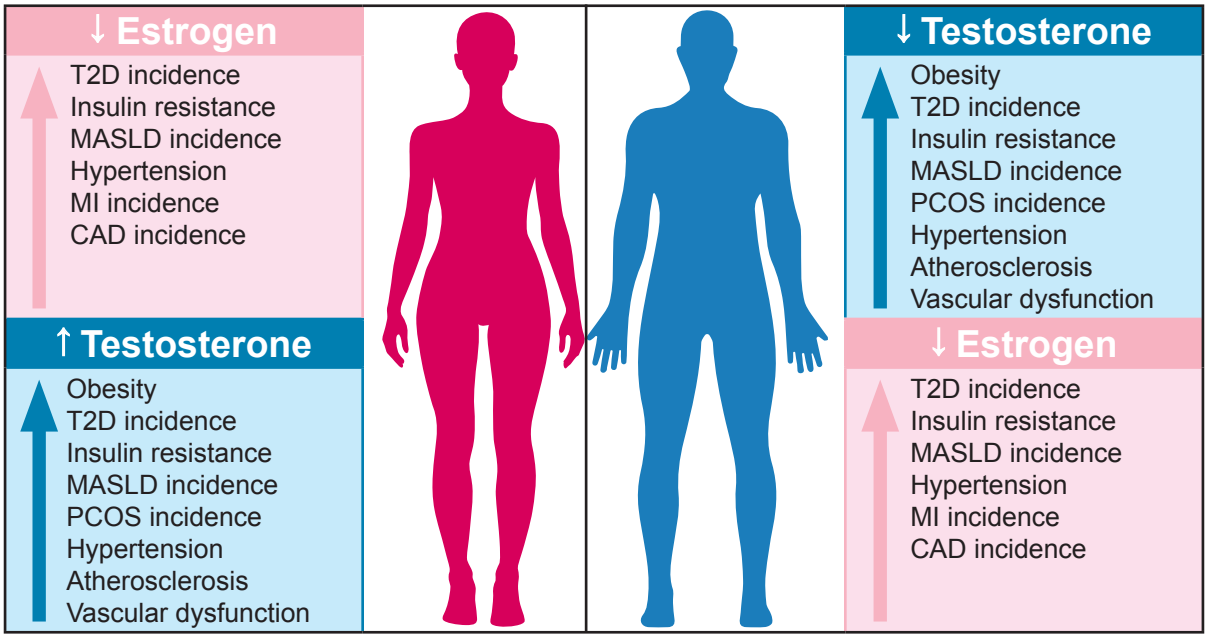

Fig. 1. Impact of sex hormones on the development of MASLD and CVD.[16]

Premenopausal women exhibit a metabolically favorable profile compared to both men and postmenopausal women, emphasizing the hepatoprotective role of estrogen. Estrogen mitigates lipolysis, limits the influx of free fatty acids to the liver, suppresses de novo lipogenesis, and enhances fatty acid oxidation—mechanisms that collectively prevent hepatic lipid accumulation. Furthermore, it reduces the risk of metabolic syndrome and cardiovascular disease. Estrogen deficiency, irrespective of age or adiposity, is associated with increased risk of MASH and hepatic fibrosis. Several studies report comparable MASLD and MASH prevalence between men and postmenopausal women, though fibrosis severity tends to be greater in the latter.[17]

The hepatic actions of estrogen are primarily mediated through estrogen receptor alpha (ERα), which orchestrates metabolic homeostasis and sex-specific transcriptional regulation. Experimental studies indicate that estrogen deficiency, such as following ovariectomy, induces hepatic transcriptomic remodeling, characterized by upregulation of lipid storage genes and downregulation of amino acid metabolism genes. These effects are further intensified in liver-specific ERα knockout models. ERα also influences PPARα-regulated genes involved in fatty acid oxidation. Loss of ERα results in partial masculinization of hepatic gene expression through STAT5B-dependent pathways. Clinical observations in obese postmenopausal women with MASLD demonstrate similar molecular patterns, reinforcing ERα's pivotal role in maintaining hepatic metabolic balance in females.[18]

Androgens exert sex-specific effects on hepatic metabolism. Both androgen excess in women and androgen deficiency in men predispose individuals to central obesity, insulin resistance, and MASLD. Physiological androgen concentrations are essential for metabolic equilibrium. However, certain metabolites, including dehydroepiandrosterone (DHEA) and its sulfate form (DHEAS), have been associated with insulin resistance and histologic alterations characteristic of MASLD. In women, androgen excess, commonly observed in polycystic ovary syndrome (PCOS), correlates with MASLD prevalence ranging from 15% to 55%. Notably, approximately 77% of women with MASLD present with PCOS, underscoring the mechanistic link between hyperandrogenism and hepatic steatosis.[17]

In men, physiological androgen levels exert a protective effect against hepatic lipid accumulation, while androgen deficiency contributes to steatosis. Testosterone and dihydrotestosterone interact with androgen receptors to modulate lipid metabolism, protein synthesis, and muscle mass. Low testosterone levels—documented in approximately 26% of men with MASLD—are associated with higher rates of MASH (88% vs. 67%) and fibrosis (27% vs. 14%). Testosterone deficiency enhances SREBP-1 expression and reduces AMPK activity, thereby decreasing fatty acid oxidation and promoting hepatic fat deposition. Low testosterone and reduced sex hormone-binding globulin (SHBG) independently predict metabolic syndrome, highlighting hypogonadism as a key risk factor for MASLD.[19]

Androgens play a multifaceted role in hepatic metabolism. In men, reduced testosterone concentrations are linked to an increased risk of MASLD. Testosterone and dihydrotestosterone, the principal androgens, act via the androgen receptor (AR), which is expressed at levels nearly 20 times higher in men than in women.[11] A study in Taiwanese men demonstrated that MAFLD is associated with an elevated risk of testosterone deficiency (TD), particularly in the absence of metabolic syndrome (MetS), suggesting MAFLD may serve as an early indicator of TD.[20] Testosterone deficiency promotes MASLD development, either directly or through increased insulin resistance and total body fat accumulation.[20] Androgen deficiency may further enhance hepatic steatosis by stimulating de novo lipogenesis.[21]

Men with MASLD typically exhibit lower testosterone concentrations than those without the condition, and a proportional relationship exists between decreasing testosterone levels and increasing MASLD risk. However, findings from a longitudinal cohort of 1,944 Korean men revealed that baseline testosterone levels, when adjusted for percent weight change, did not independently influence MASLD progression. Similarly, a multiethnic cross-sectional study of men with type 2 diabetes and biopsy-confirmed data found that testosterone levels correlated with hepatic triglyceride content but not with other histological features of MASH. Cross-sectional evidence also suggests that testosterone inversely associates with hepatic steatosis index but not with non-invasive fibrosis risk indices. Collectively, these results imply that the link between low testosterone and MASLD may arise from associated metabolic risk factors such as obesity and insulin resistance, or through a direct influence of testosterone on intrahepatic triglyceride metabolism.[21]

Parallel trends have been observed for SHBG levels, which are lower in men with MASLD than in controls and independently correlate with increased MASLD risk after adjusting for age, BMI, and waist circumference. Furthermore, lower sperm concentration, total sperm count, and motility have been reported in men with MASLD.[21] Testosterone levels also demonstrate a significant association with body fat distribution.[20]

In a study of 631 Taiwanese men aged 40–80 years, individuals with MAFLD showed significantly higher prevalence of total testosterone (TT) levels below 300 ng/dL, TD, and MetS compared with those without MAFLD. They also exhibited

elevated serum leptin and RBP-4 levels and decreased serum adiponectin concentrations, suggesting a link with insulin resistance. Among men without MetS, those with MAFLD had a greater prevalence of TT levels below 300 ng/dL and TD. After adjusting for confounders, MAFLD remained significantly associated with increased risk of both low TT and TD, highlighting a potential role of MAFLD in TD development in individuals without MetS.[20]

Hypogonadism is a prevalent condition among men, particularly in older, obese, and diabetic populations. It is estimated to affect approximately 35% of men over 45 years of age and 30–50% of men with obesity or type 2 diabetes.[22]

Female-Specific Endocrine Conditions and MASLD Risk

Menopause marks a pivotal transition in MASLD pathogenesis, with estrogen loss driving hepatic lipid deposition, insulin resistance, and fibrosis.[7,23] Hormone therapy may confer hepatic and systemic benefits in this setting.

PCOS affects 6–15% of reproductive-age women and doubles MASLD risk.[19,24] Mechanisms include hyperandrogenism and insulin resistance: hyperinsulinemia stimulates androgen synthesis, reduces hepatic SHBG, and increases free androgen levels. Two PCOS phenotypes, reproductive (high SHBG, low BMI/insulin) and metabolic (low SHBG, high BMI/insulin), illustrate the heterogeneity of disease mechanisms. Androgen-mediated activation of SREBP1 enhances hepatic lipogenesis and inflammatory cytokine production, worsening liver injury.[19]

During pregnancy, MASLD is linked to a threefold higher risk of gestational diabetes and preeclampsia, with possible transgenerational effects on metabolic and hepatic health. Extended breastfeeding (>6 months) may offer protection.[24]

Although MASLD is more prevalent in men, disease severity increases markedly after menopause. Estrogen remains protective, while testosterone exerts sex-specific metabolic effects. Innate immune cells also display sexual dimorphism, with male immune cells demonstrating a more pro-inflammatory phenotype that may exacerbate disease progression.[25]

Genetic Determinants of MASLD and Sex-Specific Interactions

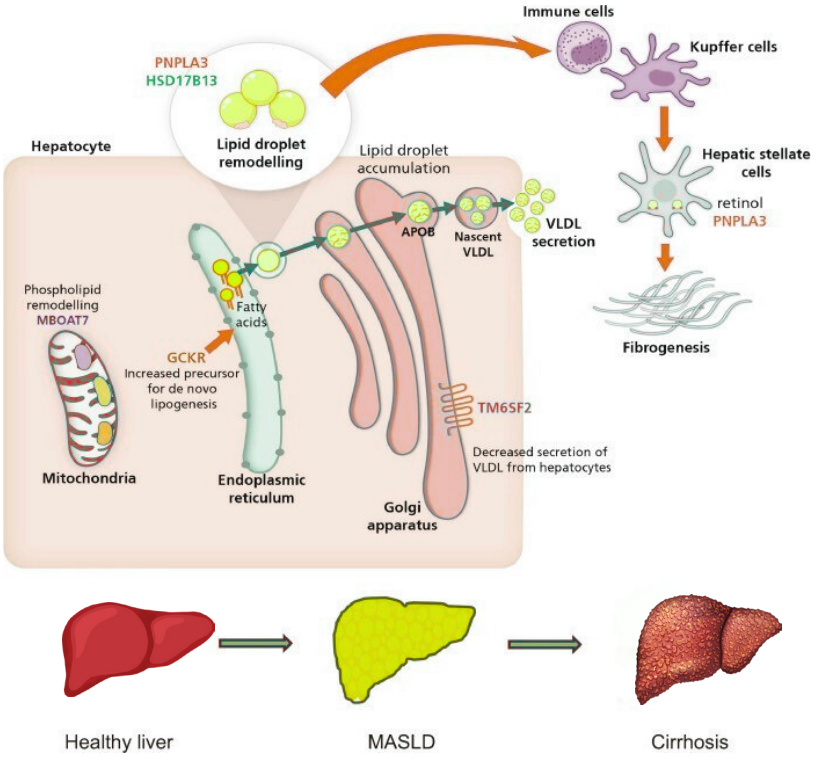

Fig 2. Genetic loci involved in the susceptibility and pathophysiology of fatty liver disease.[26]

Abbreviations: PNPLA3, patatin-like phospholipase domain-containing protein 3; HSD17B13, hydroxysteroid 17-beta dehydrogenase 13; VLDL, very low-density lipoprotein; APOB, apolipoprotein B; MBOAT7, membrane bound O-acyltransferase domain-containing 7; GCKR, glucokinase regulator; TM6SF2, transmembrane 6 superfamily member 2; MASLD, metabolic dysfunction-associated steatotic liver

MASLD outcomes differ across racial and ethnic groups due to combined genetic, environmental, and socioeconomic influences. Variants such as PNPLA3, TM6SF2, and MBOAT7 significantly affect MASLD susceptibility and progression. The PNPLA3 I148M variant, more prevalent among Hispanics, contributes to their higher disease risk relative to non-Hispanic Whites and Blacks.[15]

Genetic variants including PNPLA3, TM6SF2, GCKR, MBOAT7, and HSD17B13 show strong associations with MASLD onset and progression, influencing lipid remodelling, VLDL secretion, and de novo lipogenesis.[26] Environmental modifiers, diet, physical activity, and healthcare access, can amplify or mitigate these genetic risks. Adverse social determinants of health (SDOH), including low income and limited education, further intensify MASLD severity, particularly among Hispanic populations.[15]

Familial aggregation studies indicate that first-degree relatives of MASLD patients have up to a 12-fold increased risk compared with the general population. In one study, MASLD prevalence reached 59% in siblings and 78% in parents of affected children, independent of age, sex, race, and BMI. Twin studies estimate heritability between 35% and 61%. A Swedish multigenerational cohort of 38,000 adults with biopsy-confirmed MASLD reported 1.8-, 1.52-, and 2.14-fold higher rates of hepatocellular carcinoma, major liver events, and liver-related mortality, respectively, among first-degree relatives versus controls.[26]

Sex Differences in Body Composition and Fat Distribution

Sex-specific variations in adipose distribution significantly affect metabolic risk. Men accumulate more visceral adipose tissue (“apple-shaped”), which is metabolically active and directly exposes the liver to free fatty acids and adipokines. In contrast, premenopausal women predominantly store subcutaneous fat (“pear-shaped”), which is metabolically protective and associated with higher adiponectin levels. After menopause, fat redistributes toward visceral depots, increasing metabolic syndrome and MASLD risk.[6] Elevated body fat percentage in MASLD patients with normal BMI underscores adiposity as a stronger predictor of hepatic risk than BMI alone. Waist circumference and central fat accumulation independently correlate with hepatic steatosis, emphasizing the pathogenic role of visceral adiposity.[27]

Sarcopenia also contributes to MASLD progression, independent of obesity or insulin resistance.[27] Reduced skeletal muscle mass correlates with increased BMI and fat mass, with sex-specific differences largely driven by hormonal regulation. Estrogen enhances hepatic–adipose communication and promotes metabolic resilience via increased adiponectin and PPAR signalling, whereas men exhibit greater JNK activation, predisposing to insulin resistance and hepatocyte injury.[6]

Microbiome and Bile Acid Modulation in MASLD

Alterations in gut microbiota and bile acid metabolism play critical roles in MASLD pathogenesis. Dysbiosis compromises intestinal integrity, allowing bacterial metabolites and endotoxins to enter the portal circulation, triggering hepatic inflammation, steatosis, and fibrosis. The farnesoid X receptor (FXR) pathway regulates bile acid synthesis and lipid, glucose metabolism through FGF15/19 signalling. Gut microbial composition varies with age, sex, and menopausal status, linking estrogen levels and microbial diversity to metabolic outcomes. Further research is needed to elucidate how gut–liver–sex interactions influence MASLD progression.[6]

Gender Differences in Immune and Inflammatory Responses in MASLD

Hepatic sexual dimorphism has been recognized since the 1960s; however, mechanistic understanding of its molecular and physiological basis has evolved considerably in the past two decades with advancements in technology. One of the earliest studies by Bond (1960) identified a male-specific cytoplasmic liver protein, termed the “mystery protein”, using chromatography, later shown to be under sex hormone regulation. Early histological analyses using hematoxylin and eosin (H&E) staining and immunohistochemistry revealed structural differences in hepatocyte morphology, nuclear size, and Kupffer cell distribution. More recently, integrated liver and serum proteomic studies have provided deeper insights into sex-based variations in immune response proteins.[11]

Growth hormone (GH) signalling serves as a crucial modulator of hepatic dimorphism and interacts closely with estrogen and androgen pathways. These hormonal interactions contribute to the greater visceral fat accumulation, lower adiponectin levels, and enhanced inflammatory response observed in men compared with premenopausal women. GH also regulates

hepatic circadian gene expression, influencing overall metabolic homeostasis. Sex-specific differences in GH-regulated transcriptional activity may partly explain the variation in MASLD susceptibility and severity between men and women.[11]

MASLD demonstrates clear gender-based disparities, reflecting hormonal modulation of immune and inflammatory pathways. Sex hormones regulate both innate and adaptive immune responses, shaping hepatic inflammation and fibrogenesis. Ballooned hepatocytes release pro-inflammatory mediators that activate macrophages, stellate cells, and T cells, perpetuating hepatic injury. PU.1 and EF-hand domain family member D2 (EFHD2) have been identified as immune regulators upregulated in hepatic macrophages during MASH; inhibition of these mediators has been shown to alleviate metabolic dysfunction and hepatic inflammation in preclinical models.[25] Targeting Th17-related pathways, such as modulation of secreted phosphoprotein 1 (SPP1) through ursolic acid, has also shown therapeutic potential in attenuating MASLD-associated immune activation.[28]

Innate immune cells exhibit notable sex-related functional differences in MASLD. Male immune cells display a more migratory and pro-inflammatory phenotype compared to female cells. Molecular data further demonstrate that sex significantly influences innate immune mechanisms involved in MASLD pathogenesis. Despite this, research on innate immune sexual dimorphism remains limited, and most drug discovery programs do not consider gender-specific immune regulation.[25]

Animal studies further support these findings. In a model employing male and female Balb/c and CD1d–/– mice (deficient in NKT cells) fed a high-fat, choline-deficient diet, female mice exhibited less severe steatohepatitis than males. In males, absence of NKT cells aggravated hepatic injury, inflammation, and fibrosis, indicating a protective role of NKT cells. In contrast, in females, NKT cells appeared to play a minimal role in early disease progression, possibly due to their lower hepatic abundance.[29]

Adipose tissue also contributes significantly to sexual dimorphism in liver disease. Premenopausal women tend to accumulate more subcutaneous fat and secrete higher levels of adiponectin, enhancing insulin sensitivity and providing anti-inflammatory benefits. In contrast, men predominantly store visceral fat, which is metabolically active and pro-inflammatory. These fat depots release cytokines and free fatty acids into the portal circulation, promoting hepatic steatosis and inflammation.[29]

Sex-Specific Patterns in Fibrosis Progression, Cirrhosis, and Hepatocellular Carcinoma (HCC)

Sex exerts a substantial influence on the severity and progression of chronic liver diseases. Women generally experience a more favorable disease course in the early stages, showing higher spontaneous clearance rates of HCV infection and slower fibrosis progression from viral or metabolic causes, particularly before menopause. However, findings in advanced liver disease remain inconsistent. While several studies have reported higher cirrhosis-related mortality among men, others have shown no significant difference once disease stage and etiology are matched.[30]

In hepatocellular carcinoma (HCC), androgens function as tumour promoters. Overexpression of the androgen receptor (AR) has been identified in approximately one-third of HCCs and is closely associated with tumour progression and poorer prognosis.[11] Mechanistically, AR activation stimulates oncogenic pathways and alters non-coding RNA expression, thereby enhancing tumour growth. Conversely, oestrogens demonstrate anti-tumorigenic effects by modulating immune responses, suppressing inflammatory signalling, and potentially reducing oxidative stress. These protective hormonal effects contribute to a lower incidence of HCC, better therapeutic response, and longer survival in women, whereas male sex remains an independent predictor of early recurrence and overall mortality in HCC.[11]

A large U.S.-based cohort study involving privately insured patients with cirrhosis revealed that men had a more than twofold higher risk of developing HCC, a 63% greater risk of undergoing liver transplantation (LT), and a 16% higher risk of decompensated cirrhosis (DC) compared with women, despite similar population sizes. The disparity was more pronounced in non-viral liver diseases, reflecting the increasing contribution of metabolic etiologies. Parallel findings from inpatient and outpatient databases indicated lower rates of hepatic decompensation and portal hypertension–related complications among women.[30]

Sex-related differences were most evident in HCC, with men showing a 110% higher risk. These disparities are attributed to both biological and behavioural factors, including androgen-driven tumour promotion, estrogen-mediated protection, and lifestyle influences such as alcohol consumption, smoking, and central obesity. Additionally, men exhibit lower adherence to surveillance programs, often leading to delayed HCC diagnosis and poorer outcomes.[30]

Although women have lower cirrhosis-related mortality, liver transplantation rates remain disproportionately lower among them. Potential explanations include a lower frequency of LT indications (owing to fewer DC and HCC cases), sex

bias in the MELD score due to creatinine-based underestimation of renal dysfunction in women, and challenges in organ size matching. The LT disparity appears more pronounced in HCC-related cirrhosis, possibly because women undergo earlier surgical resections, thereby reducing the need for transplantation.[30]

An Indian population-based study demonstrated that severe hepatic steatosis was significantly more prevalent among individuals with abdominal obesity, defined as waist circumference ≥100 cm in men and ≥90 cm in women. Severe fibrosis was also more frequent in participants with abdominal obesity in both sexes; however, statistical significance was achieved only in men. Interestingly, women with abdominal obesity displayed higher frequencies of both severe steatosis and fibrosis compared with men. Consistent with these findings, our study observed that a greater proportion of women with abdominal obesity presented with advanced grades of steatosis and fibrosis than men. Furthermore, a systematic review and meta-analysis reported that although women generally have a lower overall risk of developing MASLD, once established, the likelihood of progression to advanced fibrosis is higher in women, particularly those above 50 years of age.[31]

Collectively, these findings underscore that severe steatosis and fibrosis occur more frequently in women with increased waist circumference than in men with comparable degrees of abdominal obesity, highlighting a distinct sex-specific trajectory in MASLD progression within the Indian population.[31]

Conclusion

Metabolic dysfunction–associated steatotic liver disease (MASLD) exhibits marked sex- and gender-based differences driven by hormonal, genetic, metabolic, and immunological factors. Estrogen confers hepatoprotective effects through enhanced lipid metabolism, reduced inflammation, and improved insulin sensitivity, whereas androgen imbalance, either deficiency in men or excess in women, predisposes to hepatic steatosis and fibrosis. Postmenopausal estrogen loss, central adiposity, and immune dysregulation further amplify disease risk in women, while men experience earlier onset and greater progression to hepatocellular carcinoma (HCC). These biological differences are compounded by sociocultural influences, body composition, and ethnic variation. Recognizing and integrating sex-specific mechanisms into clinical practice, preventive strategies, and therapeutic development is crucial for advancing precision medicine in MASLD management.

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